Adverse events of fecal microbiota transplantation: a meta-analysis of high-quality studies

Lamprinos Michailidis, Alden C. Currier, Michelle Le, Deborah R. Flomenhoft

University of Kentucky College of Medicine, Lexington, KY, USA

Abstract	**Background** Fecal microbiota transplantation (FMT) has shown excellent efficacy in treating *Clostridioides difficile* infection, as well as promise in several other diseases. The heightened interest is accompanied by concerns over adverse events (AE) and safety. To further understand that in FMT, we performed a systematic review of the literature and a meta-analysis of high-quality, prospective randomized controlled trials FMT.

Methods Studies were selected based on predefined exclusion criteria and were assessed for quality. Only prospective, randomized, controlled studies of high quality were included in the final analysis. Data were extracted on demographics, AE, indication, delivery method and follow-up duration.

Results Out of 334 articles reviewed, 9 high quality studies with 756 FMTs were selected for final analysis. The pooled rate of AE was 39.3% (95% confidence interval [CI] 0.19-0.642) as they were reported by 112 patients who received FMT. The SAE rate was 5.3% (95%CI 3.1-8.8%). The most common AE reported was abdominal pain, followed by diarrhea. The most common SAE was *Clostridium difficile* infection. Upper gastrointestinal tract delivery was associated with a higher rate of total AE, but not SAE.

Conclusions Based on the selected studies, the AE rate of FMT is 39.3%, with most AE being mild and self-limiting. SAE were uncommon at 5.3%, and many were only possibly related to the FMT. Adherence to standardized reporting of AE as well as longitudinal studies and registries will help further clarify the safety of FMT in the future.

Keywords Fecal micobiota transplantation, adverse events, safety, meta-analysis, systematic review

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Introduction

Fecal microbiota transplantation (FMT) is the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient in order to directly change the recipient's gut microbial composition and confer a health benefit [1]. FMT has a long history, as it was first used to treat gastrointestinal (GI) disorders in the fourth century by a Chinese Doctor named Ge Hong [2]. It was used in veterinary medicine as early as 1973

Department of Digestive Diseases and Nutrition, University of Kentucky College of Medicine, Lexington, KY, USA

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Correspondence to: Lamprinos Michailidis, MD, University of Kentucky College of Medicine 800 Rose Street Room MN649, Lexington, KY 40536, USA, e-mail: lamich@gmail.com

to reduce salmonella carriage in poultry [3]. In the modern era, Eiseman [4] first reported the use of FMT enemas in humans in 1958 to treat pseudomembranous colitis (a form of *Clostridium difficile* [*C. difficile*] infection); it was next reported in 1984 [5] and its application has expanded since. During the past decade, research interest in FMT has increased greatly. In 2009, there were 2 articles published about FMT in the Medline database, whereas in 2019 a PubMed search returned 600 articles. The most established indication for FMT is recurrent *C. difficile* infection (rCDI), for which it has been extensively studied and demonstrated good efficacy [1,6-10], cost effectiveness [11-13], and safety [14-16]. FMT has been studied in inflammatory bowel disease with mixed results [9,17-22], as well as a plethora of other diseases of the GI tract: irritable bowel syndrome [23-26], obesity [27], insulin resistance [28], multi drug-resistant organism (MDRO) decolonization [29], constipation [30], hepatic encephalopathy [31], pouchitis [32], primary sclerosing cholangitis [33], and checkpoint inhibitor-induced colitis [34]. Furthermore, recent insights into the microbiome and gut-brain axis have led to small reports of

FMT use in other neuropsychiatric, autoimmune and metabolic disease states, such as anorexia [35,36], multiple sclerosis [37], autism [38], sepsis [39], and others [40]. As of July 2020, there are over 300 clinical trials of FMT registered with the National Institutes of Health, indicating the worldwide enthusiasm with FMT and hinting at hopes it will be a "panacea" of sorts.

This enthusiasm has been tempered by safety concerns surrounding the use of FMT [127,128]. The treatment appears to be fairly safe in the short term, but serious adverse events (SAE) have been described, such as aspiration pneumonia, bacteremia, and death [21,41-43], and the long-term safety profile remains unclear. In 2019, the Food and Drug Administration (FDA) issued a safety communication regarding extended-spectrum β-lactamase producing *Escherichia coli* (*E. coli*) infections transmitted from FMT that resulted in the death of one patient [44]. The complex nature of the intestinal microbiome introduces a variability in FMT, unlike any other widespread treatment, as every treatment is different. Furthermore, published studies vary in their quality, methodology, donor selection, mode of FMT delivery and follow up. Thus, it is unclear what the rates and severity of adverse events (AE) are, or whether there are any risk factors for the occurrence of such events. We decided to perform a meta-analysis of rigorously selected, high-quality, randomized controlled trials (RCTs) of FMT to obtain reasonable estimates of that risk.

Materials and methods

Literature search

A systematic literature search was performed in August 2019 of the MEDLINE (PubMed) and Science direct databases to identify studies for inclusion. The exact search terms can be seen in Appendix 1. The search was performed within the title, abstract and key words. The references of relevant articles were reviewed and additional abstracts were added. The search strategy is detailed in Fig. 1. After removal of duplicates, 334 original articles were screened further.

Study selection and exclusion criteria

Two reviewers (LM & CC) independently searched the literature and identified studies for inclusion. Disagreements were resolved by consensus between the 2 authors and discussion with a senior author (DF) when necessary. To minimize publication bias, case reports or case series with fewer than 20 (n<20) were excluded from analysis. Other exclusion criteria were: article published in language other than English; abstract form only with no full text available; review articles; and series including a pediatric patient population or non-relevant to the research question. In addition, studies that did not report AE clearly, or did not report the incidence of AE as a percentage of the patients who underwent FMT,

were excluded. For example, if a study only reported AE as a percentage of the number of FMTs performed, and patients could have received more than a single FMT, the study was excluded so as to not interfere with the analysis. After these criteria were applied, 60 studies were selected for preliminary analysis.

Data extraction and quality assessment

Data included the following predefined characteristics and variables: first author last name, year of publication, study design, patient demographics (mean age, sex), follow-up duration in weeks, number of patients, number of FMTs performed, indication, delivery method, rate of AE, rate of SAE. We recorded rates of all AE as they were reported by authors, based on their definitions of what constitutes an AE. We also noted whether the authors used the Common Terminology Criteria for Adverse Events (CTCAE) [45] or some other standardized methodology in reporting AE. It should be noted that there was significant heterogeneity in AE reporting. Reported rates ranged widely, from 5.5-90.5% of patients experiencing at least one AE.

The quality of studies was assessed using the revised Cochrane risk-of-bias tool for randomized trials, version 2 [46]. After quality assessment, we selected for final analysis 9 studies that had a prospective, randomized methodology, a follow-up period of at least 6 weeks, and a low risk of bias on quality assessment.

Heterogeneity testing

Assessment of heterogeneity was performed by calculating Cochran's Q statistic, τ^2 (estimates the between-study variance) and I^2 (quantifies the degree of heterogeneity) with P-values <0.1 considered statistically significant [47,48]. Publication bias was assessed using a funnel plot. Heterogeneity was assessed for each individual outcome (total AE and SAE) and during subgroup analysis. Irrespective of heterogeneity, the random-effects model was used to calculate pooled effects for each outcome and subgroup.

Outcomes measured

The outcomes measured were: 1. the total rate of AE observed during the follow-up period; 2. the total rate of SAE observed during the follow-up period; and 3. the risk factors associated with AE development, using subgroup and meta-regression analyses.

Statistical analysis

The final analysis included the 9 highest quality studies. The total number of patients who received FMT and the
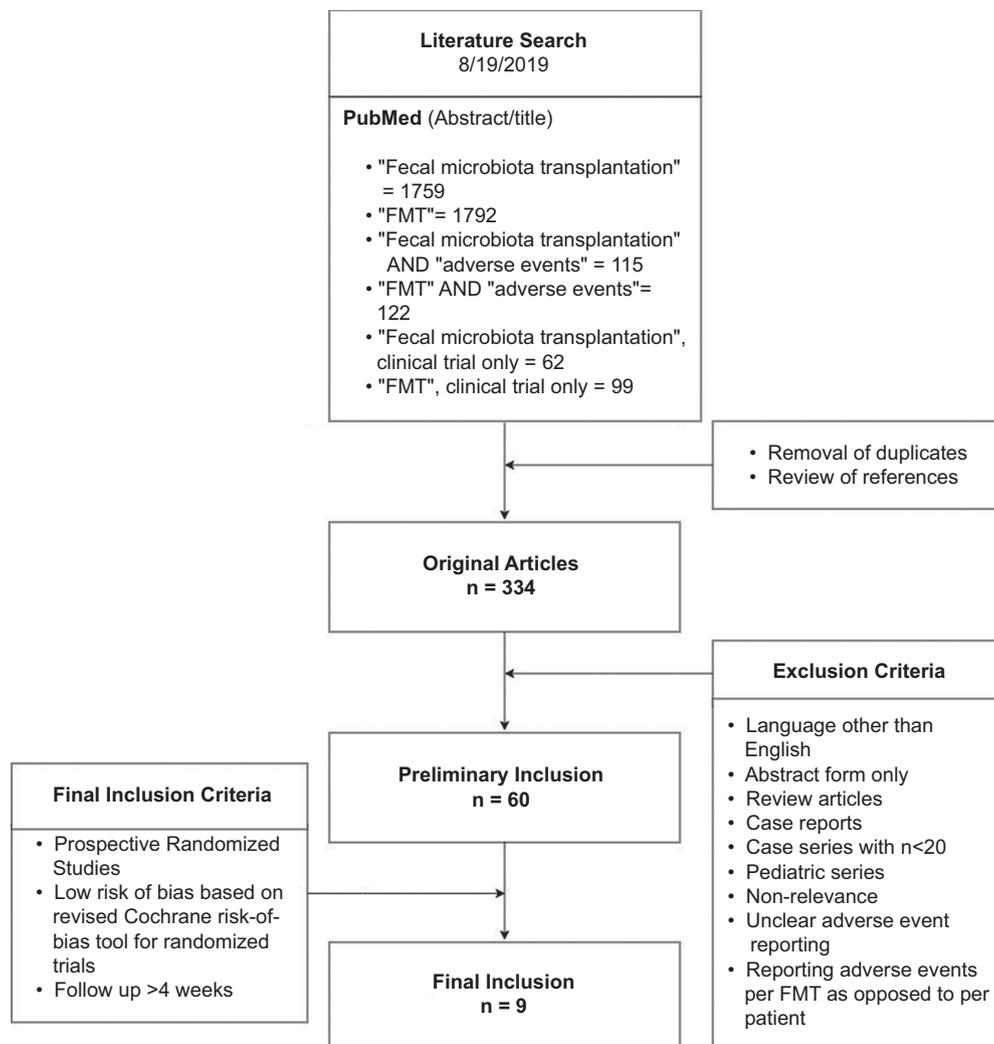
Figure 1 Literature search strategy
FMT, fecal microbiota transplantation

total number of AE (as defined by authors) observed during the follow-up period were noted for each study. The same was done for SAE, again as per author definition. Only the patients for whom final outcomes were reported were included in the analysis. Patients lost to follow up were not included. Variables of interest were treated as continuous variables with means and variations [49]. We conducted a meta-regression analysis on the 9 highest quality studies with regard to delivery method for both outcomes. Under the random-effects model, the Q statistic, τ^2 and I^2 were calculated to test the model and attempt to explain the variance between studies. The R^2, the proportion of variance explained by the covariates, was also calculated. The correlation of each individual covariate with AE rates was assessed for statistical significance under both models. Scatterplots were generated for all covariates under both models. The models were underpowered because of missing data in the case of SAE. The lower GI delivery group was used as a reference group, and studies with mixed methods of FMT delivery were excluded from this particular analysis as potential confounders. In an attempt to determine certain

subgroups that might experience a higher SAE rate and identify potential risk factors, we decided to expand the analysis to the 60 original studies. We calculated the AE and SAE rates of different subgroups based on delivery method and indication. Finally, we performed a meta-regression analysis to identify risk factors for AE development.

The optimal regression model included the following covariates: delivery method, follow up in weeks, and percentage of female patients. Several studies reported median ages and/or median durations of follow up; for these studies, means and variances were recalculated, using a formula previously described by Hozo *et al* [49], and mean values were included in the analysis. Again, the lower GI delivery group was used a reference group, and studies with mixed methods of FMT delivery were excluded from this particular analysis as potential confounders. A total of 26 studies with fully available covariates were included in this additional analysis. Statistical analyses were performed using Comprehensive Meta-Analysis software, version 3.3.070 (Biostat, Englewood, NJ 07631, USA).

Results

Descriptive assessment of included studies

Our initial literature search yielded 3949 articles. After removal of duplicates and review of references, 334 articles were selected and reviewed further. Of these, 60 studies were selected for preliminary inclusion after application of the exclusion criteria. We further selected for final inclusion 9 prospective, randomized studies [9,17,22,23,50-54] that had a low risk of bias based on our quality assessment using the revised Cochrane risk-of-bias tool for randomized trials.

The studies finally included were published between 2014 and 2019. All studies were prospective and controlled, and 5 of the 9 were also blinded [9,17,22,23,52]. Five of the 9 studies were performed in Europe [9,23,50-52], one in Australia [22], 2 in Canada [17,53], and one in the United States [54]. The studies described a total of 756 FMT procedures performed in 388 patients. The mean age of the participants was 50.4±12 years and 70±11% were female. Follow up had a mean duration of 17±14 weeks and ranged from 6 to 52 weeks. Indications were: rCDI in 3 studies [51,53,54], ulcerative colitis (UC) in 3 studies [9,17,22], irritable bowel syndrome (IBS) in 2 studies [23,52], and MDRO colonization in one study [50]. FMT delivery methods included: colonoscopy [22,23], enema [17], nasoduodenal tube [9], capsules [52], and various methods in 4 of the studies [50,51,53,54]. All of the patients included in the analysis received heterologous, or donor-stool FMT. One of the studies included autologous FMT cases as the control arm [9]. We decided not to include these patients in the final analysis as autologous FMT may have a different AE profile than heterologous FMT [55].

All studies reported AE and SAE incidence rates as percentages of the patients that received FMT. Only 2 of the authors used published guidelines on defining and reporting AE. Hvas *et al* used guidelines published by the European Commission [56]. Youngster *et al* used a modification of the CTCAE [57]. Certain authors specified whether the AE were thought to be related, possibly related or unrelated to the FMT procedure. If an AE was deemed to be unrelated by the authors, it was not included in the analysis. That was also the case for the analysis of the 60 studies included in the preliminary selection. A detailed description of the included studies can be seen in Table 1.

Total AE rate

One of the primary outcomes was to calculate the total rate of AE observed after FMT. A total of 124 of the 388 patients who received FMT experienced at least one AE during follow up. The pooled rate of AE was calculated at 39.3% (95% confidence interval [CI] 0.19-0.642; 2-sided P=0.4). A forest plot of pooled AE rates can be seen in Fig. 2. The vast majority of AE were mild. The most common AE in every study were: bloating [9,51,54], abdominal pain [23,53], worsening of colitis [17,22], nausea/vomiting [52], and diarrhea [50]. Overall, the most common AE was abdominal pain, reported in 5.9% of the patients, followed by diarrhea, reported in 5.2% of the patients. A detailed description of all AE can be seen in Table 2.

SAE

Another primary outcome measure was the rate of SAE. Serious adverse drug experiences, as defined by US Federal Code [58], are those that result in death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. We analyzed SAE as they were reported by the authors. A total of 11 of the 388 patients experienced at least one SAE
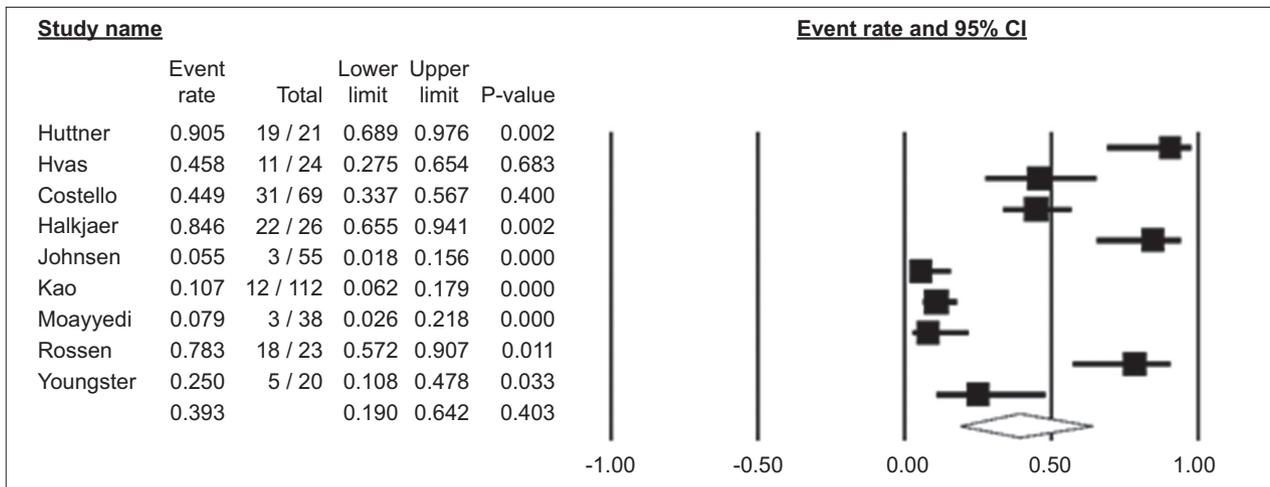

Study name	Event rate	Total	Lower limit	Upper limit	P-value	Event rate and 95% CI
Huttner	0.905	19 / 21	0.689	0.976	0.002	
Hvas	0.458	11 / 24	0.275	0.654	0.683	
Costello	0.449	31 / 69	0.337	0.567	0.400	
Halkjaer	0.846	22 / 26	0.655	0.941	0.002	
Johnsen	0.055	3 / 55	0.018	0.156	0.000	
Kao	0.107	12 / 112	0.062	0.179	0.000	
Moayyedi	0.079	3 / 38	0.026	0.218	0.000	
Rossen	0.783	18 / 23	0.572	0.907	0.011	
Youngster	0.250	5 / 20	0.108	0.478	0.033	
	0.393		0.190	0.642	0.403	

Figure 2 Forest plot of total adverse event rate
CI, confidence interval

Table 1 Characteristics of the included studies

First author, year [Ref.]	Indication	Number of patients	Average age	Percentage female sex	Number of patients with AE	Most common AE	SAE	Routes of infusion	Average follow-up time (weeks)
Huttner, 2019 [50]	MDRO colonization	21	70	54.6%	19	Diarrhea (57%)	Hepatic encephalopathy (4.8%)	Colonoscopy & Capsule	6
Hvas, 2019 [51]	rCDI	24	68	83.3%	11	Bloating (21%)	Sepsis (4.2%), small bowel bacterial overgrowth (4.2%)	Colonoscopy & NJ	8
Costello, 2019 [22]	UC	69	38.5	45.2%	31	Worsening colitis (21%)	Worsening colitis (4.3%), pneumonia (1.4%), rCDI requiring colectomy (1.4%)	Colonoscopy	8
Halkjær, 2018 [52]	IBS	26	37.3	68%	22	Nausea & emesis (35%)	None	Capsule	24
Johnsen, 2017 [23]	IBS	55	44	65%	3	Abdominal pain (5%)	None	Colonoscopy	52
Kao, 2017 [53]	rCDI	112	58.7	70.5%	12	Abdominal pain (5%)	None	Colonoscopy & Capsule	12
Moayyedi, 2015 [17]	UC	38	42.4	53%	3	Worsening Colitis (8%)	Patchy colitis & rectal abscess (5.3%), CDI (2.6%)	Enema	7
Rossen, 2015 [9]	UC	23`	40.5	54.1%	18	Bloating (59%)	None	Enteroscopy	12
Youngster, 2014 [54]	rCDI	20	54.5	55%	5	Bloating (20%)	None	Colonoscopy & NGT	24

MRDO, multidrug resistant organism; rCDI, recurrent Clostridium difficile infection; SAE, serious adverse events; AE, adverse events; NGT, nasogastric tube; NJ, nasojejunal tube; IBS, irritable bowel syndrome; UC, ulcerative colitis

during the follow-up period. The reported SAE rates ranged from 0-7.3%. There was little heterogeneity observed (Q=7.7, I^2=0, τ^2=0). The pooled rate of SAE was calculated at 5.3% (95%CI 0.031-0.088; 2-sided P<0.001). A forest plot of pooled SAE rates can be seen in Fig. 3. The most common SAE was *C. difficile* infection, reported in 3 of the 388 patients (0.8%). A list of SAE can be seen in Table 2. No deaths attributed to FMT were reported in these 9 studies. A detailed description of causes of death can be seen in Table 3.

Impact of covariates on AE

We hypothesized that the method of delivery may be correlated with the rate of AE. To test that, we decided to perform a meta-regression analysis of the 9 studies selected for final inclusion. We divided the mode of delivery into 4 groups: Upper GI (nasoduodenal tube), Capsules, Lower GI (colonoscopy and enemas), and Mixed (more than a single method used in the same study). We excluded the Mixed group from the analysis to avoid confounding the results and used Lower GI as the reference group, as that is the method most commonly performed in clinical practice. Five studies were included in this model. Both the Capsules (coefficient=3.3, 95%CI 1.08-5.64; P=0.0039) and Upper GI (coefficient=2.9, 95%CI 0.69-5. 19; P=0.01) groups were associated with more total AE than the Lower GI group. This model explained 76% of the between-study variance with an R^2 value of 0.76. A regression figure with the logit AE rates in relation to delivery can be seen in Fig. 4. No other covariates were found to be associated with a difference in AE rates.

We attempted a meta-regression with regard to SAE rates and delivery method, but the models were underpowered to explain the variance between the groups. Thus, we decided to expand our analysis to the 60 studies included in the preliminary selection to attempt to identify risk factors associated with higher SAE rates.

Table 2 Description of adverse events of fecal microbiota transplantation

Adverse events	Total number of patients (N= 388)
Abdominal pain	23 (5.93%)
Diarrhea	20 (5.16%)
Nausea	18 (4.64%)
Bloating	15 (3.87%)
Worsening colitis	13 (3.35%)
Weight gain	13 (3.35%)
Vomiting	9 (2.32%)
Weight loss	8 (2.10%)
Headache	8 (2.10%)
Fever	6 (1.55%)
Flatulence	4 (1.03%)
Fecal incontinence	4 (1.03%)
Dizziness	4 (1.03%)
ALT elevation	4 (1.03%)
Anemia	3 (0.77%)
Obstipation	3 (0.77%)
Constipation	2 (0.52%)
Alkaline phosphatase increase	2 (0.52%)
Reflux	2 (0.52%)
Small bowel bacterial overgrowth	1 (0.26%)
Fatigue	1 (0.26%)

Serious adverse events	Total number of patients (N= 388)
Clostridium difficile infection	3 (0.77%)
Rectal abscess	2 (0.52%)
Patchy colonic inflammation in ulcerative colitis	2 (0.52%)
Pneumonia	1 (0.26%)
Systemic inflammatory response syndrome	1 (0.26%)
Hepatic encephalopathy exacerbation	1 (0.26%)
Small intestinal bacterial overgrowth	1 (0.26%)

ALT, alanine aminotransferase

Expanded analysis

We performed an additional analysis that included all 60 studies of the preliminary selection [7-9,14-17,22,23,50-54,59-104]. Those described 3595 FMTs performed in 2921 patients with a mean age of 58±13.3 years, of whom 60±16% were female. Mean duration of follow up was 18.9±18.8 weeks. As was the case with the final inclusion studies, very few authors utilized some standardized guideline of AE reporting. Only 6/60 studies used the CTCAE [54,60,72,74,85,97] and Hvas *et al* [51] used guidelines published by the European Commission. Indications were rCDI in 42/60 studies, UC in 7/60, Crohn's disease

Table 3 Deaths described in the included studies

Cause of death	(N=6)	Related to FMT?
Unspecified cardiopulmonary disease	2	No
Malignancy	3	No
COPD exacerbation	1	No

Deaths in supplemental studies	(N=89)	Related to FMT?
Unspecified causes	54	No
Malignancy	7	No
Worsening *Clostridium difficile* infection	6	No
Aspiration pneumonia	4	Yes
Pneumonia	4	No
Chronic obstructive pulmonary disease	2	No
Cerebrovascular accident	2	No
Pre-existing sepsis	2	No
Urosepsis	2	No
Concussion due to traumatic fall	1	No
Pulmonary embolism	1	No
Renal failure	1	No
Arterial thrombus	1	No
Chronic respiratory failure	1	No
Complications due to hemodialysis	1	No

FMT, fecal microbiota transplantation; COPD, chronic obstructive pulmonary disease

in 3/60, IBS in 3/60, metabolic syndrome in 2/60, MDRO colonization in 1/60, and mixed indication in 2/60. The mode of delivery varied, with 5/60 using capsules, 10/60 some method of esophagogastroduodenoscopy or nasogastric/nasoenteric tube delivery (Upper GI group), 23/60 colonoscopy or enema (Lower GI group), and the remaining 22/60 using various method of delivery (Mixed group). Heterogeneity in rates of SAE was low, with I^2=0%. The pooled rate of SAE was calculated at 3.0% (95%CI 0.0171-0.0505; 2-sided P<0.001). We performed analyses of subgroups by indication and delivery method. Patients with Crohn's disease had the lowest point estimate of SAE rate, at 1.3% (95%CI 0.0027-0.064; 2-sided P=0.001), and patients with UC had the highest, at 5.3% (95%CI 0.0293-0.0952; 2-sided P=0.001). In terms of delivery method, the Lower GI delivery subgroup had the highest SAE rate point estimate at 4.3% (95%CI 0.0302-0.0620; 2-sided P=0.001) and the Upper GI delivery subgroup had the lowest SAE rate point estimate at 1.5% (95%CI 0.0063-0.0334; 2-sided P=0.001).

To identify independent predictors of SAE development, we performed a meta-regression analysis on 26 of the studies that had complete data available for the covariates assessed. The optimal model included the mode of delivery (with the Mixed group removed), follow up in weeks and percentage of females as covariates. This model explained 85% of the between-study variance, with an R^2 value of 0.85. Interestingly, the only factor
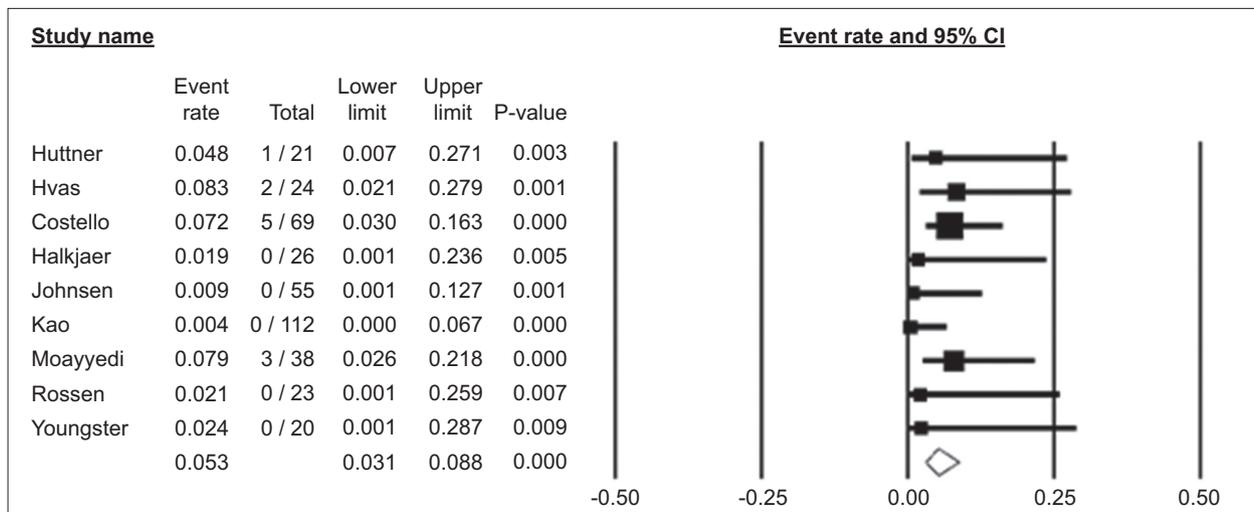
Figure 3 Forest plot of serious adverse event rate
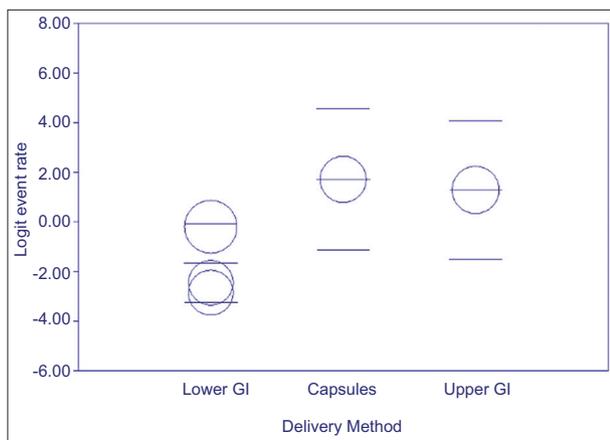*CI, confidence interval*

Figure 4 Regression analysis of impact of delivery method on logit of total adverse event rate*
*Based on data of from 5 studies from included in the original analysis
GI, gastrointestinal

independently associated with lower SAE rates was an Upper GI method of delivery (coefficient=-1.4, 95%CI -2.37-0.92; P=0.02). There was a trend toward lower rates of SAE as the percentage of female patients increased that did not reach statistical significance (P=0.056). Duration of follow up was not independently associated with SAE rates, neither was FMT indication in separate analysis. Fig. 5 depicts logit SAE rates in relation to delivery method and Fig. 6 depicts logit SAE rates in relation to the percentage of female subjects.

Discussion

The primary goal of our meta-analysis was to obtain accurate estimates of the total rates of AE and SAE after FMT. All the studies selected for final inclusion were prospective,

randomized controlled trials with rigorous methodology and a low risk of bias, based on a validated assessment tool [46]. Some of the studies were blinded [9,17,22,23,52]. Furthermore, they all included a fairly large number of subjects (n≥20), encompassed a broad age range, had a wide array of FMT indications and included all the different modes of FMT delivery. We consider that this study selection adds to the strength of our analysis.

We found the pooled AE of FMT to be 39.3%, with a wide CI and significant heterogeneity between different studies. We believe this wide variability stems from the different methods authors used to capture AE and different definitions of relatedness of an AE to the procedure. The vast majority of AE recorded were mild and self-limited, such as abdominal pain, bloating, nausea and vomiting. The reason abdominal pain was the most commonly reported AE is unknown. Details on the severity of pain were not reported by authors and it should be noted that pain scales are subjective. It is possible that pain or other effects, such as nausea, could be related to the procedures, such as colonoscopy, as opposed to the effect of the microbiota. Four studies did describe rates of AE in the placebo arm [9,17,23,50,52]. For example, Halkjaer *et al* reported an AE rate of 57.7% in the placebo group and the only AE significantly more common in the intervention group was diarrhea. Overall, of the 135 patients in the placebo arms, 49 developed AE (36.3%), and 4 had SAE (2.96%). The differences in AE and SAE rates between both arms were not statistically significant.

The pooled rate of SAE was calculated at 5.3%, with a narrow CI and low heterogeneity, and probably represents a more accurate estimate than total AE rate. Despite the high quality of the studies, few authors followed specific criteria to determine the seriousness of AE. Again, it should be noted that AE and SAE were included in the analysis only if deemed related or possibly related to FMT by the authors, but the criteria for that decision were mostly unclear. In general, the SAE rates appeared similar between both study arms. For example, in the study by Moayeddi *et al* [17] there was no difference in SAE rates between the FMT and control groups.
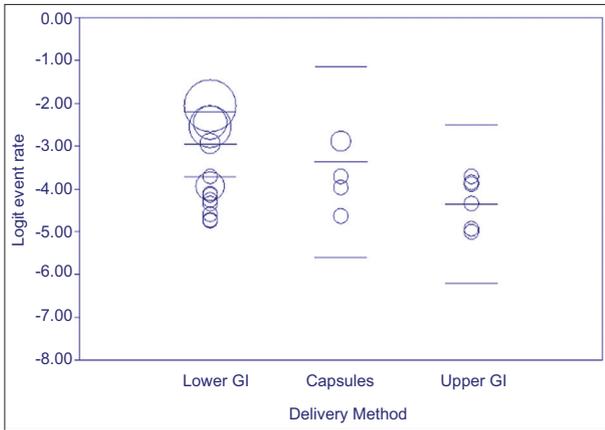
Figure 5 Regression analysis of impact of delivery method on logit of serious adverse event rate*

*Based on 26 studies from the expanded analysis
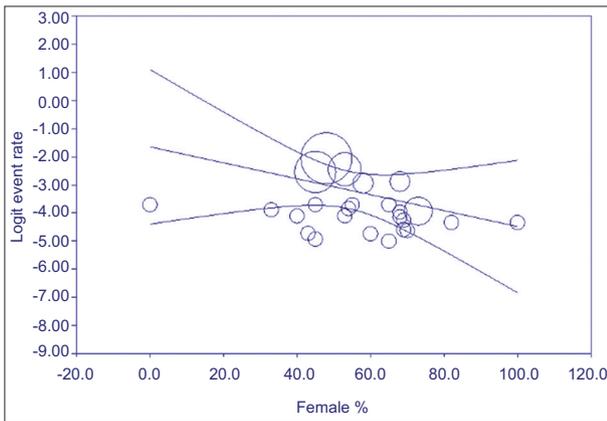
GI, gastrointestinal

Figure 6 Regression analysis of impact of patient gender on logit of serious adverse event rate*

*Based on 26 studies from the expanded analysis

Our secondary objective was to attempt to identify risk factors for AE development. Among the 9 studies finally included, it appeared that upper GI delivery through capsules or nasoduodenal tube was associated with a higher rate of AE development. No other covariates were significantly associated with different AE rates in regression analysis. A possible explanation for this finding is that sedation during colonoscopy minimizes patient perception and reporting of the mild, self-limited AE of the procedure.

We also performed a more expanded analysis of 60 studies to attempt to identify risk factors for development of SAE. Results of this analysis should be considered less accurate, as the included studies had lower overall quality, a higher risk of bias and it could not be determined whether there might be some duplicate reporting of cases. Interestingly, upper GI delivery (excluding capsules) was the only risk factor independently associated with a lower rate of SAE.

One of the main concerns regarding the use of FMT is the possible transmission of infectious diseases. Since the earliest studies [1], rigorous donor screening and testing has been proposed to minimize that risk. In 2019, the FDA raised alarm by issuing a series of safety communications describing the cases of 2 immunocompromised adults who developed infection with extended-spectrum β-lactamase-producing *E. coli* after receiving FMT prepared with stool from the same donor—one of the patients died [44]. As a result, the FDA now recommends MDRO testing and exclusion of persons at risk of MDRO carriage (such as healthcare workers) from donating stool. Few infectious complications characterized as SAE occurred in the 9 series of our analysis; those can be seen in Table 1. The biggest theoretical concern involves immunocompromised patients, although the use of FMT has been shown to be relatively safe in this group, in both case reports [105-107] and cohort studies [98,108,109]. That includes patients with cirrhosis [110,111]. There is also theoretical concern that FMT will promote the transfer of donor viral communities that could cause infectious or immunologic complications in the recipient. Norovirus gastroenteritis after FMT has been reported [112]. Chehoud *et al* [113] demonstrated transfer of viral communities with FMT, but no viruses pathogenic to humans were found to be transferred. Other studies have linked virome changes with treatment response [114,115]. More studies are needed before conclusions can be drawn about the clinical impact of viral community transfer with FMT. The emergence of the novel coronavirus, which has been documented to be present in stool [116,117], has added safety concerns to FMT and complicated the workflow of stool donation and FMT research [118]. All of the studies included in our analysis preceded the emergence of the disease. Finally, it has been postulated that autologous FMT may have decreased infectious risks [55]. Thirty-four patients who received autologous FMT were included in one of the examined studies [22]. Rossen *et al* [9] compared duodenal infusions of donor to autologous feces and found similar AE and SAE rates between the 2 groups. Further studies are needed to clarify whether autologous FMT has a favorable safety profile.

Another theoretical concern of FMT revolves around long-term safety, and more specifically its ability to induce immunologically mediated complications in the host that are not initially evident. The long-term safety has been explored in several studies, with follow-up periods of about 1 year [14,119]. In our analysis, the study by Johnsen *et al* [52] had the longest follow up of 52 weeks. None of the participants reported any new diagnoses or lasting side-effects 1 year after FMT. Agrawal *et al* [14] reported new diagnoses of microscopic colitis, Sjögren syndrome, contact dermatitis, Bence-Jones proteinuria, follicular lymphoma and laryngeal cancer in patients who had FMT. However, patients had clear risk factors for some, and for others they mentioned there was no evidence for or against causation by FMT. Worsening of underlying inflammatory bowel disease post FMT has also been previously reported [18,120,121], and was also seen in the studies we analyzed. Finally, there have been case reports linking FMT to obesity [122] and, interestingly, there were 13 cases of weight gain after FMT reported in the included studies. Discerning whether long-term new AE diagnoses are attributable to FMT poses several methodological risks. Randomized controlled trials with long follow-up duration and national FMT registries that have been recently started in

America, China and Europe [2,123,124] should help answer this difficult question in the future.

Another important question is what the estimated mortality associated with FMT is. In the 9 high-quality prospective studies no deaths were encountered. However, in the supplemental studies 4 deaths were encountered and were all periprocedural. Aspiration of fecal contents was the most common event and occurred in 3 patients, all treated using 3 different methods of upper GI administration, including via nasojejunal or nasoduodenal tube, and gastroscopy (Goldenberg, Van Beurden, Cohen). The fourth patient whose death was related to FMT aspirated during sedation prior to administration of fecal contents via colonoscopy. Based on our literature review, it appears that the highest risk for patient mortality is during sedation or administration of fecal contents via upper GI administration.

Further review of other studies not included in this review provided 3 studies in which death was potentially related to FMT, based on the authors' conclusions. One patient received FMT via a pre-existing G-tube placed for oropharyngeal malignancy, the procedure was uncomplicated, but 3 days later he developed septic shock with toxic megacolon and multiple organisms were isolated in blood cultures including *E. coli* and *Lactobacillus casei*. He underwent emergent colectomy, but unfortunately died the following day. It should be noted however, that he was being treated for *C. difficile* infection and antibiotics were immediately discontinued on the day of FMT [122]. Another study noted a death following aspiration which occurred during sedation for FMT via colonoscopy [123]. Finally, the third death occurred 48 days after regurgitation of fecal material administered via gastroscope in the distal duodenum. The patient remained hospitalized during the entire 48 days and ultimately succumbed to his pneumonia [124]. The conclusion of the third study was that administration of upper GI FMT should only be performed in awake patients; based on our findings, this may be an appropriate way to reduce procedural related mortality to FMT, but clinical context should always be taken into account when deciding whether sedation is warranted.

Our study has several limitations. Firstly, the search was limited by our terms and criteria and only included studies until August 2019. Differences between studies in duration of follow up, patient characteristics and methodology have the potential to confound the results. Follow-up duration is likely insufficient to detect long-term AE and the number of patients is insufficient to detect very rare AE. As with any meta-analysis there is a risk of publication bias. We cannot exclude its presence based on our analysis (see funnel plots). Our regression analysis was also limited by the small number of studies (particularly in the case of SAE) and by not being able to include all possible risk factors (for example fresh vs. frozen stool preparation). Most importantly, our study is limited by the inherent methodological difficulties of AE reporting in RCTs [125,126] and the inconsistencies in AE reporting among authors. This could indicate some underlying reporting/misclassification bias. We were limited to using rates of AE and SAE as defined by authors. Few authors adopted standardized guidelines for determining the seriousness,

expectedness and relatedness of AE. This probably led to the significant heterogeneity in the total rates of AE.

In conclusion, FMT appears to be a safe treatment modality. Most AE are mild and occur in the short term. There is wide variability in reporting methodology, even among high-quality studies. The rate of SAE is estimated at 5.3% and mortality is low. Upper GI and capsule delivery were associated with lower rates of total AE, but only capsule delivery was associated with lower SAE. Determining the relation of AE to the procedure is challenging, and authors should consider using standardized criteria. Longitudinal studies will be needed to determine the long-term risks.

Summary Box

What is already known:

- Fecal microbiota transplantation (FMT) is an established treatment modality for recurrent Clostridium difficile infection and has shown promise in multiple disease states
- There are safety concerns in FMT, primarily with regards to long-term risk

What the new findings are:

- FMT appears to be safe in the short to mid-term with a pooled serious adverse event rate of 5.4% based on high quality data
- Lower gastrointestinal tract delivery of FMT is correlated with a lower total adverse event rate

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