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Adverse events in fecal microbiota transplantation: a systematic review and meta-analysis

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Abstract

Background Fecal microbiota transplantation (FMT) is a highly efficacious procedure used most commonly for the treatment of recurrent Clostridioides difficile infection (CDI). Despite the high value of incorporating FMT into practice, there remain concerns about its safety. To the best of our knowledge, there has not been an updated meta-analysis reporting pooled rates of adverse events in FMT for CDI.

Methods A search for studies of FMT in patients with CDI was performed with the rate of serious adverse events (SAEs) related to FMT evaluated as the primary outcome. Secondary outcomes included SAEs unrelated to FMT and minor adverse events associated with FMT. A pooled analysis was then performed.

Results Initial search identified 378 reference articles. Data were extracted from the 61 of these studies that met the inclusion criteria, comprising 5099 patients. Pooled analysis showed that SAEs related to FMT developed in less than 1% of patients. The pooled rate of SAEs not related to FMT was higher at 2.9%. The pooled rate of minor adverse events also showed infrequent self-limited gastrointestinal and systemic discomfort.

Conclusions This meta-analysis supports FMT as a safe option for treating recurrent CDI. Future randomized trials are needed to improve our current understanding of FMT safety and further examine the improvements in the quality of life of patients treated with FMT compared to standard therapy of antibiotics.

Keywords Fecal microbiota transplantation, *Clostridioides difficile*, adverse events

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Introduction

Clostridioides difficile infection (CDI) has emerged as a significant cause of human morbidity and mortality [1]. It is now estimated that CDI has an incidence up to 32.6 per 100,000 person-years, with a direct care cost of $4.8 billion per year in the USA alone [2]. This gram-positive, spore-forming anaerobe is the most common cause of pseudomembranous colitis—a condition characterized by intractable diarrhea with the formation of intestinal pseudomembranes of cellular material in the colon [3]. As a result of these physical characteristics, as well as the development of multidrug resistance, the challenge of effectively treating CDI continues to grow [1].

Given the prevalence and increasing antibiotic resistance of CDI, fecal microbiota transplantation (FMT) is emerging as an exciting alternative to antibiotic therapies in preventing recurrent and complicated CDI. Since its initial implementation, the frequency of use has grown significantly. Current guidelines recommend FMT for patients with multiple recurrences of antibiotic-treated CDI [4]. Accurate study of FMT is challenging, given the heterogeneity of administration protocols. One issue that arises is the variation in stool preparation—studies have described usage of both fresh and frozen stool, various sources of stool (family, pooled, or standardized preparation), and inconsistent donor and stool screening protocols [5,6]. An additional challenge has been the quality of these studies; many of the randomized controlled trials that have compared FMT

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to antibiotic therapy have limited follow up as well as antibiotic protocols not within the standard of care [5]. Regardless, FMT has been shown to be of comparable efficacy to standard medical management [7,8]. Evidence regarding its efficacy with various routes of administration shows inconsistent results, but has widely demonstrated significant efficacy [8,9].

These data speak to the exciting role FMT is coming to play in the treatment of CDI. However, many continue to have concerns about the procedure's safety [5,6,10-14]. Recent studies have shown that many patients are unsure of whether they would accept FMT as a treatment option [15,16]. A major concern expressed by many patients is consequences arising from insufficient donor screening for infectious agents [16]. Some physicians also echo this fear, with many citing the need for further research on the topic, even voicing concerns of harms outweighing benefits [17,18]. With the increasing utilization of antibiotics and chemotherapeutic agents, the incidence of CDI will continue to rise. It is crucial to understand the risks of FMT so that patients may be counseled appropriately before undergoing the procedure. Moreover, awareness of FMT-related complications may drive the development of improved treatment modalities and protocols. There has not, to our knowledge, been a meta-analysis defining the pooled rates of major and minor adverse events for CDI in the general population. This information is vital for ensuring patients and providers are able to make informed decisions regarding their treatment.

Materials and methods

Search methodology

A literature search was conducted using the electronic database engines MEDLINE through PubMed, Ovid, Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) and EMBASE, from January 1st 2015 to January 1st 2021, to identify published articles and reports addressing the use of FMT in patients with CDI. The combinations of keywords used were ("Enterocolitis, Pseudomembranous"[Mesh] OR "CDI") AND ("Fecal Microbiota Transplantation"[Mesh] OR "FMT"). The reference list of all eligible studies was reviewed to identify additional studies. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Titles and abstracts selected from the initial search were scanned, and the full papers of potentially eligible studies were reviewed.

Study eligibility

Published studies were eligible for inclusion if they reported the use of FMT for the management of CDI. Articles were excluded if they were not written in English or did not have English translations, if they included a pediatric population or studied FMT for non-CDI indications, or if no outcomes were reported. In studies using multiple modalities for the management of CDI, data from the cohort of patients who underwent FMT were collected and analyzed. Two reviewers (ER, MB) independently performed study selection according to eligibility criteria. Disagreements were resolved by discussion or a third reviewer. The agreement between reviewers for the collected data gave a Cohen κ value of 1.0.

Data extraction

The following data were independently abstracted onto a standardized form: study characteristics (primary author, time period of study, year of publication, and country of the population studied), study design, baseline characteristics of the study population (the numbers of patients enrolled, participant demographics, route of FMT), the intervention details and outcomes (adverse events). Risk of bias was rated for each study by 2 authors independently, using the Cochrane criteria for randomized controlled trials [19].

Outcome definition

The primary outcome of interest was the rate of serious adverse events (SAEs) (NCI Common Terminology Criteria for Adverse Events grade 3-5) related to FMT. The rate of SAEs determined to be unrelated to FMT, minor adverse events (grades 1-2) and the rate of specific SAEs were evaluated as a secondary outcome.

Statistical analysis

This meta-analysis was performed by calculating pooled proportions. First, the individual study proportions were transformed into a quantity using the Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird weights for the random effects model [20]. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forest plots indicates the weight assigned to that study. The heterogeneity among studies was tested using the I^2 statistic and Cochran Q test based upon inverse variance weights [20]. I^2 values of 0-39% were considered as nonsignificant heterogeneity, 40-75% as moderate heterogeneity, and 76-100% as considerable heterogeneity. If the P-value is >0.10, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested using the Harbord-Egger bias indicator [21].

Results

A total of 378 studies were found using the above search criteria. After removing duplicated studies, studies that did

not describe adverse events, studies that focused primarily on pediatric populations, and studies for non-CDI indications, 61 remained (Table 1) [22-82]. A Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram for the

Table 1 Characteristics of studies reviewed

Study [ref.]	Study design	Number of patients	Average patient age	Percent female	Percent immuno suppressed	Percent with active inflammatory bowel disease	Number of transplants	Number of transplants via upper GI route	Number of transplants via lower GI route
Ianiro *et al* 2018 [22]	Randomized Controlled Trial	56	74.5	70	0	0	84	0	84
Hvas *et al* 2019 [23]	Randomized Controlled Trial	24	68	83	17	21	24	5	19
Jiang *et al* 2018 [24]	Randomized Controlled Trial	65	65	71	NR	NR	65	31	34
Kao *et al* 2017 [25]	Randomized Controlled Trial	116	58	68	15	5	116	57	59
Hota *et al* 2017 [26]	Randomized Controlled Trial	16	78	69	0	0	16	0	16
Friedman-Korn *et al* 2018 [27]	Randomized Controlled Trial	11	78	45	0	0	11	7	4
Camacho-Ortiz *et al* 2017 [28]	Randomized Controlled Trial	7	40	43	29	0	10	9	1
Jiang *et al* 2017 [29]	Randomized Controlled Trial	72	67	72	NR	NR	72	0	72
Webb *et al* 2016 [30]	Case Series	7	43	43	100	0	8	1	7
Lee *et al* 2016 [31]	Randomized Controlled Trial	219	73	67	11	3	350	0	219
Orenstein *et al* 2015 [32]	Case Series	31	66.8	74	0	0	46	0	46
Lagier *et al* 2015 [33]	Case Series	19	84	NR	0	0	33	NR	NR
Cammarota *et al* 2015 [34]	Randomized Controlled Trial	20	71	60	0	0	29	0	29
Kelly *et al* 2016 [35]	Randomized Controlled Trial	46	51	80	0	0	56	0	56
Staley *et al* 2017 [36]	Prospective Cohort Study	49	62	88	0	0	49	49	0
Quera *et al* 2018 [37]	Case Series	8	50	75	0	13	8	7	1
Ponte *et al* 2018 [38]	Case Series	28	79	64	0	0	34	24	4
Girotra *et al* 2016 [39]	Case Series	29	80	79	NR	NR	35	35	35
Alghamdi *et al* 2019 [40]	Case Series	29	65	83	3	10	31	9	20
Allegretti *et al* 2019 [41]	Case Series	37	37.6	57	NR	NR	40	NR	NR

(Contd...)

Table 1 *(Continued)*

Study [ref.]	Study design	Number of patients	Average patient age	Percent female	Percent immuno suppressed	Percent with active inflammatory bowel disease	Number of transplants	Number of transplants via upper GI route	Number of transplants via lower GI route
Abdallah *et al* 2019 [42]	Retrospective Cohort Study	59	57	73	22	19	61	0	59
Bobilev *et al* 2019 [43]	Randomized Controlled Trial	25	NR	NR	0	0	25	25	0
Cheng *et al* 2019 [44]	Case Series	69	61.9	52	32	19	80	65	4
Gjini *et al* 2019 [45]	Retrospective Cohort Study	139	61.5	53	NR	NR	139	45	94
Loudin *et al* 2019 [46]	Retrospective Cohort Study	30	63.3	77	23	7	30	30	0
Khanna *et al* 2019 [47]	Randomized Controlled Trial	30	NR	NR	NR	NR	30	40	0
Tirumanisetty *et al* 2019 [48]	Retrospective Cohort Study	30	66	63	NR	NR	30	0	30
Hassoun *et al* 2018 [49]	Prospective Cohort Study	35	77	60	NR	NR	36	13	23
Shin *et al* 2018 [50]	Case Series	27	NR	NR	NR	NR	27	NR	NR
Cheng *et al* 2018 [51]	Retrospective Cohort Study	94	56.3	50	100	17	131	NR	107
Stein *et al* 2018 [52]	Prospective Single Arm Trial	8	69	50	0	0	9	9	0
Juul *et al* 2018 [53]	Randomized Controlled Trial Multicenter	9	NR	NR	NR	NR	9	NR	NR
Allegretti *et al* 2018 [54]	Retrospective Cohort Study	47	61	66	NR	NR	47	47	0
Tabbaa *et al* 2018 [55]	Case series	77	NR	NR	NR	NR	80	NR	NR
Ng *et al* 2017 [56]	Randomized Controlled Trial	15	NR	NR	NR	NR	15	15	0
Tseng *et al* 2017 [57]	Retrospective Cohort Study	234	62	NR	NR	NR	234	0	234
Mosby *et al* 2017 [58]	Prospective Cohort trial	41	65	NR	NR	NR	41	4	37
Mamo *et al* 2017 [59]	Case Series	137	NR	NR	NR	NR	137	NR	NR
Dupont *et al* 2017 [60]	Randomized Controlled Trial	54	71	69	NR	NR	71	71	0
Ulmer *et al* 2017 [61]	Prospective Cohort Study	46	56	67	NR	NR	46	NR	NR
Mitchell *et al* 2017 [62]	Retrospective Cohort Study	20	NR	NR	NR	NR	20	10	10
Habib *et al* 2017 [63]	Retrospective Cohort Study	37	63	NR	11	0	52	3	49

(Contd...)

Table 1 *(Continued)*

Study [ref.]	Study design	Number of patients	Average patient age	Percent female	Percent immuno suppressed	Percent with active inflammatory bowel disease	Number of transplants	Number of transplants via upper GI route	Number of transplants via lower GI route
Fischer *et al* 2017 [64]	Retrospective Cohort Study	47	NR	NR	100	0	64	0	64
El-Nachef *et al* 2017 [65]	Case Series	11	NR	NR	NR	NR	11	11	0
Cicerone *et al* 2017 [66]	Prospective Cohort Study	8	69	NR	NR	NR	11	0	11
hefazi *et al* 2016 [67]	Case Series	16	74	50	100	0	18	0	18
Rezk *et al* 2016 [68]	Retrospective Cohort Study	52	54	69	0	0	56	0	56
Le *et al* 2016 [69]	Case Series	5	NR	NR	100	0	10	NR	NR
Ianiro *et al* 2016 [70]	Prospective Cohort Study	10	73	70	NR	NR	30	0	30
Curry *et al* 2016 [71]	Case Series	19	68	58	21	0	19	12	7
Pennell *et al* 2016 [72]	Retrospective Case Series	22	NR	NR	NR	NR	26	NR	NR
Zeitler *et al* 2016 [73]	Retrospective Cohort Study	13	69	NR	54	0	15	15	0
Osman *et al* 2016 [74]	Retrospective Cohort Study	2050	NR	NR	NR	NR	2050	728	1322
Van Beurden *et al* 2016 [75]	Prospective Cohort Study	59	NR	NR	NR	NR	62	62	0
Ramsauer *et al* 2016 [76]	Retrospective Cohort Study	16	76.2	63	NR	NR	21	NR	NR
Greenberg *et al* 2018 [77]	Retrospective Cohort Study	111	70	58	17	18	115	61	50
Fischer *et al* 2016 [78]	Retrospective Cohort Study	67	45	58	64	100	76	0	67
Agrawal *et al* 2016 [79]	Retrospective Cohort Study	146	78.6	68	3	10	160	NR	NR
Peri *et al* 2019 [80]	Retrospective Cohort Study	256	75	61	26	0	298	154	107
Aroniadis *et al* 2016 [81]	Retrospective Cohort Study	17	66	76	NR	NR	20	1	16
Cohen *et al* 2016 [82]	Retrospective Cohort Study	22	72	41	9	5	22	10	12

GI, gastrointestinal; NR, not reported

review process is shown in Fig. 1 [83]. Of these 61 studies, 16 were randomized control trials. Pooled estimates were calculated by the fixed effect model for better accuracy, based on the nature of individual study characteristics and heterogeneity. Data were collected for a total of 5099 patients receiving 5551 FMTs. An upper gastrointestinal route was specified in 30% of cases of FMTs and a lower gastrointestinal route in 56%. In the overall population of patients, 4.8% of recipients had inflammatory bowel disease and 8.0% were immunosuppressed.

Primary outcome

In pooled analysis, the overall rate of SAEs related to FMT was 0.65% (95%CI 0.45-0.89; P<0.001). A forest plot diagram of this pooled analysis is shown in Fig. 2. Publication bias calculated using the Harbord-Egger bias indicator gave a value of 1.10 (95%CI 0.26-1.94; P=0.02), indicating no publication bias. Fig. 3 is a funnel plot assessing the publication bias for the same variable.

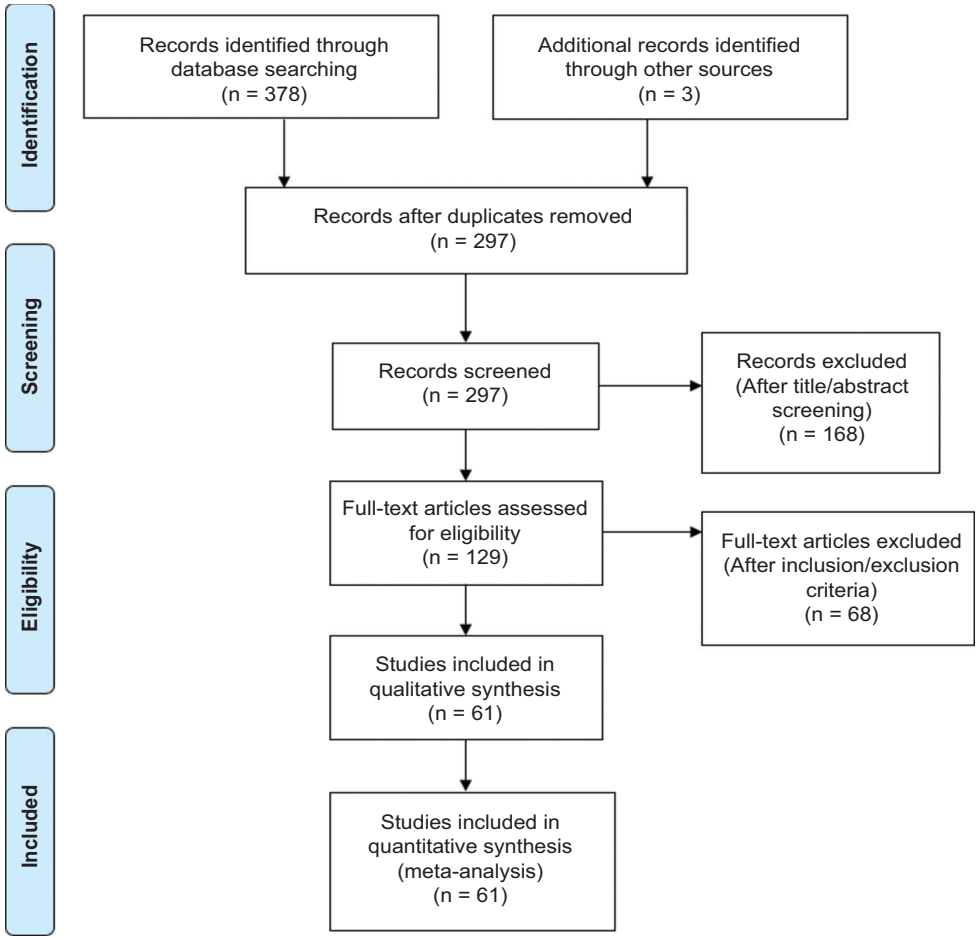

Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram detailing the review process

Secondary outcomes

Rate of individual SAEs

Sepsis or sepsis-like conditions were reported in 0.19% (95%CI 0.09-0.31), aspiration pneumonia in 0.27% (95%CI 0.15-0.43), and bowel perforation was noted after 0.20% (95%CI 0.09-0.34) of FMTs. The pooled rate of SAEs not related to FMT was 2.91% (95%CI 2.47-3.39).

Rate of minor adverse events

Among minor adverse events, constipation was reported in 1.03% (95%CI 0.77-1.33), abdominal pain in 1.66% (95%CI 1.33-2.03), nausea in 0.92% (95%CI 0.67-1.20), vomiting in 0.34% (95%CI 0.20-0.52), flatulence in 0.70% (95%CI 0.49-0.94), and febrile episodes were noted after 0.33% (95%CI 0.19-0.50) of FMTs.

Discussion

FMT is rapidly gaining acceptance as a treatment for CDI. In an episode of CDI, major dysbiosis is commonly seen, with suppression of native *Bacteroidetes* and *Firmicutes* species and an increase in *Proteobacteria* [84]. FMT has been shown to restore this balance, with evidence that the composition of an FMT recipient's microbiome retains similarity to the donor's for months to years [85]. With the complexity of the microbiota being transplanted, several mechanisms have been observed. The first consists of direct competition of the transplanted microorganisms—through both resource competition and production of antimicrobial peptides [85]. Additionally, FMT restores a normal balance of bile acid metabolization in the gut, a process demonstrated to affect cellular signaling and spore germination [84,85]. Finally, it has been suggested that the protection FMT offers the mucosal barrier of the colon plays a role in favorably altering the immune system's response to CDI [85].

A wealth of randomized clinical trials supports the effectiveness of FMT for recurrent CDI. This progress is vital, given the heavy disease burden CDI carries and the major risks associated with uncontrolled CDI [4,7,8]. Antimicrobial success rate in recurrent CDI is low, only about 35%, and surgery has very poor outcomes, with mortality up to 50% [86,87]. FMT involves the infusion of stool from a healthy donor to an infected patient with the goal of restoring a healthy microbiome, and exists as an exciting alternate approach for treatment that utilizes a novel and exciting mechanism [85]. However, there is still hesitancy regarding

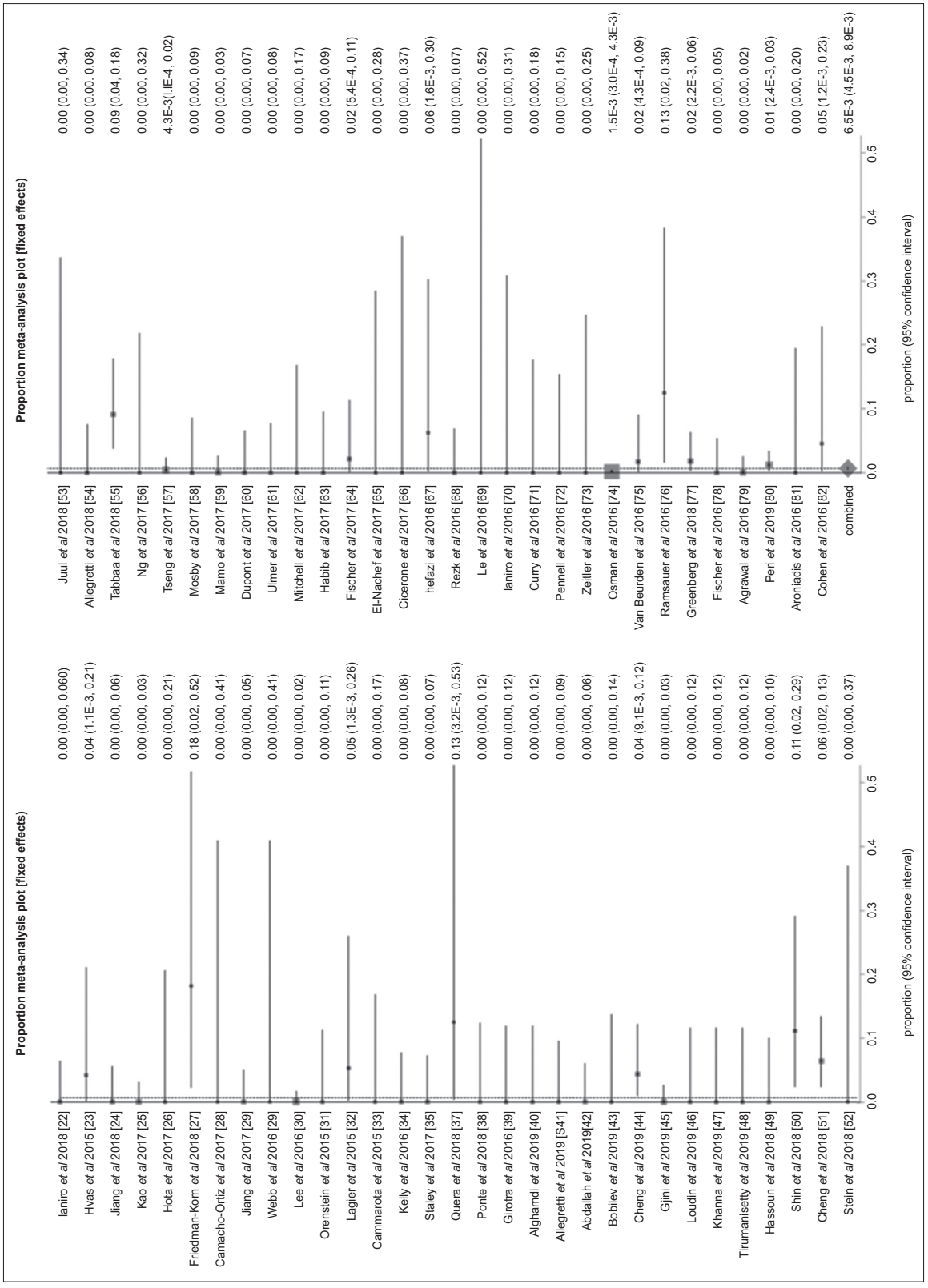

Figure 2 Forest plot. Individual study proportions and the pooled estimate of the rate of serious adverse events related to fecal microbiota transplantation (random effect)

Table 2 Outcomes of reviewed studies

Study [ref.]	Number of patients	Number of transplants	Related serious adverse events (per transplant)	Related serious adverse events (per person)	Specific serious adverse event	Minor adverse events (per person)
Ianiro *et al* 2018 [22]	56	84	0	0		1.393
Hvas *et al* 2019 [23]	24	24	0.083	0.083	Sepsis, bacterial overgrowth	1.042
Jiang *et al* 2018 [24]	65	65	0	0		3.615
Kao *et al* 2017 [25]	116	116	0	0		0.112
Hota *et al* 2017 [26]	16	16	0	0		5.750
Friedman-Korn *et al* 2018 [27]	11	11	0.182	0.182	Aspiration leading to death; propofol toxicity leading to pneumonia	0.000
Camacho-Ortiz *et al* 2017 [28]	7	10	0	0		0.000
Jiang *et al* 2017 [29]	72	72	0	0		2.778
Webb *et al* 2016 [30]	7	8	0	0		0.857
Lee *et al* 2016 [31]	219	350	0	0		2.078
Orenstein *et al* 2015 [32]	31	46	0	0		6.065
Lagier *et al* 2015 [33]	19	33	0.03	0.053	Acute cardiac insufficiency	1.316
Cammarota *et al* 2015 [34]	20	29	0	0		2.150
Kelly *et al* 2016 [35]	46	56	0	0		0.022
Staley *et al* 2017 [36]	49	49	0	0		0.265
Quera *et al* 2018 [37]	8	8	0.125	0.125	Bacteremia in a patient with Crohn's	0.250
Ponte *et al* 2018 [38]	28	34	0	0		0.000
Girotra *et al* 2016 [39]	29	35	0	0		0.172
Alghamdi *et al* 2019 [40]	29	31	0	0		0.000
Allegretti *et al* 2019 [41]	37	40	0	0		NR
Abdallah *et al* 2019 [42]	59	61	0	0		NR
Bobilev *et al* 2019 [43]	25	25	0	0		0.520

(Contd...)

Table 2 *(Continued)*

Study [ref.]	Number of patients	Number of transplants	Related serious adverse events (per transplant)	Related serious adverse events (per person)	Specific serious adverse event	Minor adverse events (per person)
Cheng *et al* 2019 [44]	69	80	0.038	0.043	Not specified	0.319
Gjini *et al* 2019 [45]	139	139	0	0		0.137
Loudin *et al* 2019 [46]	30	30	0	0		0.867
Khanna *et al* 2019 [47]	30	30	0	0		NR
Tirumanisetty *et al* 2019 [48]	30	30	0	0		0.067
Hassoun *et al* 2018 [49]	35	36	0	0		NR
Shin *et al* 2018 [50]	27	27	0.111	0.111	Aspiration	0.111
Cheng *et al* 2018 [51]	94	131	0.046	0.064	Diarrhea ×3; Crohn's flare	0.191
Stein *et al* 2018 [52]	8	9	0	0		0.750
Juul *et al* 2018 [53]	9	9	0	0		NR
Allegretti *et al* 2018 [54]	47	47	0	0		NR
Tabbaa *et al* 2018 [55]	77	80	0.088	0.091	Colectomy secondary to toxic megacolon ×1; Inflammatory bowel flares ×6	0.649
Ng *et al* 2017 [56]	15	15	0	0		NR
Tseng *et al* 2017 [57]	234	234	0.004	0.004	Colonic perforation	NR
Mosby *et al* 2017 [58]	41	41	0	0		0.488
Mamo *et al* 2017 [59]	137	137	0	0		NR
Dupont *et al* 2017 [60]	54	71	0	0		0.000
Ulmer *et al* 2017 [61]	46	46	0	0		0.022
Mitchell *et al* 2017 [62]	20	20	0	0		1.200
Habib *et al* 2017 [63]	37	52	0	0		0.000
Fischer *et al* 2017 [64]	47	64	0.016	0.021	Aspiration	NR

(Contd...)

Table 2 *(Continued)*

Study [ref.]	Number of patients	Number of transplants	Related serious adverse events (per transplant)	Related serious adverse events (per person)	Specific serious adverse event	Minor adverse events (per person)
El-Nachef *et al* 2017 [65]	11	11	0	0		NR
Cicerone *et al* 2017 [66]	8	11	0	0		NR
hefazi *et al* 2016 [67]	16	18	0.056	0.063	Pneumonia 15 days post-FMT	0.375
Rezk *et al* 2016 [68]	52	56	0	0		0.135
Le *et al* 2016 [69]	5	10	0	0		NR
Ianiro *et al* 2016 [70]	10	30	0	0		NR
Curry *et al* 2016 [71]	19	19	0	0		0.474
Pennell *et al* 2016 [72]	22	26	0	0		NR
Zeitler *et al* 2016 [73]	13	15	0	0		NR
Osman *et al* 2016 [74]	2050	2050	0.001	0.001	Not specified	NR
Van Beurden *et al* 2016 [75]	59	62	0.016	0.017	Pneumonia leading to death	NR
Ramsauer *et al* 2016 [76]	16	21	0.095	0.125	Small bowel perforation; bacteremia	0.125
Greenberg *et al* 2018 [77]	111	115	0.017	0.018	Aspiration leading to death ×1; aspiration leading to ICU admission ×1	0.153
Fischer *et al* 2016 [78]	67	76	0	0		NR
Agrawal *et al* 2016 [79]	146	160	0	0		NR
Peri *et al* 2019 [80]	256	298	0.01	0.012	Aspiration ×2; Hemorrhage ×1	0.074
Aroniadis *et al* 2016 [81]	17	20	0	0		0.412
Cohen *et al* 2016 [82]	22	22	0.045	0.045	Aspiration	NR

NR, not reported; FMT, fecal microbiota transplantation; ICU, intensive care unit

the implementation of FMT in the standard of care [15-18]. Our analysis seeks to further explore the safety of FMT, to ensure patients and physicians have an optimal data-driven approach to considering FMT.

To our knowledge, this is the largest published systematic review with a meta-analysis of adverse events for FMT in CDI, and it offers several advantages compared to the previously published literature. This meta-analysis establishes that FMT is safe when used for CDI, with significant adverse events noted in less than 1% of the patients. This knowledge is invaluable in aiding decision making for patients and physicians and supports FMT as an excellent alternative option to standard therapy with antibiotics—especially for recurrent CDI. The majority of the significant adverse events noted in our review were unrelated

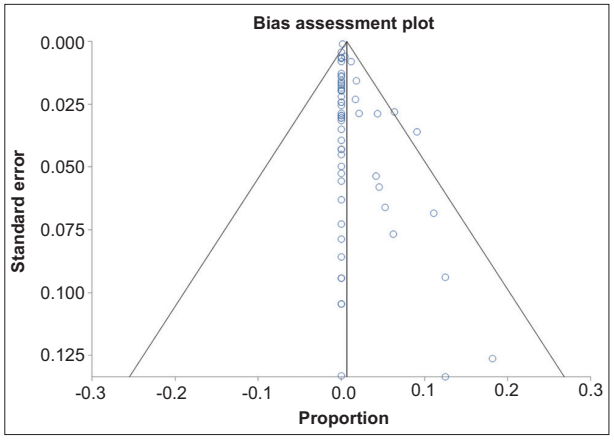

Figure 3 Bias assessment plot of publication bias in reporting serious adverse events in fecal microbiota transplantation

to the FMT itself, which is unsurprising given that FMT is often administered in patients with severe, treatment-refractory CDI with multiple baseline medical comorbidities. Additionally, a relatively high percentage of the included patients were immunosuppressed, which could account for exaggeration of negative sequelae. Finally, minor adverse events, including nausea, vomiting, abdominal pain and constipation, were also noted very rarely, with an individual pooled rate of less than 2%, lower than previously reported [10,14].

The primary challenge faced by our review was the determination of SAE causality. The process for determining whether or not to attribute an adverse event to FMT was based on each study's own standards. An area that highlights this difficulty is the unclear causality of inflammatory bowel disease flares and FMT. While some studies listed this as a sequela of FMT, others ruled it to be unrelated. An additional challenge was the mild inconsistency in several of the measured outcomes. This can probably be attributed to the heterogeneous patient populations and study protocols. Similarly, the average duration of follow up varied widely, as did symptom reporting. Missing data on demographics, method of stool transplantation, volume and amount of stool, and relationships of donor and recipients were also common [6].

This study, despite its limitations, demonstrated that FMT is a largely safe procedure. As the understanding of the effects of the fecal microbiome expands, causal relationships with new adverse events and long-term sequelae of FMT may continue to be discovered. Nevertheless, our current knowledge of both related and unrelated SAEs indicates that FMT should be a therapy strongly considered for patients with recurrent CDI.

This meta-analysis supports FMT as a safe option for treating recurrent CDI. While the short-term safety of fecal microbiota transplantation for treating recurrent CDI is promising from our meta-analysis, the potential long-term consequences of altering a patient's gut microbiota are not fully known. Future randomized trials are needed to improve our current understanding of FMT safety and further clarify the improvements in the quality of life of patients treated with FMT compared to standard antibiotic therapy.

Summary Box

What is already known:

- Fecal microbiota transplantation (FMT) is a highly efficacious procedure used in the treatment of recurrent *Clostridioides difficile* infection
- A residual concern in the integration of FMT is concerns about the safety of the procedure
- Published studies have struggled with heterogeneous protocols that display various durations of follow up

What the new findings are:

- Our analysis shows a very low pooled rate of significant adverse events related to FMT, in total less than 1%, despite a significant portion of patients being immunocompromised or having underlying gastrointestinal conditions
- The pooled rate of minor adverse events was also relatively rare, and were most commonly diarrhea, constipation, abdominal pain, nausea and vomiting
- Further high-quality randomized control trials are necessary to evaluate the longer-term safety of FMT and its impact on quality of life

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