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Fecal microbiota transplantation for recurrent *C. difficile* infection in patients with inflammatory bowel disease: A systematic review and meta-analysis

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ABSTRACT

Fecal microbiota transplantation (FMT) is known to be highly effective in patients with recurrent *Clostridioides difficile* infection (rCDI), but its role in patients who also suffer from inflammatory bowel disease (IBD) is unclear. Therefore, we performed a systematic review and meta-analysis to evaluate the efficacy and safety of FMT for the treatment of rCDI in patients with IBD.

We searched the available literature until November 22, 2022 to identify studies that included patients with IBD treated with FMT for rCDI, reporting efficacy outcomes after at least 8 weeks of follow-up. The proportional effect of FMT was summarized with a generalized linear mixed-effect model fitting a logistic regression accounting for different intercepts among studies.

We identified 15 eligible studies, containing 777 patients. Overall, FMT achieved high cure rates of rCDI, 81% for single FMT, based on all included studies and patients, and 92% for overall FMT, based on nine studies with 354 patients, respectively. We found a significant advantage of overall FMT over single FMT in improving cure rates of rCDI (from 80% to 92%, $p = 0.0015$). Serious adverse events were observed in 91 patients (12% of the overall population), with the most common being hospitalisation, IBD-related surgery, or IBD flare.

In conclusion, in our meta-analysis FMT achieved high cure rates of rCDI in patients with IBD, with a significant advantage of overall FMT over single FMT, similar to data observed in patients without IBD. Our findings support the use of FMT as a treatment for rCDI in patients with IBD.

1. Introduction

Clostridioides difficile infection (CDI) is the most common healthcare-associated infectious disease, and its incidence, recurrence, severity, and mortality has increased dramatically in recent years [1]. Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract that includes Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBD-U) [2]. Generally, IBD is associated with a higher prevalence of CDI [3,4] and, more notably, a remarkable increase of CDI incidence has been observed in patients with IBD in the last 20 years [5,6].

Cure of CDI in patients with IBD is challenging because these individuals are less likely to respond to medical therapies [7,8], and the risk of CDI recurrence after antibiotic therapy is higher in this patient group than in the general population [9,10]. Consequently, patients with IBD are also at increased likelihood for CDI-related hospitalizations, longer hospital stays, escalation of IBD therapy, colectomy, death, and higher healthcare costs [11].

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Fecal microbiota transplantation (FMT) is an established therapy for curing recurrent CDI (rCDI) [12], and preventing its complications [13], and international guidelines now recommend FMT for this condition [14–16]. Increasing evidence suggests that FMT is safe and effective in patients with IBD and rCDI, and single cohort studies without comparators have shown that it improves disease activity indices and reduces the need for escalation of IBD therapy [17–21]. Moreover, preliminary findings suggest that overall FMT may be more effective in IBD than single infusions [21], as has already been shown in severe CDI in the general population [12,13]. However, current data come mostly from single cohorts, meaning an overall estimate of the benefit of FMT in this patient group is lacking. We, therefore, performed a systematic review and meta-analysis of available evidence to evaluate the efficacy and safety of FMT for the treatment of rCDI in patients with IBD.

2. Methods

This systematic review and meta-analysis was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Table 1) [22]. Ethics committee approval was not needed for the study.

2.1. Eligibility criteria

We considered eligible all original reports with the following characteristics: (a) inclusion of human subjects of any age with IBD treated with FMT for recurrent or refractory CDI; (b) reported efficacy outcomes after FMT, after at least 8 weeks of follow-up, as current guidelines recommend a follow-up of at least 8 weeks after therapy (including FMT) to assess for evidence of recurrence [14–16]. If studies did not report efficacy outcomes but were otherwise eligible to be included in the systematic review, we contacted authors to obtain efficacy data from them. We excluded animal studies, studies investigating microbiota modulators other than FMT (e.g., synthetic microbiota suspensions or probiotics), those including subjects with pouchitis, or studies of patients who received FMT for IBD without rCDI. We did not include papers published in other languages than English, conference abstracts, case reports and case series with less than 10 participants.

2.2. Information sources, search strategy and study selection

We searched PubMed Central/MEDLINE, SCOPUS, and Web of Science (ISI) for records up to November 22, 2022, using the following search: ((*Clostridium difficile*) OR (Clostridioides difficile) OR (*C. difficile*) OR (*Clostridium difficile* infection) OR (pseudomembranous colitis) OR (CDI)) AND ((Inflammatory bowel disease) OR (Crohn's disease) OR (ulcerative colitis) OR (IBD) OR (CD) OR (UC)) AND ((Faecal microbiota transplantation) OR (Fecal microbiota transplantation) OR (Faecal microbiota transplant) OR (Fecal microbiota transfer) OR (Faecal microbiota transfer) OR (Fecal microbiota transfusion) OR (Faecal microbiota infusion) OR (Fecal microbiota infusion) OR (faecal transplant) OR (fecal transplant) OR (faecal suspension) OR (fecal suspension) OR (faecal transplantation) OR (fecal transplantation) OR (faecal donation) OR (fecal donation) OR (faecal transfer) OR (fecal transfer) OR (faecal infusion) OR (fecal infusion) OR (bacteriotherapy) OR (FMT)). Moreover, we hand searched reference lists of potentially eligible articles.

Two investigators (GI and SP) reviewed and assessed titles and abstracts of retrieved studies independently. Studies that fulfilled the eligibility criteria were evaluated for analysis. In the case of any discrepancies, full texts of articles were reviewed, and any disagreements were resolved by the arbitration of a third reviewer (GC).

2.3. Assessment of outcomes

Our primary outcome was cure of rCDI at 8-week follow-up, defined

Table 1
PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7,8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8–9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9,10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative	10

(*continued on next page*)

Table 1 (*continued*)

Section/topic	#	Checklist item	Reported on page #
		evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11,33
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-13,38-40
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	34,35,42-44
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15,34,35
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16–18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	32

as either resolution of diarrhea (below three stools daily) or persistent diarrhea but with a negative CD test. Secondary outcomes included the clinical activity of underlying IBD after FMT and adverse events occurring after FMT.

2.4. Data extraction

Data were extracted independently by two reviewers (SP and GI) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA), and outcome data were crosschecked by a third reviewer (SMDB). Any disagreement was resolved by the opinion of a third investigator (GC). If different studies described the same cohort of patients, only the study including the most complete dataset was included. If cohorts mixed patients from former cohorts and newly included ones, only the latter were analyzed. The following data were extracted for each included study: study characteristics (year of publication, country of origin, study site, study design, primary outcome, secondary outcomes, length of follow-up); baseline characteristics of patients (population sample, sex, mean age, IBD type, extent of disease, severity of disease, clinical disease activity, endoscopic disease activity, number of prior CDI episodes, CDI severity, concomitant IBD therapy); FMT characteristics (antibiotic pre-treatment, use of related or universal donors, use of frozen or fresh feces, weight and volume of feces, route of delivery, number of fecal infusions); and clinical outcomes after FMT (CDI cure rates, clinical disease activity, endoscopic disease activity, IBD therapy, adverse events). If necessary, we sought further information from original investigators.

2.5. Quality assessment and risk of bias

The study quality assessment was evaluated with the Newcastle-Ottawa scale (NOS) for cohort studies [23]. The NOS score ranges from 0 (low) to 9 (high) and evaluates studies according to general domains and prespecified quality markers for comparability related to the topic as defined by the quality assessors. For FMT, the important comparability markers were whether the study reported processing method and dose (one point) and if the study reported the number of prior CDI episodes, demographics, adverse events, and severity of IBD.

2.6. Data synthesis and statistical analysis

We stratified the primary outcome according to the effect from a single FMT and following overall FMT. Overall FMT represents the cumulative sum of fecal infusions provided to the single patient. If studies evaluated the primary outcome at a follow-up longer than 8 weeks, results were combined with those coming from studies evaluating outcomes at 8-week follow-up.

For statistical analysis, we used the statistical software R version 3.6.1 with the metafor and meta packages [24]. For meta-analysis, we used a random effects model with maximum-likelihood tau^2 estimator and Z-based statistics for evaluation of statistical precision. Where applicable, we summarized the results in forest plots. The data were presented with 95% confidences intervals (CIs) according to Clopper Pearson. P-values below 0.05 were considered statistically significant.

The proportional effect of FMT was summarized with a generalized linear mixed-effect model (GLMM) fitting a logistic regression accounting for different intercept among studies, e.g., true variance in effect. All analysis was stratified according to single and overall FMT. Single and overall FMT were compared using one-proportion Z statistics, assuming no difference in gain of effect in the transformed effect from single to overall FMT. Only studies reporting both single and overall FMT data were included in the analysis of effect. For all stratified analysis, we provided prediction intervals estimating the anticipated effect ranges for future studies. To investigate whether extreme study outliers skewed the precision of the analysis too heavily, we performed leave-one-out and outlier analysis. An extreme study outlier was defined as a study whose CIs did not overlap with the 95% CIs of the overall estimate.

Study heterogeneity, reflecting variance other than statistical probability, was quantified with the I^2 statistic and graded according to the following definitions as: 0–24% being minimal heterogeneity, 25%–49% as low heterogeneity, 50%–74% as moderate heterogeneity, and $\geq$75% as high heterogeneity [25]. As the GLMM fitting of random effects in one analysis quantifies heterogeneity, confidence intervals were not applicable. The study heterogeneity influence was assessed secondary to the robustness testing with the leave-one-out and extreme outlier analysis.

The presence of publication bias was evaluated from visual inspections of funnel plots and tested for asymmetry with the Peter's test when eleven or more studies were included in the analysis. To guide the direction of potential publication bias, we used the Duval trim-and-fill procedure.

3. Results

3.1. Study selection and characteristics of included studies

Fig. 1 shows the flow diagram of study selection. Table 2 summarizes the characteristics of included studies and patients at baseline. The search strategy identified 1239 items after removal of duplicates. Sixty-three of these were retrieved as full texts. Fifteen studies, published between 2014 and 2022, including 777 patients overall, fulfilled eligibility criteria and were included in the final analysis. All were non-randomized cohort studies, of which six were prospective [19–21,26–28], and nine were retrospective [18,29–36]. All studies were carried out in the USA, apart one in Italy [21]. Six were multi-center studies [18,20,29–31,35], and the remaining nine were single-center studies [19,21,26–28,32–34,36].

3.2. Quality of included studies

Study quality of the included studies was moderate quality with a NOS score ranging from 5 to 9, with 9 being the highest (Table 3). The quality appraisal indicated the studies were of good generalizability.

3.3. Characteristics of cohorts and patients

Population samples ranged from 12 to 148 included subjects, with 777 patients included overall. Sex was detailed in all but two studies [29,30], with a total of 339 males and 344 females. Age of participants, reported in all but one study [30], ranged from 8 to 93 years old. IBD type was defined in all but one study [29]; there were 402 patients with UC and 312 with CD. Extent or location of disease, based on Montreal classification [37], was reported in only seven studies [18,20,21,28,31,33,35]. Among those with UC, 10 patients had proctitis (E1), 45 had left-sided colitis (E2), and 127 had pancolitis (E3), while in the CD cohort 48 patients presented with ileal disease alone (L1), 85 had colonic involvement alone (L2), and 79 had ileocolonic disease (L3). Only seven studies reported disease activity, with a total of 124 patients in remission and 357 patients with active disease [18,19,21,28,31,33,35]. When reported, 88 patients presented with mild disease, 20 patients with mild-to-moderate disease, 74 patients with moderate disease, and 46 patients with severe disease at the time of FMT [18,21,28,31,33]. Eleven studies reported quantitative data on concomitant IBD therapy at the time of FMT, with the most commonly prescribed drugs being biologics (N = 273), corticosteroids and immunosuppressants (N = 439), or aminosalicylates (N = 224) [18,19,21,28,29,31–36]. The number of CDI recurrences was available in all but three studies [26,33,34], and in

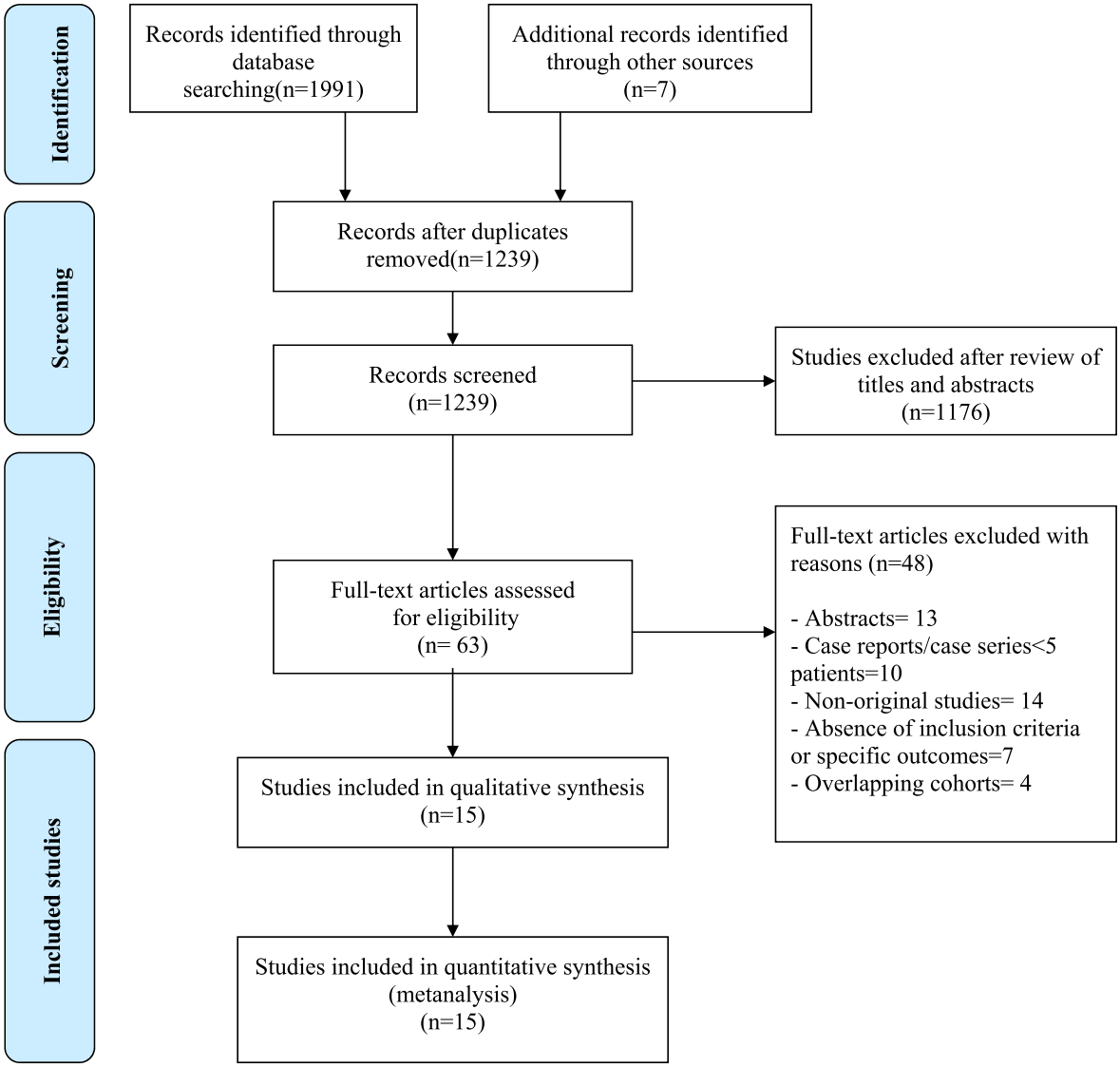

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the search process.

Table 2
Characteristics of included studies and patients.

STUDY CHARACTERISTICS							BASELINE CHARACTERISTICS OF PATIENTS								
Year	First author	Country	Study site	Design	Outcomes	Follow-up	Number (patients with IBD)	Sex	Age	IBD type	Extension of IBDN (%)	Severity of IBD N (%)	Concomitant IBD therapy	N° of prior CDI episodes	CDI severity
2014	Kelly [29]	USA	Multi-center	Retrospective	CDI cure and any SAEs or AEs within 12 weeks post FMT (primary outcomes). CDI recurrence, need for colectomy and response to overall FMT (secondary outcomes)	12 weeks	36	NA	Mean 53 years (20–88)	NA	NA	NA	Anti-TNF = 16 (44%); Alpha-4 integrin inibithors = 2 (6%); Immunosuppressants and steroids = 50 (50%)	At least 2	NA
2016	Khoruts [26]	USA	Single-center	Prospective	Recurrence of CDI, or FMT failure, at 8 weeks	8 weeks	43	F = 22 (51%) M = 21 (49%)	Median 32 years (16–84)	UC = 21 (49%) CD = 22 (51%)	NA	NA	NA	At least 2	NA
2016	Fischer [30]	USA	Multi-center	Retrospective	Early FMT failure (non-response or CDI recurrence within 4 weeks post FMT); late FMT failure (CDI recurrence 4–12 weeks post FMT)	4–12 weeks	63	NA	NA	UC = 25 (8%) CD = 33 (10%) IBD-U = 5 (8%)	NA	NA	NA	At least 2	NA
2016	Fischer [31]	USA	Multi-center	Retrospective	CDI recurrence at 12 weeks post FMT (primary outcome). IBD activity and severity at 12 weeks and FMT safety (secondary outcome).	12–156 weeks	67	F = 39 (58%) M = 28 (42%)	Mean 45 years (SD 17.33)	UC = 31 (46%) CD = 35 (52%) IBD-U = 1 (2%)	UC: E1 = 3 (10%); E2 = 5 (16%); E3 = 23 (74%) CD: L1 = 6 (17%); L2 = 19 (54%); L3 = 12 (29%)	Remission = 7 (10%); Mild = 29 (43%); Moderate = 16 (24%); Severe = 15 (23%)	5-ASA = 28 (42%) Biologics = 20 (29%) Prednisone = 21 (31%) Budesonide = 5 (7%) Immunosuppressants = 14 (21%) non-CDI antibiotics = 2 (3%)	At least 1	Mild = 67 (91%) Severe = 6 (9%)
2017	Chin [19]	USA	Single-center	Prospective	Rates of rCDI (at 8 weeks) and IBD treatment escalation	8 weeks	35	F = 16 (46%) M = 19 (54%)	Mean 43 years (8–93)	UC = 22 (63%); CD = 13 (37%)	NA	Remission = 22 (63%) Active = 13 (37%)	5-ASA = 16 (46%) Biologics = 11 (31%) Prednisone = 8 (23%) Immunosuppressants = 3 (9%)	At least 2	NA

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Table 2 (*continued*)

STUDY CHARACTERISTICS							BASELINE CHARACTERISTICS OF PATIENTS								
Year	First author	Country	Study site	Design	Outcomes	Follow-up	Number (patients with IBD)	Sex	Age	IBD type	Extension of IBDN (%)	Severity of IBD N (%)	Concomitant IBD therapy	N° of prior CDI episodes	CDI severity
2012	Hamilton [27]	USA	Single-center	Prospective	Negative testing for *C. difficile* toxin B for 8 weeks	8 weeks	14	F = 11 (79%) M = 3 (21%)	Mean 44.6 years (SD 5.8)	UC = 4 (28.5%) CD = 6 (43%) LymphocyticColitis = 4 (28.5%)	NA	NA	NA	At least 2	NA
2017	Khanna [28]	USA	Single-center	Prospective	Changes in gut microbial ecology in response to FMT	104 weeks	12	F = 8 (67%) M = 4 (33%)	Median 27.6 years (23.3–74.9)	UC = 6 (50%) CD = 6 (50%)	UC: E2 = 2 (33%) E3 = 4 (67%) CD: L2 = 6 (100%)	UC: Remission = 1 (16.6%) Mild = 1 (16.6%) Moderate = 1 (16.6%) Severe = 3 (50%) CD: Remission = 2 (33.3%) Mild = 0 Moderate = 2 (33.3%) Severe = 2 (33.3%)	5-ASA = 5 (59%) Biologics = 5 (50%) Corticosteroids = 6 (58%) Immunosuppressants = 4 (33%)	At least 3	NA
2017	Meighani [32]	USA	Single-center	Retrospective	Treatment response (resolution of diarrhea within 7 days)	12 weeks	20	F = 10 (50%) M = 10 (50%)	Mean 46.9 years (SD 19.97)	UC = 10 (50%) CD = 6 (30%) IBD-U = 4 (20%)	NA	NA	Immunosuppressants = 13 (65%)	At least 2	Mild = 15 (75%) Severe = 5 (25%)
2017	Newman [33]	USA	Single-center	Retrospective	Negative testing for *C. difficile* or diarrhea resolution at 8 weeks	8 weeks	56	F = 24 (44%) M = 32 (56%)	Mean 38.2 years (SD 16.9)	UC = 28 (50%) CD = 28 (50%)	UC: E2 = 10 (36%) E3 = 18 (64%) CD: L1 = 8 (29%) L2 = 8 (29%) L3 = 12 (43%)	UC: Remission = 0 Mild = 15 (54%) Moderate = 9 (32%) Severe = 4 (14%) CD: Remission = 2 (7%) Mild = 13 (46%) Moderate = 12 (43%) Severe = 1 (4%)	Corticosteroids, immunosuppressants, biologics = 29 (52%)	At least 1	NA

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Table 2 (*continued*)

STUDY CHARACTERISTICS							BASELINE CHARACTERISTICS OF PATIENTS								
Year	First author	Country	Study site	Design	Outcomes	Follow-up	Number (patients with IBD)	Sex	Age	IBD type	Extension of IBDN (%)	Severity of IBD N (%)	Concomitant IBD therapy	N° of prior CDI episodes	CDI severity
2018	Tabbaa [34]	USA	Single-center	Retrospective	Primary cure, defined as diarrhea-free and negative stool *C. difficile* testing results for ≥52 weeks; secondary cure, defined as resolution of CDI post FMT with either another course of antibiotics or overall FMT (primary outcomes). Efficacy of FMT in patients with CDI who has IBD vs. not (secondary outcome).	100 weeks	21	F = 9 (43%) M = 12 (57%)	Mean 47.6 years (SD 20.7)	UC = 13 (62%) CD = 8 (38%)	NA	NA	5-ASA = 16 (76%), Biologics = 8 (38%) Corticosteroids = 7 (33%) Immunosuppressants = 5 (24%)	At least 1	Mild = 21 (100%)
2020	Allegretti [20]	USA	Multi-center	Prospective	FMT failure through week 8, defined as diarrhea + positive *C. difficile* toxin (primary outcome) *C. difficile* colonization, defined as positive *C. difficile* toxin without diarrhea (secondary outcome).	12 weeks	50	F = 29 (58%) M = 21 (42%)	Mean 43 years (21–91)	UC = 35 (70%); CD = 15 (30%)	UC: E1 = 3 (9%) E2 = 9 (25%) E3 = 21 (60.0%) Unknown = 2 (6%) CD: L2 = 3 (20.0%) L3 = 10 (67%) Unknown = 2 (13%)	NA	NA	At least 2	NA
2020	Tariq [18]	USA	Multi-center	Retrospective	Resolution of symptoms	1–204 weeks	145	F = 75 (52%) M = 70 (48%)	Median 46 years (19–83)	UC = 89 (61%) CD = 53 (37%) IBD-U = 3 (2%)	UC and IBD-U: NA CD: L1 = 27 (18.5%) L2 = 21 (14.5%) L3 = 5 (3.5%)	Remission = 57 (39%) Mild = 26 (18%) Mild to moderate = 20 (14%) Moderate = 24(17%) Severe = 17 (12%)	5-ASA = 55 (38%) Biologics = 56 (39%) Corticosteroids = 57 (40%) Immunosuppressants = 36 (25%)	At least 3	NA

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Table 2 (*continued*)

STUDY CHARACTERISTICS							BASELINE CHARACTERISTICS OF PATIENTS								
Year	First author	Country	Study site	Design	Outcomes	Follow-up	Number (patients with IBD)	Sex	Age	IBD type	Extension of IBDN (%)	Severity of IBD N (%)	Concomitant IBD therapy	N° of prior CDI episodes	CDI severity
2021	Ianiro [21]	Italy	Single-center	Prospective	Negative *C. difficile* toxin 8 weeks post FMT (primary outcome); IBD activity and safety of FMT at 8 week follow-up (secondary outcomes)	8 weeks	18	F = 8 (45%) M = 10 (55%)	Median 50 years (21–79)	UC = 16 (89%) CD = 2 (11%)	UC: E1 = 2 (12%) E2 = 6 (38%) E3 = 8 (50%) CD: L1 = 1 (50%) L3 = 1 (50%)	UC: Mild = 3 (19%) Moderate = 10 (622%) Severe = 3 (19%) CD: Mild = 1 (50%) Severe = 1 (50%)	Systemic 5-ASA = 12 (67%) Topic 5-ASA = 6 (33%) Biologics = 7 (39%) Systemic corticosteroids = 5 (28%) Topic corticosteroids = 5 (28%) Azathioprine = 1 (5%)	At least 2	Mild = 16 (89%) Severe = 2 (11%)
2021	Nicholson [35]	USA	Multi-center	Retrospective	Success rate of FMT, defined as no recurrence of CDI within 12 weeks post FMT (primary outcome) Identification of factors associated with a successful FMT among IBD patients (secondary outcome)	12 weeks	148	F = 64 (43%) M = 84 (57%)	Mean 14 years (9–16)	UC = 73 (49%) CD = 66 (45%) IBD-U = 9 (6%)	UC E1 = 2 (3%) E2 = 13 (19%) E3 = 53 (78%) CD L1 = 6 (9%) L2 = 27 (41%) L3 = 39 (59%)	Remission = 33 (22%) Active = 115 (78%)	5-ASA = 86 (58%) Biologics = 72 (49%) Systemic corticosteroids = 64 (43%) Topical corticosteroids = 16 (11%) Immunosuppressants = 68 (46%) Enteral therapy = 10 (7%)	At least 3	NA
2022	Suchman [36]	USA	Single-center	Retrospective	Adjusted primary cure rate, defined as patients not requiring overall CDI treatment, within 8 weeks (primary outcome). Adjusted overall cure rate, defined as resolution of CDI symptoms post FMT (secondary outcome)	8 weeks	53	F = 29 (55%) M = 24 (45%)	Mean 51.8 years	UC = 29 (55%) CD = 19 (36%) IBD-U = 5 (9%)	NA	NA	Biologics = 47 (89%) Corticosteroids = 9 (17%) Methotrexate = 6 (11%) Mercaptopurines = 7 (13%)	At least 1	Mild = 48 (91%) Severe = 5 (9%)

CD= Crohn's disease; F= Female; FMT= Fecal Microbiota Transplantation; IBD= Inflammatory Bowel Disease; IBD-U= Undetermined IBD; M = Male.
NA= Not Available; rCDI = recurrent *Clostridioides difficile* infection; TNF = Tumor Necrosis Factor; UC= Ulcerative Colitis; USA= United States of America.

Table 3
Quality assessment of included studies based on the Newcastle-Ottawa Scale.

Year	First author	Country	Study site	Design	NewCastle-Ottawa quality assessment
2014	Kelly	USA	Multi-center	Retrospective	6/9
2016	Khoruts	USA	Single-center	Prospective	9/9
2016	Fischer[27]	USA	Multi-center	Retrospective	6/9
2016	Fischer[28]	USA	Multi-center	Retrospective	6/9
2017	Chin	USA	Single-center	Prospective	5/9
2012	Hamilton	USA	Single-center	Prospective	8/9
2017	Khanna	USA	Single-center	Prospective	7/9
2017	Meighani	USA	Single-center	Retrospective	6/9
2017	Newman	USA	Single-center	Retrospective	8/9
2018	Tabbaa	USA	Single-center	Retrospective	6/9
2020	Allegretti	USA	Multi-center	Prospective	6/9
2020	Azimirad	Iran	Single-center	Prospective	6/9
2020	Tariq	USA	Multi-center	Retrospective	8/9
2021	Gholam-Mostafaei	Iran	Single-center	Prospective	8/9
2021	Ianiro	Italy	Single-center	Prospective	8/9
2021	Kellermayer	USA	Single-center	Prospective	5/9
2020	Saha	USA	Single-center	Retrospective	8/9
2021	Nicholson	USA	Multi-center	Retrospective	7/9
2022	Suchman	USA	Single-center	Retrospective	6/9

most studies patients with at least three CDI episodes were enrolled, while four studies also included patients with their first recurrence [31,33,34,36]. CDI severity was reported in seven studies [21,29–32,34,36], with 511 patients presenting with mild (86%) and 87 with severe disease (14%).

3.4. Characteristics of FMT protocols

Table 4 summarizes the characteristics and outcomes of FMT among included studies. The use of antibiotics against CDI as pre-treatment before FMT was reported in all but two studies [19,36] and the antibiotic class was not specified in another two studies [20,30]. Where reported, the most commonly used antibiotic was vancomycin [18,21,26,29,31,35], followed respectively by fidaxomicin [18,21,26,28,29,31,33–35], metronidazole [18,21,26,28,29,31,34,35], rifaximin [26,29,31,33,35], and nitazoxanide [35]. Relatedness with the donor was reported in all but two studies [26,29], and two studies enrolled only related donors [30,31], while both related and unrelated donors were used in six studies [18,27,28,32,34,36], and solely unrelated donors were used in the remaining studies. Where reported, patients received only fresh feces in two studies [28,31], and frozen feces in four studies [19–21,33], while both preparations were used in another six studies [26,27,30,32,35,36]. The amount of infused feces was detailed in only four studies [19,21,27,28], and was ≥50 g in all but one study [19], which used 41 g.

The route of delivery was detailed in all studies but one [29]. No studies used combined routes of delivery. When reported, colonoscopy (including lower enteroscopy and sigmoidoscopy) was the preferred route of delivery, as it was used in all studies. Colonoscopy was the only route of administration in nine studies [18,20,26–28,30,31,33,36], while in the other studies a proportion of patients received FMT via enema [32,34], upper delivery (nasogastric/nasoduodenal tube or gastroscopy) [19,32,35], or capsules [19,35].

3.5. FMT outcomes

3.5.1. Cure of rCDI

Efficacy outcomes of FMT are summarized in Figs. 2 and 3. Pooled estimates of rCDI cure rates were, respectively, 81% (95% CI 77%–85%) for a single FMT, based on 15 studies including 777 patients [18–21,26–36], and 92% (95% CI 86%–96%) for overall FMT, based on nine studies containing 354 patients [20,21,26,27,29,31,33,34,36]. Although Nicholson et al. also offered overall FMT to recurring patients, we excluded this study from our latter analysis as only a subgroup of recurrent patients were treated with overall FMT, while others received antibiotic regimens [35].

We observed moderate heterogeneity across studies in both subgroups (I^2 for single FMT: 48%; I^2 for overall FMT: 61%). No study outliers were identified, either for single FMT, or for overall FMT. The omission of studies one-by-one (all studies) did not influence the overall efficacy rates but reduced the substantial study heterogeneity to minimal (I^2: 13%) for single FMT and moderate (I^2:44%) for overall FMT.

In a series of stratified subgroup analyses, the influence of the following factors on study heterogeneity was assessed: the average number of CDI episodes per patient in each study, the reporting of IBD severity, and whether the study as single-center or multi-center (Supplementary Figs. 1–6). For single FMT, multi-center studies had lower among study heterogeneity (Multi-center $I^2 = 0\%$, single-center $I^2 = 68\%$). For overall FMT, studies reporting IBD severity had lower study heterogeneity (reported $I^2 = 0\%$, not-reported $I^2 = 73\%$).

For single and overall FMT, visual inspection of funnel plots suggested the presence of publication bias among small studies, or other small study effects, with a lack of studies with non-significant effects of FMT being published. For single FMT, the asymmetry was not statistically significant (Peter's $P = 0.10$).

For comparison of single and overall FMT, pairwise effect estimates for single and overall FMT was reported in nine studies including 362 patients [20,21,26,27,29,31,33,34,36], and we found a significant increase in overall cure rates of rCDI from 80% (95% CI 74%–86%; I^2: 44%) for single FMT to 92% (95% CI 84%–96%; I^2: 61%) for overall FMT ($p = 0.0015$).

3.5.2. Changes in clinical activity of underlying IBD after FMT

Data on clinical activity of underlying IBD after FMT were described in all but two studies [20,30]. One hundred and fifty-six patients from six studies experienced an improvement of underlying IBD after treatment [18,21,27,31,34,35], while worsening or flare of IBD after FMT was reported in 95 patients by eight studies [18,19,26,29,31,33–35]. In other patients, including two full cohorts [28,32], the clinical activity of IBD was not affected by treatment with FMT.

3.5.3. Adverse 1 events after FMT

Adverse events data were not reported in two studies [28,30], and three studies only reported absence of serious adverse events (SAEs) after FMT [21,27,32]. Among the remaining studies, 91 patients (12% of the overall population) reported a SAE. The most common adverse event was hospitalisation, reported by nine studies in a total of 45 patients [18,19,26,29,31,33–36]. Twenty-seven patients underwent IBD-related surgery (colectomy or ileal resection) in seven studies [19,26,31,33–36], 14 patients experienced an IBD flare in two studies [26,29], and four patients died in two studies [27,29]. Other reported adverse events included predominantly gastrointestinal complaints, including abdominal pain/discomfort in two patients [18], perianal abscess in two patients [19], cytomegalovirus-related colitis, pancreatitis, and small bowel obstruction, each in a single patient [30], and two SAEs unrelated

Table 4
Characteristics of and outcomes of FMT in included studies.

First Author	FMT CHARACTERISTICS						OUTCOMES AFTER FMT		
	Antibioticpre-treatment	Donors	Fresh vs frozenfeces	Grams/ volume of feces	Route of delivery	Overall FMT after failure	CDI cure rates - N (%)	Changes in clinical activity of IBD	Adverse events
Kelly [29]	Vancomycin Metronidazole Fidaxomicin Rifaximin	NA	NA	NA	NA	Yes	Single FMT = 31 (78%) Overall = 34 (89%)	IBD flare = 3 (8%)	Death = 2; Hospitalisation = 10 IBD flare = 3
Khoruts [26]	Vancomycin Metronidazole Fidaxomicin Rifaximin	NA	Fresh and frozen	NA	Colonoscopy	Yes	Single FMT = 32 (74%) Overall = 36 (83%)	IBD flare = 11 (26%)	Hospitalisation = 2 Colectomy = 3 IBD flare = 11
Fischer [30]	Anti-CDI antibiotics	Related	Fresh and frozen	NA	Colonoscopy	No	50 (79%)	NA	NA
Fischer [31]	Vancomycin Metronidazole Fidaxomicin Rifaximin	Related	Fresh	NA	Colonoscopy Sigmoidoscopy	Yes	Single FMT = 53 (79%) Overall = 60 (90%)	IBD improvement = 25 (70%) IBD worsening = 9 (13%)	Hospitalisation = 2 Colectomy = 1 Small bowel obstruction = 1 CMV colitis = 1 Pancreatitis = 1
Chin [19]	NA	Unrelated	Frozen	NA	Colonoscopy NGT Oral capsule	No	34 (97%)	Need of treatment escalation: 19 (54%)	Surgery = 2 Perianalabscess = 3
Hamilton [27]	Vancomycin	Related and unrelated	Fresh and frozen	50gr/250 ml	Colonoscopy	Yes	Single FMT = 37 (86%) Overall = 41 (95%)	Overall improvement	No SAEsreported
Khanna [28]	Vancomycin Metronidazole Fidaxomicin	Related and unrelated	Fresh	50gr/250 ml	Colonoscopy	No	12 (100%)	No	NA
Meighani [32]	Vancomycin	Related and unrelated	NA	NA	Colonoscopy NGT Enema	No	15 (75%)	No	No SAEsreported
Newman [33]	Vancomycin Fidaxomicin Rifaximin	Unrelated	Frozen	NA	Colonoscopy	Yes	Single FMT = 48 (86%) Overall = 53 (95%)	IBD worsening = 14 (25%)	Hospitalisation = 3 Colectomy = 5
Tabbaa [34]	Vancomycin Metronidazole Fidaxomicin	Related and unrelated	Fresh and frozen	NA/250-1200 ml	Colonoscopy SigmoidoscopyG/ J tube Enema	Yes	Single FMT = 15 (71%) Overall = 19 (90%)	IBD improvement = 6 (28%) IBD worsening = 1 (5%)	Hospitalisation = 5 Colectomy = 2 Ilealresection = 1
Allegretti [20]	Anti-CDI antibiotics	Unrelated	Frozen	NA	Colonoscopy	Yes	Single FMT = 40 (92%) Overall = 40 (100%)	NA	2 SAEs not related to therapy
Tariq [18]	Vancomycin Metronidazole Fidaxomicin	Related and unrelated	NA	NA	Colonoscopy	No	116 (80%)	IBD improvement = 48 (33.1%) IBD worsening = 11 (7.6%)	Hospitalisation (transient hypotension) = 1 Abdominal pain = 2
Ianiro [21]	Vancomycin Metronidazole Fidaxomicin	Unrelated	Frozen	50–60 g/ 250 ml	Colonoscopy	Yes	Single FMT = 9 (60%) Overall = 17 (94%)	Clinical remission = 10 (59%) Clinical amelioration = 4 (24%)	No SAEsreported
Nicholson [35]	Vancomycin Metronidazole Fidaxomicin Rifaximin Nitazoxanide	Unrelated	Fresh and frozen	NA	Colonoscopy Upperendoscopy Capsule	No	Single FMT = 112/148 (76%) Overall = 119/125 (95%)*	Improved IBD = 49 (38%) IBD worsening = 27 (20%)	Hospitalisation = 19 IBD-related surgery post-FMT = 9
Suchman [36]	NA	Related and unrelated	Fresh and frozen	NA	Colonoscopy Sigmoidoscopy Enteroscopy	Yes	Single FMT = 47 (89%) Overall = 51 (96%)	IBD treatment diversification = 17 (32%)	Hospitalisation = 8 Colectomy = 4 Death = 2

AEs = adverse events; CRP= C Reactive Proteine; ESR = Erythrocyte Sedimentation Rate; FMT= Fecal Microbiota Transplantation; G = Gastrostomy; J = Jejunostomy; IBD= Inflammatory Bowel Disease; NA= Not Available; NGT= Nasogastric Tube; rCDI = recurrent *Clostridioides difficile* infection; SAEs: Severe Adverse Events; TNF = Tumor Necrosis Factor. *FMT was repeated in only 23 of 36 patients who recurred after single FMT.

to FMT [20].

4. Discussion

In this systematic review and meta-analysis, we evaluated the efficacy of FMT as a treatment for rCDI in patients with underlying IBD. Fifteen studies that fulfilled inclusion criteria were considered eligible for the final analysis, including a total of 777 patients. Overall, FMT achieved high cure rates in this population, 81% for single FMT, based on 15 studies and 777 patients, and 92% for overall FMT, based on nine studies with 354 patients, respectively. Interestingly, when we compared the effects of single and overall FMT in these nine studies, we

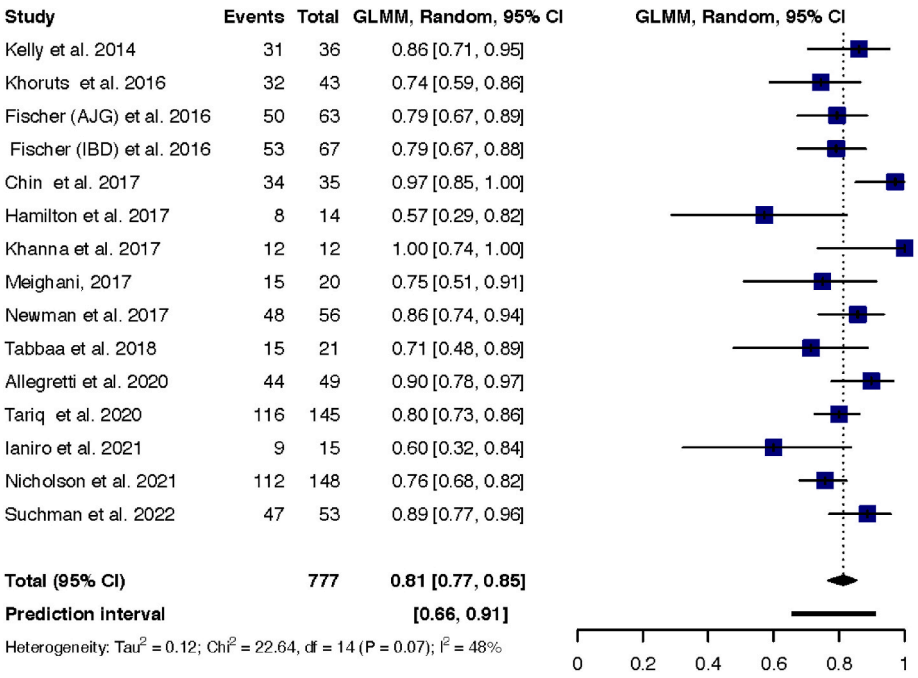

Fig. 2. Resolution of rCDIat week 8 following a single FMT.

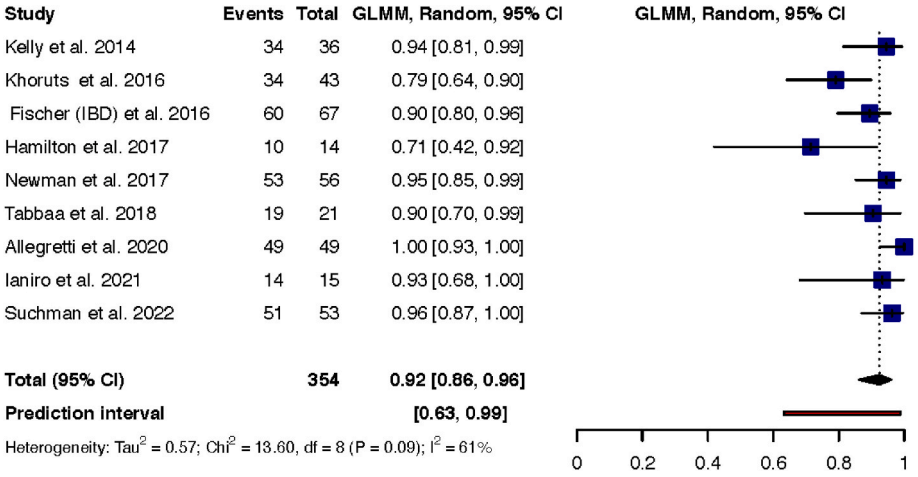

Fig. 3. Resolution of rCDIat week 8 following overall FMT after failure of a single FMT.

found a significant advantage of overall FMT over single FMT in improving cure rates of rCDI. Our results confirm the effect previously described in other systematic reviews and meta-analyses evaluating the same patient group. In 2018, Chen and colleagues reported that cure rates of rCDI were 81% after single FMT and 89% after overall FMT [38], while, more recently, Tariq and colleagues reported a 79% efficacy rate for single FMT and an 89% efficacy rate for overall FMT, respectively [39].

These findings are comparable with those reported in systematic reviews and meta-analyses of patients with rCDI without IBD, where similar efficacy rates of single and overall FMT were observed, as reported by Ianiro et al. (76% for single FMT versus 93% for overall FMT) [40], and Baunwall et al. (84% for single FMT versus 91% for overall FMT) [41], with a significant advantage of overall FMT over single infusions in both studies. These data suggest that FMT is an effective treatment for rCDI and that underlying IBD does not affect efficacy rates, as already suggested by Fischer and colleagues [30], who did not identify IBD as a risk factor for FMT failure in multivariate analysis. In contrast with this body of evidence, Khoruts and colleagues reported, in a single-cohort study, higher cure rates of CDI for single FMT in patients without IBD (92.1%) than those obtained in patients with underlying IBD (74.4%) [26]. The high efficacy rates of FMT for CDI in patients with IBD could be explained by several factors, including biological and methodological explanations. First, CDI and IBD are known to share alterations of gut microbiome and immunity [42–44],which may both benefit from FMT. Additionally, the ecological dynamics of FMT success, at least if the outcome is cure of CDI, in our population appears closer to that observed in CDI, rather than that occurring when FMT is used to induce remission in IBD. Patients with overlapping diseases appear to have a different, and more altered microbiome, to those with IBD alone [45], which could be restored more easily, as CDI is an acute dysbiosis that is less complex than the chronic dysbiosis of patients with IBD [46].

Although underlying IBD could influence changes in gut microbial ecology after FMT in patients with rCDI [28], a complete restoration of the gut microbiome is not necessary to cure CDI [47]. Moreover, successful engraftment of the donor microbiome into the recipient intestine

has been associated with clinical response and is known to be higher in patients with infectious diseases and with a history of antibiotic pre-treatment before FMT [48]. Although data on patient microbiome shifts and donor microbiome engraftment were not available for most studies identified, and were not investigated in this meta-analysis, the use of antibiotics pre-treatment in the majority of studies and the presence of an infectious disease, CDI, in all patients may have increased the likelihood of post-FMT engraftment, and consequently of clinical response, in this specific population, compared with when FMT is used as a treatment for patients with IBD without CDI.

Another explanation of our findings may relate to the working protocols of the included studies. In our meta-analysis, FMT was delivered by colonoscopy in most studies, and, when reported, at least 50–60 g of feces were used. Both these characteristics have been associated with higher cure rates of CDI in patients without IBD [42], and could represent the explanation for the relatively high efficacy rates also observed in patients with IBD.

Finally, our results may relate to the clinical characteristics of included patients. In our meta-analysis, where reported, 14% of patients presented with severe or severe-complicated CDI, a clinical condition where multiple FMT is known to be significantly more effective than single FMT [49].As previous meta-analyses also included patients with severe CDI, this methodological factor may explain the comparability of results in the two groups [41,42].

Despite the satisfactory results obtained for CDI, in our meta-analysis, FMT did not have a comparable effect on underlying IBD activity, as only 164 patients (18% of the total population) experienced an improvement in disease activity after treatment, while in the remainder clinical activity was worsened or unchanged by FMT. These findings reflect the relatively low efficacy of FMT as a treatment for IBD alone [50], although cure of CDI is known to ameliorate the overall clinical conditions in this population, including the response to IBD-related therapies [4].

Although the FMT efficacy rates demonstrated in our meta-analysis of patients with IBD and CDI were similar to those observed in patients with CDI alone, we found differences between these two populations when evaluating safety. In 13 studies included in our meta-analysis we observed 91 SAEs, which occurred in12% of the total population, including hospitalisation, colectomy, or ileal resection, IBD flares, or death. The rate of SAEs in our analysis appears to be higher than that observed in a meta-analysis of studies investigating FMT in different disorders, where they were reported in 1.4% of patients [51], and in another meta-analysis of FMT in patients with CDI, where SAEs were reported to be uncommon [52]. As FMT has been shown to be safe in immunosuppressed patients [29], this increased rate of SAEs is unlikely to be associated with IBD-related immunosuppression, but could rather be attributed to injury to the mucosal barrier [51], which is typical of IBD. Moreover, some adverse events, mainly IBD flares and IBD-related surgery, may depend on worsening of underlying disease potentially due to overwhelming CDI, reflecting a lack of efficacy of FMT, rather than a safety issue. However, based on available data we were not able to separate out SAEs potentially due to FMT failure and CDI worsening. Notably, two patients experienced a perianal abscess after FMT. Although a clear causal relationship with FMT cannot be stated, this finding suggests using caution in offering FMT to patients with fistulizing CD, due to the potential risk of donor microbiome translocation.

Our study has some limitations. First, available studies showed a moderate quality, and a moderate heterogeneity, that may limit the methodological strength of our meta-analysis. Specifically, the included studies differed for several characteristics of FMT working protocols, including the selection of donors, the route of delivery, the number of fecal transplants, as well as for concomitant IBD medications used by patients. These differences could have influenced results and represent relevant confounders of our findings.

Moreover, a considerable number of studies had a retrospective design, that, beyond decreasing the quality, also complicates the collection of data. Indeed, we were not able to retrieve complete data for IBD activity and concomitant therapy, CDI severity, and some aspects of FMT working protocols. Moreover, most cohort studies lacked controlled groups. Future studies may benefit from harmonizing reporting and design. Finally, several studies had a relatively small sample size, that may prevent us generalizing our findings. Larger and more rigorous cohort studies are needed to confirm our results and paint a clearer landscape of FMT in patients with IBD and rCDI.

5. Conclusion

In conclusion, our meta-analysis of 15 studies and 777 patients, found that FMT achieved high cure rates of CDI in patients with IBD, with a significant advantage of overall FMT over single FMT, similar to data observed in patients without IBD. However, FMT did not have a comparable effect on clinical activity of underlying IBD. Moreover, SAEs occurred in 12% of the total population, with a higher rate than in patients with CDI alone. Our findings support the use of FMT as a treatment for rCDI in patients with IBD, although caution and close monitoring of patients after the procedure are suggested. Future studies aimed at investigating the relevance of specific variables, including baseline clinical, microbial, and therapy features, as well as FMT working protocols, in influencing the safety and efficacy of FMT in this population, are advocated.

Authors contribution

SP, GC and GI conceived anddrafted the study. SP, SMDB, AO and GI collected all data. SP, SMDB and GI analyzed and interpreted the data. SP, SMDB, AO and GIwrote the initial draft of the manuscript. All authors revised the manuscript for important intellectual content and approved the final manuscript.

Declaration of competing interest

A.G. reports personal fees for consultancy from Eisai Srl, 3PSolutions, Real Time Meeting, Fondazione Istituto Danone, SinergieSrl, Board MRGE and Sanofi SpA personal fees for acting as a speaker for Takeda SpA, AbbVie and Sandoz SpA and personal fees for acting on advisory boards for VSL3 and Eisai. G.C. has received personal fees for acting as advisor for Ferring Therapeutics. G.I. has received personal fees for acting as speaker for Biocodex, Danone, Sofar, Malesci, Metagenics and Tillotts Pharma, and for acting as consultant and/or advisor for Ferring Therapeutics, Giuliani, Malesci and Tillotts Pharma. All other authors have no conflicts of interest to disclose.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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