



Fecal microbiota transplantation for the treatment of irritable bowel syndrome: A systematic review and meta-analysis

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is the most prevalent gastrointestinal disorder in

developed countries and reduces patients' quality of life, hinders their ability to work, and increases health care costs. A growing number of trials have demonstrated an aberrant gut microbiota composition in IBS, also known as 'gut dysbiosis'. Fecal microbiota transplantation (FMT) has been suggested as a treatment for IBS.

AIM

To assess the efficacy and safety of FMT for the treatment of IBS.

METHODS

We searched Cochrane Central, MEDLINE, EMBASE and Web of Science up to 24 October 2022 for randomised controlled trials (RCTs) investigating the effectiveness of FMT compared to placebo (including autologous FMT) in treating IBS. The primary outcome was the number of patients with improvements of symptoms measured using a validated, global IBS symptoms score. Secondary outcomes were changes in quality-of-life scores, non-serious and serious adverse events. Risk ratios (RR) and corresponding 95%CI were calculated for dichotomous outcomes, as were the mean differences (MD) and 95%CI for continuous outcomes. The Cochrane risk of bias tool was used to assess the quality of the trials. GRADE criteria were used to assess the overall quality of the evidence.

RESULTS

Eight RCTs (484 participants) were included in the review. FMT resulted in no significant benefit in IBS symptoms three months after treatment compared to placebo (RR 1.19, 95%CI: 0.68-2.10). Adverse events were reported in 97 participants in the FMT group and in 45 participants in the placebo group (RR 1.17, 95%CI: 0.63-2.15). One serious adverse event occurred in the FMT group and two in the placebo group (RR 0.42, 95%CI: 0.07-2.60). Endoscopic FMT delivery resulted in a significant improvement in symptoms, while capsules did not. FMT did not improve the quality of life of IBS patients but, instead, appeared to reduce it, albeit non significantly (MD -6.30, 95%CI: -13.39-0.79). The overall quality of the evidence was low due to moderate-high inconsistency, the small number of patients in the studies, and imprecision.

CONCLUSION

We found insufficient evidence to support or refute the use of FMT for IBS. Larger trials are needed.

Key Words: Fecal microbiota transplantation; Irritable bowel syndrome; Meta-analysis; Systematic review

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Core Tip: We did not find evidence to support the use of fecal microbiota transplantation (FMT) for irritable bowel syndrome (IBS) patients outside of clinical trials in this systematic review and meta-analysis. We report possible beneficial effects when FMT is delivered by endoscopy (colonoscopy or gastroscopy). FMT appears to be safe compared to placebo in patients with IBS, regardless of route of administration. Further randomised clinical trials are necessary to clarify the effect, if any, of FMT in IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is the most prevalent gastrointestinal disorder in developed countries, affecting around 11% of the adult population[1]. The condition reduces patients' quality of life, hinders their ability to work, and increases health care costs[2,3]. A diagnosis of IBS is based on symptoms, assessed using the Rome criteria, that include abdominal pain and altered bowel habits combined with the absence of organic or structural causes[4]. The criteria have changed over time and the most recent are the Rome IV criteria[5]. IBS can be sub-categorised as diarrhoea-predominant, constipation-predominant, mixed, or unclassified[5]. In most patients, IBS is chronic, with symptoms that fluctuate

over time.

The pathogenic mechanisms underlying IBS remain more or less unknown. Genetics[6,7], dietary habits[8], post-infectious conditions[9] and psychological mechanisms[10] are all suspected to be involved. In recent years an increasing number of trials have demonstrated an aberrant gut microbiota composition in IBS[11-14], although not all trials report this aberration and descriptions of it vary between studies[15]. The microbial pathophysiology of IBS remains unknown.

Treating IBS poses a challenge; the syndrome probably represents a heterogeneity of disease mechanisms, which makes it difficult to develop effective therapeutic strategies[16]. Understanding the causes of gut dysbiosis in IBS is crucial[17]. Some trials indicate that probiotics and prebiotics can reduce the symptoms of IBS[18,19]. Fecal microbiota transplantation (FMT) might be an effective therapeutic intervention in IBS[16,20].

FMT is the transfer of stool from a healthy donor to a patient[21]. FMT has been described as far back as the fourth century in China[22]. In modern times, the first published FMT treatment is from 1958, when it was used successfully in four patients with pseudomembranous colitis[23]. Pseudomembranous colitis is now known to be caused by *Clostridioides difficile* infection (CDI). Based on subsequent placebo-controlled studies, FMT is now accepted in daily clinical practice for the treatment of recurrent CDI[24]. In addition, FMT is being investigated as a treatment option in a range of other diseases, *e.g.*, metabolic syndrome, inflammatory bowel diseases, hepatic encephalopathy and multiple sclerosis[25]. The most promising results with FMT, apart from treating recurrent CDI, are for the treatment of inflammatory bowel disease[26-28].

FMT donors can be healthy relatives or anonymous donors. The advantages of the latter are the possibility of selecting donors with a high microbiota diversity and to store screened donor stool in freezers, to be made use of for multiple patients[29]. A European consensus report recommends that donors are chosen based on detailed information about illnesses with a presumed link to intestinal dysbiosis and rigorous testing of faecal and blood samples to avoid the transfer of infectious diseases [30].

FMT can be delivered in several ways, including through upper or lower endoscopic procedures, or by a gastro-duodenal or a rectal tube[31]. Additionally, capsules can release the stool in the small intestines and have been used successfully for the treatment of CDI[32-34]. In the treatment of recurrent CDI, the highest cure rates have been reported with repeated treatments delivered through lower endoscopy[35]; FMT has proven highly effective and patients are willing to undergo the treatment[36].

The microbial pathophysiology of IBS is not clearly understood, as microbiota alterations in IBS could either be a cause of the disease or a consequence of intestinal secretion and motility altered by IBS[37]. The prevailing hypothesis is that FMT might correct the dysbiosis associated with IBS[38,39], leading to a reversal or improvement of symptoms. Gut dysbiosis in IBS is characterised by a lower diversity of bacteria in the microbiota and abnormal proportions of specific bacteria as compared to the microbiota of healthy individuals[37,40]. In IBS and in other patient groups, FMT has resulted in increased bacterial diversity[41,42] and the coexistence of donor and recipient microbiota strains up to one year after treatment[43-45]. However, this is a new and developing field of study and the long-term effects of FMT on the microbiota remain largely unknown, not least of all because donor stools contain many things other than bacteria.

There is increasing evidence for a connection between gut dysbiosis and IBS[46,47]. The administration of FMT by various methods has been described in published case reports and abstracts, as compiled in an earlier review[48]. A number of smaller trials have examined the effect of FMT on IBS specifically[49-57], and several randomised controlled trials (RCTs), using different methods of administration, have been published with mixed results[43,44,58-63]. The effect of FMT can be difficult to assess due to the absence of reliable outcome measures and high placebo response rates[64]. The short- and long-term safety of FMT in patients with IBS is currently unclear.

The objectives of this systematic review were to examine the benefits and harms of FMT *vs* placebo (including autologous FMT, *i.e.*, a participant's own faecal material) for the treatment of patients with IBS.

MATERIALS AND METHODS

We conducted a systematic review and meta-analysis following the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions[65]. The systematic review was registered *a priori* as a protocol[66].

We included RCTs comparing FMT to placebo for the treatment of IBS, regardless of publication status and language of publication. For cross-over trials only data from the first intervention were used. For multi-arm trials only the data from intervention groups relevant to the review were used. We excluded trials with quasi-random designs and cluster RCTs. Trials with mixed disease populations were excluded.

Trials were included if their participants were diagnosed with IBS by a physician or according to accepted, symptom-based diagnostic criteria, such as the Rome III or IV criteria[67] (Supple-

mentary Table 1). We only included trials that had follow-up after FMT for one week or more. Participants were included regardless of their gender and age.

FMT could be administered in different ways and at different frequencies as there was no standardised procedure. Therefore, we included trials irrespective of FMT procedure, in terms of the quantity of faeces used, the form of faeces (fresh or frozen), the route of administration, the frequency of treatment (*i.e.*, single *vs* multiple infusions) and donor selection (relatives or not). Only trials that used the whole gut microbiome from the donor were included. Trials that used a placebo, or autologous FMT as a placebo, were included. Trials that used selective microbial communities were excluded.

Primary outcomes

The primary outcome was the proportion of patients experiencing an improvement of symptoms (patient-reported), as measured by a validated, global IBS symptoms score (*e.g.*, IBS severity scoring system), as defined by each trial's organisers.

Secondary outcomes

Secondary outcomes were the change in quality of life, as measured by a validated quality of life assessment, *e.g.*, IBS-specific quality-of-life (IBS-QoL), the proportion of patients with non-serious adverse events and serious adverse events according to International Conference on Harmonization-Good Clinical Practice, and dropouts due to adverse events. Outcomes were measured after three and six months.

Literature search

We searched Cochrane Central, MEDLINE, EMBASE and Web of Science. No language or publication date restrictions were applied to the searches. The detailed search strategy is provided in **Supplementary Table 2**.

We searched the following sources from the inception of each database up until 24 October 2022 and placed no restrictions on the language of publication (**Supplementary Table 2**): Cochrane Central (*via* the Ovid Evidence-Based Medicine Reviews Database, from inception); MEDLINE (*via* Ovid from 1946); and EMBASE (*via* Ovid from 1974).

We also searched for ongoing trials on ClinicalTrials.gov (<https://clinicaltrials.gov/>) and the World Health Organisation International Clinical Trials Registry Platform (<https://trialsearch.who.int/>).

The reference lists of all trials identified were then scanned for additional relevant trials. We also contacted the first authors of published and ongoing trials to request recent data or additional data, as needed.

Data collection and analysis

Two independent authors performed the study selection (BL, SIH). Disagreements were resolved by consensus using a third author (AMP). The search results were first screened by title and abstract and subsequently excluded if found non-relevant; the remaining results were screened by full text. Data were extracted independently by two investigators (BL, SIH). Any discrepancies were resolved by consensus using a third author (LLG). An attempt to contact the corresponding author by e-mail was made if data were not available.

A data extraction protocol was developed based on the Cochrane Consumers and Communication Review Group's data and results template and refined accordingly[68]. The following information was extracted from each trial: (1) Author, year of publication, trial design, and study site (country); (2) the mean or median (SD or IQR) change in symptoms, as measured by IBS scoring systems, at the end of the trial; (3) the mean or median (SD or IQR) change in quality of life, as measured by IBS quality of life scoring systems; (4) treatment description (including route of administration, mixed or single donor and fresh or frozen transplant); (5) reported non-serious adverse events and serious adverse events; and (6) dropouts due to adverse events.

Assessment of risk of bias in the studies

The risk of bias was independently assessed by two investigators (BL, FC) using the Cochrane risk of bias tool[69] and the following seven domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (**Supplementary Table 3**).

The risk of bias for each domain was rated as either 'high', 'unclear' or 'low'. We classified the overall risk of bias in the trials as low if all the bias domains were classified as being at low risk of bias; we classified the overall risk as high if one or more of the bias domains were classified as having an unclear or high risk of bias. Any disagreement was solved by consensus using a third author (LLG).

Data synthesis

We compared the fixed-effects and random-effects estimates of the intervention effect. If the estimates were similar, we assumed that any small-study effects had a minimal impact on the intervention effect estimate. If the random-effects estimate showed a larger statistical effect, we re-evaluated whether it

was reasonable to conclude that the intervention was more effective in the smaller trials. If the larger trials appeared to be conducted with greater methodological rigour, or were conducted in circumstances more typical of the use of the intervention in practice, we reported the results of meta-analyses only from the larger trials.

Based on predictable clinical heterogeneity, we expected that several analyses would show, at a minimum, moderate heterogeneity ($I^2 > 30\%$). For random-effects models precision decreases, and confidence intervals widen, with increasing heterogeneity. We therefore expected the random-effects model would provide the most conservative (and thus a more accurate) estimate of the intervention effect. As such, we planned to report the results of our analyses based on meta-analyses of random-effects models.

Subgroup and sensitivity analysis

We conducted a number of subgroup analyses: fresh *vs* frozen FMT; quantity of FMT; route of administration (upper gastrointestinal tract (*e.g.*, capsulated, nasogastric, nasoduodenal, gastric tube) *vs* colonic (*e.g.*, rectal)); type of donor (single *vs* mixed); frequency of administration (single *vs* multiple); IBS subtypes (diarrhoea-predominant, constipation-predominant, or mixed type).

Statistical analyses

We combined data from individual trials for meta-analysis when the interventions, patient groups, and outcomes were sufficiently similar, using the Review Manager version 5.4.1. Risk ratios (RR) were calculated for dichotomous outcomes with 95%CI. For continuous outcomes, we calculated the mean difference (MD) if all studies reported their outcomes using the same scale, and standardised MD with 95%CI if the studies used different scales to report their outcomes. We extracted data for all randomised participants and all participants with missing outcome data. Missing data were described, including dropouts and reasons for dropout, as reported by the authors.

Heterogeneity was assessed through a systematic examination of forest plots and quantified by calculating I^2 values. The classification of heterogeneity levels was established using the subsequent thresholds: 0%-40% (insignificant), 40%-60% (moderate), 60%-80% (substantial), and > 80% (considerable). Additionally, the P value for the chi-squared test was included in the evaluation[66].

The outcomes reported in protocols were compared with published trial reports. In addition, for direct meta-analyses with at least 10 randomised clinical trials, we assessed reporting biases through regression analyses and visual inspection of funnel plots from the pairwise meta-analyses.

Assessing the certainty of the evidence

We used the GRADE approach to evaluate the overall certainty of the evidence and we followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[65]. We classified the certainty of evidence as 'high', 'moderate', 'low', or 'very low'.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

RESULTS

Trial selection

A search conducted on 24 October 2022 identified 2067 records, which were imported for screening into the computer program Covidence (<https://www.covidence.org/>). Of these records, 840 were removed as duplicates. We screened the titles and abstracts of the remaining 1227. We excluded 1160 reports as non-relevant. In total, 67 records met the criteria for full-text review.

After reading the full texts, we excluded 45 as they did not fulfil our eligibility criteria. The remaining 22 texts, originating from eight different trials, were included in our systematic review (Figure 1)[43,44, 58-63].

Supplementary Table 2 contains the complete set of search terms used in each electronic database.

A summary of the trials can be found in Table 1; a full description of them is provided in Supplementary Table 4.

Table 1 Characteristics of randomised controlled trials of faecal microbiota transplantation for treating irritable bowel syndrome

Ref.	Trial design	Country	Sample size	IBS subtypes	Inclusion criteria	Frequency and route of administration	FMT-content	Placebo content	Pretreatment	Number of donors
Aroniadis <i>et al</i> [59], 2019	RCT, crossover	United States	48 (25 FMT <i>vs</i> 23 placebo)	IBS-D	Moderate-to-severe IBS symptoms (IBS-SSS > 175)	3 d of 25 oral capsules	3 × 25 frozen capsules (0.38 g donor stool/capsule) (Openbiome)	Non-toxic brown pigment	PPI for three days	One donor for one patient (four different donors)
El-Salhy <i>et al</i> [60], 2020	RCT, 3 parallel groups	Norway	164 (54/30 gram FMT, 55/60 gram FMT, 55 placebo)	All subtypes	Moderate-to-severe IBS symptoms (IBS-SSS > 175)	Single treatment <i>via</i> gastroscope to distal duodenum	Once 30 g or 60 gram of frozen feces in sterile saline solution	Autologous faeces	None	One donor
Halkjær <i>et al</i> [43], 2018	RCT, 2 parallel groups	Denmark	51 (25 FMT, 26 placebo)	All subtypes	Moderate-to-severe IBS symptoms (IBS-SSS > 175)	12 d of 25 oral capsules	25 FMT capsules (one daily dose containing approximately 12 g frozen faecal material)	Saline, glycerol and food colouring E150	Bowel cleansing	Donor mix from four donors
Holster <i>et al</i> [61], 2019	RCT, 2 parallel groups	Sweden	16 (8 FMT, 8 placebo)	All subtypes	IBS with small amounts of butyrate-producing bacteria	Single treatment <i>via</i> colonoscopy to the caecum	30 g frozen stool in sterile saline and glycerol	Autologous feces	Bowel cleansing and 4 mg loperamide	Two donors (three patients received stool from donor 1, the remaining five from donor 2)
Holvoet <i>et al</i> [44], 2021	RCT, 2 parallel groups	Belgium	62 (43 FMT, 19 placebo)	IBS-D and IBS-M	Refractory IBS with failure of at least three conventional IBS therapies	Single treatment <i>via</i> nasojejunal administration	Fresh feces mixed with saline	Autologous feces	Bowel cleansing	Two donors
Johnsen <i>et al</i> [62], 2018	RCT, 3 parallel groups	Norway	83 (26 fresh FMT, 29 frozen FMT, 28 placebo)	IBS-D and IBS-M	Moderate-to-severe IBS symptoms (IBS-SSS > 175)	Single treatment administered into the caecum <i>via</i> colonoscopy	50–80 g fresh or frozen feces mixed with saline and glycerol	Autologous feces	Bowel cleansing and 8 mg loperamid	Donor mix from two donors
Lahtinen <i>et al</i> [58], 2020	RCT, 2 parallel groups	Finland	51 (25 FMT, 26 placebo)	IBS-D, IBS-M and IBS-U	Patients who remained symptomatic despite receiving conventional treatment	Single treatment administered into the caecum <i>via</i> colonoscopy	30 g frozen suspension	Autologous feces	Bowel cleansing	One donor
Singh <i>et al</i> [63], 2022	RCT, 4 parallel groups	United States	23 (11 FMT, 12 placebo)	IBS-D	IBS-SSS > 150 or > 175	Single treatment with 19 oral capsules	Capsule contain 0.75 frozen fecal filtrate) (Openbiome)	Glycerol with brown coloring agent	Bowel cleansing	Six donors (unknown if donors were mixed)

FMT: Faecal microbiota transplantation; IBS: Irritable bowel syndrome; IBS-C: Constipation-predominant irritable bowel syndrome; IBS-D: Diarrhoea-predominant irritable bowel syndrome; IBS-M: Mixed irritable bowel syndrome; IBS-U: Unclassified irritable bowel syndrome; RCT: Randomised controlled trials; PPI: Proton pump inhibitors.

Study design and setting

We included eight trials that were published between 2018 and 2022[43,44,58–63]. These were either single-centre trials[44,60–63] or multicentre trials[43,58,59] and were conducted in Belgium[44], Denmark[43], Finland[58], Norway[60,62], Sweden[61] and the United States[59,63].

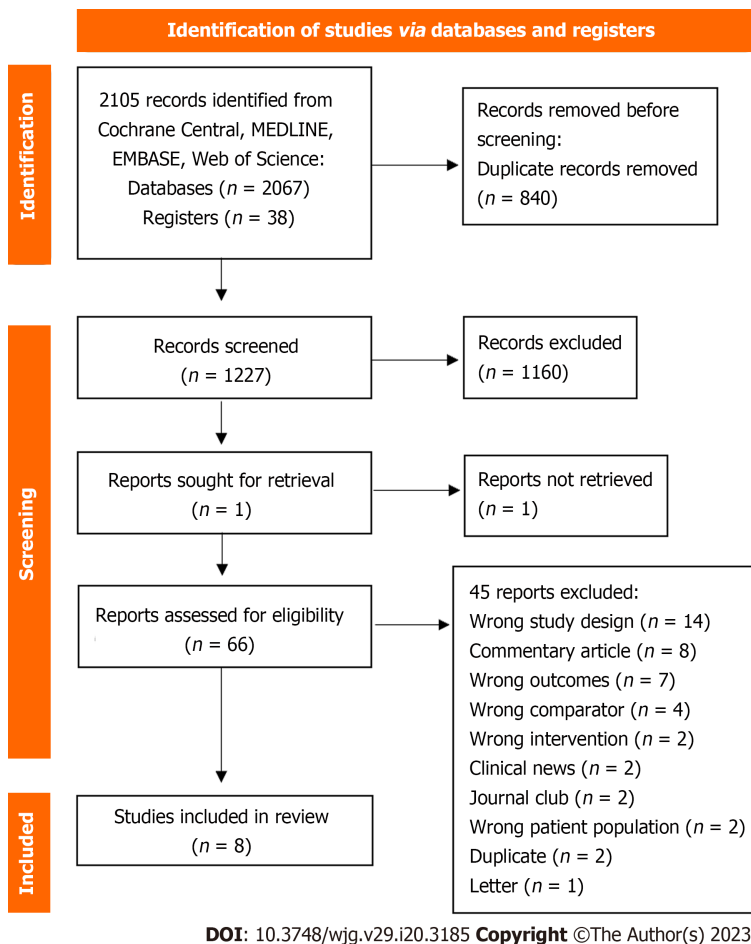


Figure 1 PRISMA flow diagram for the literature search.

All participants in the trials were diagnosed with IBS by a physician and according to accepted, symptom-based diagnostic criteria (*e.g.*, the Rome criteria)[5]. Participants in the Lahtinen *et al*[58] trial were diagnosed by a gastroenterologist, Aroniadis *et al*[59], Halkjær *et al*[43], Holster *et al*[61], Holvoet *et al*[44], Johnsen *et al*[62] and Singh *et al*[63] all used the Rome III criteria; El-Salhy *et al*[60] used the Rome IV criteria.

Four trials included participants with moderate-to-severe IBS symptoms, indicated by a score of 175 or more on the IBS severity scoring system (IBS-SSS)[43,59,60,62]. We are unsure whether Singh *et al*[63] used a score of 150 or 175 or more on the IBS-SSS, as both are referred to in their article. The remaining three trials used other criteria: Holster *et al*[61] only included participants with small amounts of butyrate-producing bacteria in faecal samples, Holvoet *et al*[44] included participants with refractory IBS who had experienced failure of at least three conventional IBS therapies, and Lahtinen *et al*[58] included participants who remained symptomatic despite receiving conventional treatment.

The trials differed in the IBS subtypes they investigated. All subtypes were included in the trials conducted by El-Salhy *et al*[60], Halkjær *et al*[43] and Holster *et al*[61]. Aroniadis *et al*[59] and Singh *et al*[63] included only diarrhoea-predominant participants. Holvoet *et al*[44] and Johnsen *et al*[62] included diarrhoea-predominant or mixed participants. Lahtinen *et al*[58] included diarrhoea-predominant, mixed or un-subtyped participants.

Characteristics of the interventions

All eight trials used faeces from healthy donors for the FMT. Supplementary Table 5 describes their inclusion and exclusion criteria for donors.

The route of administration varied between the trials. Three trials used colonoscopy[58,61,62], one used gastroscopy[60], one used the nasojejunal route[44] and three used oral capsules[43,59,63].

The frequency of administration varied between trials. El Salhy *et al*[60], Holster *et al*[61], Holvoet *et al*[44], Johnsen *et al*[62], Lahtinen *et al*[58] and Singh *et al*[63] administered FMT just once. Aroniadis *et al*[59] administered a total of three doses across three consecutive days. Halkjær *et al*[43] administered a total of 12 doses across 12 consecutive days.

The volume of FMT administered ranged from approximately 100 mL in the El-Salhy *et al*[60] trial to 300 mL in the Holvoet *et al*[44] trial. The faecal quantity varied from 30 g[58,61] to 50-80 g[62]. The

capsule trials used approximately 28.5 g of minimally processed faecal matter[59], 14.25 frozen faecal filtrate[63] and faecal matter derived from approximately 600 g of faeces[43]. Holvoet *et al*[44] used fresh FMT transplant, Johnsen *et al*[62] used both fresh and frozen FMT transplant, while the remaining trials used frozen FMT transplants[43,58-61,63].

Two trials used a single donor for all FMT treatments[58,60]. Holster *et al*[61], Holvoet *et al*[44] and Johnsen *et al*[62] used two donors. Aroniadis *et al*[59] used four donors, where each participant received a FMT from one donor. Singh *et al*[63] used six donors, where each participant received a FMT from one donor. Halkjær *et al*[43] used a FMT donor mix from four donors.

Six trials included bowel cleansing before transplantation[43,44,58,61-63]. Two trials used loperamide before endoscopy to retain the transplant[61,62]. One trial used proton pump inhibitors (PPI) for the three days prior to the transplantation[59].

Five trials used autologous faeces as an alternative to placebo for the comparison group[44,58,60-62]. In the capsule trials, Aroniadis *et al*[59] and Singh *et al*[63] used placebo capsules with a non-toxic, brown pigment and Halkjær *et al*[43] used placebo capsules made from saline, glycerol and food colouring E150.

Risk of bias in the studies

A summary of the risk of bias assessments is reported in Figure 2 and bias assessments for the individual trials are reported in Supplementary Table 4.

Overall, none of the studies had a high risk of bias in any of the seven dimensions considered. However, five of the eight trials[44,58,60,62,63] had an unclear bias for the blinding of outcomes, and four out of eight[43,58,60,61] had a similarly unclear bias in terms of how they reported the handling of incomplete data. In both cases this unclear bias was primarily due to a lack of information.

Effects of the interventions

A summary of the findings is provided in Table 2 for comparing FMT and placebo in treating IBS. We did not assess publication bias as this review only consisted of eight trials. Furthermore, we chose to report the random-effect models' results despite some of the fixed-effect models being found significant as we did not find any larger trial that was more methodologically rigorous. The significant outcomes of the fixed-effect models were most likely due to the small number of trials available in each analysis and their high heterogeneity.

The GRADE rating for the certainty of the evidence examined was low due to moderate-high inconsistency, small numbers of patients and imprecision.

Primary outcomes

Improvement of symptoms: Eight randomised trials, comprising 484 participants, examined whether IBS symptoms improved after three months. Six trials defined improvement of symptoms as a decrease in IBS-SSS of 50 or more[43,44,59,60,63], while Johnson *et al*[62] defined it as a decrease of more than 75 points. Holster *et al*[61] used the gastrointestinal symptom rating scale-IBS and defined improvement as a change of more than 30%. Sixty-four percent (185/290) of FMT participants experienced an improvement of symptoms after three months compared to 42% (82/194) in the placebo group. A meta-analysis showed there was no significant difference between FMT and placebo (RR 1.19, 95%CI: 0.68-2.10, $P = 0.54$, $I^2 = 82\%$; Figure 3).

Three trials (99 participants) reported on the improvement of symptoms after six months. Thirty per cent (14/47) of FMT participants saw an improvement of their symptoms after six months compared to 38% (20/52) of the placebo group (RR 0.88, 95%CI: 0.33-12.39, $P = 0.8$, $I^2 = 51\%$; Figure 3).

Secondary outcomes

Adverse events: Seven trials, comprising 450 participants, reported on the proportion of participants who experienced adverse events. Thirty-five per cent (97/274) of the FMT group experienced an adverse event compared to 26% (45/176) of the placebo group (RR 1.17, 95%CI: 0.63-2.15, $P = 0.62$, $I^2 = 69\%$; Figure 4).

The most frequent adverse events reported in the trials were mild and transient symptoms of the gastrointestinal system.

Serious adverse events: All eight trials, comprising 501 participants, provided data for serious adverse events. A serious adverse event was reported once in a FMT group and twice in placebo groups. In the FMT group, 0.33 per cent (1/302) reported a serious adverse event, compared to 1% (2/199) in the placebo group (RR 0.42, 95%CI: 0.07-2.60, $P = 0.35$, $I^2 = 0\%$; Supplementary Figure 1).

Holvoet *et al*[44] reported that one participant from the placebo group committed suicide 10 d after the transplantation procedure. Aroniadis *et al*[59] reported one participant from the placebo group was admitted to hospital during week 20 of the trial with acute cholecystitis. Johnsen *et al*[62] reported that one participant from the FMT group was admitted to hospital after the FMT procedure due to transient vertigo and nausea.

Table 2 Summarised findings for comparing fecal microbiota transplantation with placebo for the treatment of irritable bowel syndrome

Outcomes and timeframe	Anticipated absolute effects		Relative effect (95%CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Effect in placebo	Effect difference with FMT (95%CI)				
Improvement of symptoms after three months	42 per 100	8 or more per 100 (from 13 or fewer to 46 or more)	RR 1.19 (0.68-2.10)	484 (8 RCTs)	+++ ¹ Low	Improvement of symptoms as measured by a validated global IBS symptoms score (<i>e.g.</i> , IBS-SSS scale from 0, no symptoms, to 500, maximum symptoms) (as defined by each trial)
Improvement of symptoms after six months	38 per 100	5 or fewer per 100 (from 25 or fewer to 52 or more)	RR 0.88 (0.33-2.39)	99 (3 RCTs)	+++ ² Low	Improvement of symptoms as measured by a validated global IBS symptoms score (<i>e.g.</i> , IBS-SSS scale from 0, no symptoms, to 500, maximum symptoms) (as defined by each trial)
Adverse events prior to end of trial	26 per 100	4 or more per 100 (from 10 or fewer to 30 or more)	RR 1.17 (0.63-2.15)	450 (7 RCTs)	+++ ³ Low	Common adverse events were mild and self-limiting gastrointestinal symptoms
Serious adverse events prior to end of trial	1 per 100	1 or fewer per 100 (from 1 or fewer to 2 or more)	RR 0.42 (0.07-2.60)	501 (8 RCTs)	+++ ⁴ Low	Serious adverse events included one suicide (placebo), cholecystitis (placebo), and one admission to the hospital due to discomfort after the FMT procedure
Dropouts due to adverse events prior to end of trial	1 per 100	1 or fewer per 100 (from 1 or fewer to 1 or more)	RR 0.24 (0.03-2.17)	502 (8 RCTs)	+++ ⁵ Low	Dropouts due to adverse events include one suicide (placebo) and one for discomfort after the FMT procedure (placebo)
Improvement in QoL scores after three months	NA	NA	MD -6.30 (-13.39 to 0.79)	406 (7 RCTs)	+++ ⁶ Low	Improvement of quality of life as measured by a validated scale IBS-QoL, where 34 items are summed and averaged for a total score and then transformed to a 0-100 scale for interpretation (high scores indicate better IBS-QoL)

¹Downgraded two levels due to considerable inconsistency ($I^2 = 82\%$) and imprecision (267 events).

²Downgraded two levels due to moderate inconsistency ($I^2 = 51\%$) and serious imprecision (34 events).

³Downgraded two levels due to substantial inconsistency ($I^2 = 69\%$) and imprecision (142 events).

⁴Downgraded two levels due to serious imprecision (three events) and wide confidence interval.

⁵Downgraded two levels due to serious imprecision (two events) and wide confidence interval.

⁶Downgraded two levels due to moderate inconsistency ($I^2 = 45\%$), heterogeneous method, and a small number of participants.

Patients or population: Participants diagnosed with irritable bowel syndrome according to a physician's opinion or an accepted, symptom-based diagnostic criteria. Settings: Inpatient and outpatient. Intervention: Fecal microbiota transplantation. Comparison: Placebo (or autologous feces). FMT: Fecal microbiota transplantation; IBS: Irritable bowel syndrome; SSS: Symptom severity score; QoL: Quality of life measure; MD: mean difference; NA: Not available; RR: Risk ratio.

Dropouts due to adverse events: Eight trials, comprising 502 participants, reported on dropouts due to adverse events; there were none in the FMT groups, but two instances in the placebo groups. None (0/302) of the FMT groups had dropouts due to adverse events compared to 1% (2/200) in the placebo group (RR 0.24, 95%CI: 0.03-2.17, $P = 0.2$, $I^2 = 0\%$; [Supplementary Figure 2](#)).

Holster *et al*[61] reported that one participant from the placebo group discontinued the trial after the FMT procedure due to discomfort. The dropout due to an adverse event in Holvoet *et al*[44] was the suicide occurring 10 d after the transplantation procedure in the placebo group.

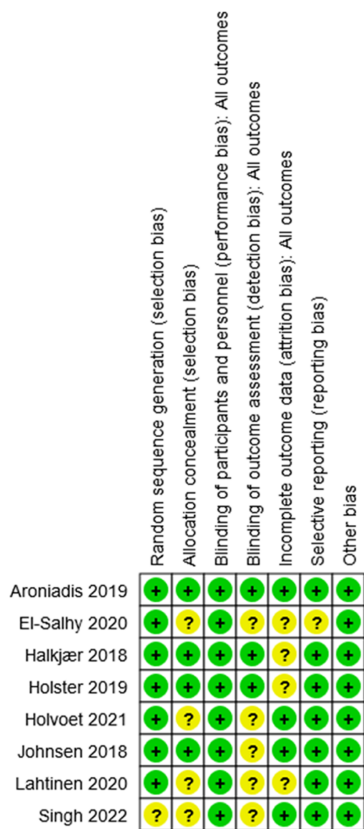
QoL measurements

Seven trials, comprising 406 participants, reported on QoL outcomes. There were no significant differences between the FMT and placebo treatment groups; however, there was a slightly favorable effect seen in the placebo groups (MD -6.30, 95%CI: -13.39 to 0.79, $P = 0.08$, $I^2 = 45\%$; [Figure 5](#)).

Subgroup analyses

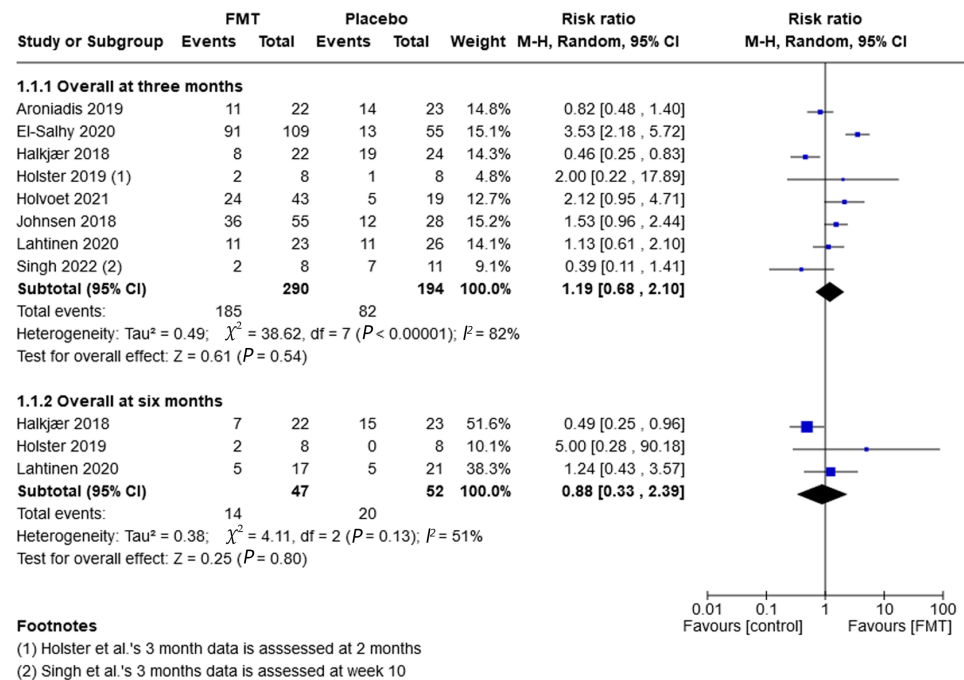
Planned subgroup analyses included fresh *vs* frozen transplant, quantity of transplant, route of administration, type of donor (single *vs* mixed donor), frequency of administration and subtype of IBS ([Supplementary Figures 3-8](#), [Figure 6](#)).

Overall, we found that endoscopic delivery (colonoscopy and upper endoscopy) of the FMT improved IBS-SSS after three months (RR 1.56, 95%CI: 1.04-2.34, $P = 0.03$, $I^2 = 0\%$ and RR 3.03, 95%CI: 1.92-4.80, $P \leq 0.00001$, $I^2 = 13\%$; [Figure 6](#)). Furthermore, administering a single, large dose of FMT resulted in a greater improvement of the IBS-SSS, while increasing the dose across several treatments was comparable to a placebo ([Supplementary Figures 4 and 6](#)). None of the other subgroup analyses



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Figure 2 Risk of bias assessments for the trials reviewed.



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Figure 3 Forest plot of randomised controlled trials of fecal microbiota transplantation for treating irritable bowel syndrome: Improvement of symptoms after three and six months. FMT: Fecal microbiota transplantation.

demonstrated an effect of FMT over placebo.

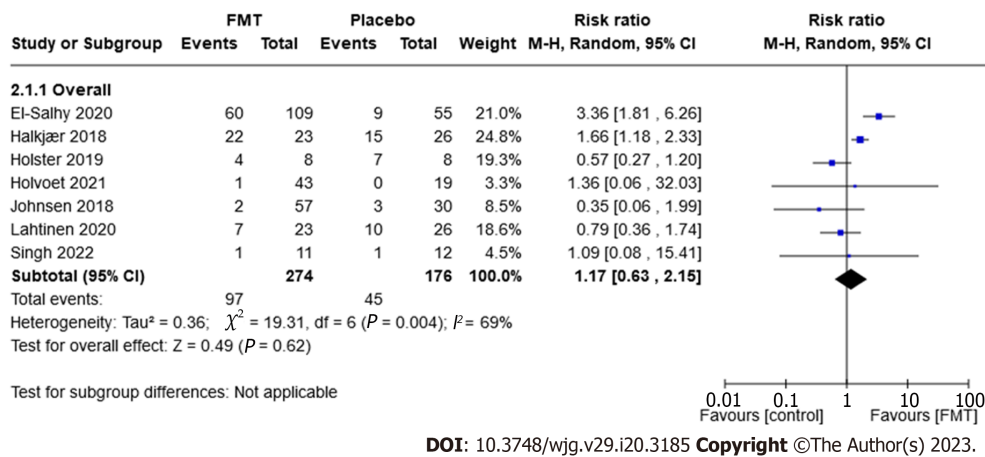


Figure 4 Forest plot of randomised controlled trials of fecal microbiota transplantation for treating irritable bowel syndrome: Adverse events. FMT: Fecal microbiota transplantation.

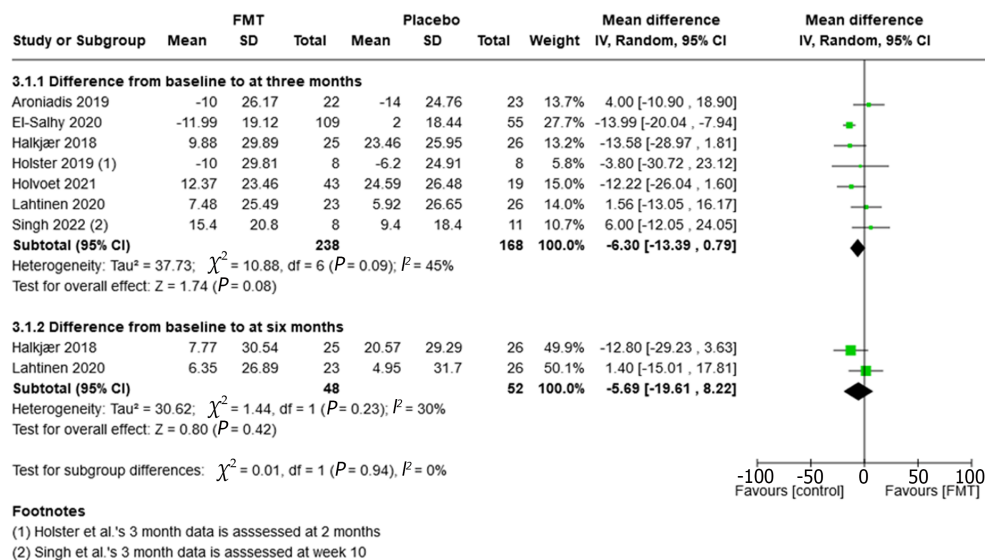


Figure 5 Forest plot of randomised controlled trials of fecal microbiota transplantation for treating irritable bowel syndrome: Quality-of-life scores after three and six months.

DISCUSSION

This review systematically examined the benefits and harms of FMT *vs* placebo or autologous FMT for the treatment of patients with IBS. Our main objective was to assess the efficacy of FMT for the improvement of symptoms in patients with IBS.

This review combined findings from eight randomised clinical trials that assessed the efficacy of FMT in 465 IBS patients. We found no significant difference in the improvement of symptoms in the FMT groups compared to the placebo groups ($P = 0.54$). The meta-analysis suggests a favorable, but non-significant, effect on quality of life in patients treated with placebo.

In general, placebo response rates are high in IBS patients. Placebo response estimates in prior meta-analyses range from 16% to 72% [64,70]. Likewise, bowel cleansing might contribute to symptom improvement; however, its effects on the microbiota seem to be transient [71,72].

FMT appears to be safe, with mild and self-limiting gastrointestinal symptoms like nausea, constipation, diarrhoea, and stomach pain - all of which are common IBS symptoms. This conclusion was also reached in a previous review assessing FMT for the treatment of inflammatory bowel disease [73]. FMT was not associated with serious adverse events in the treatment of IBS; three such events were reported in total (two in the placebo group and one in the FMT group) and none were considered to be related to the treatment.

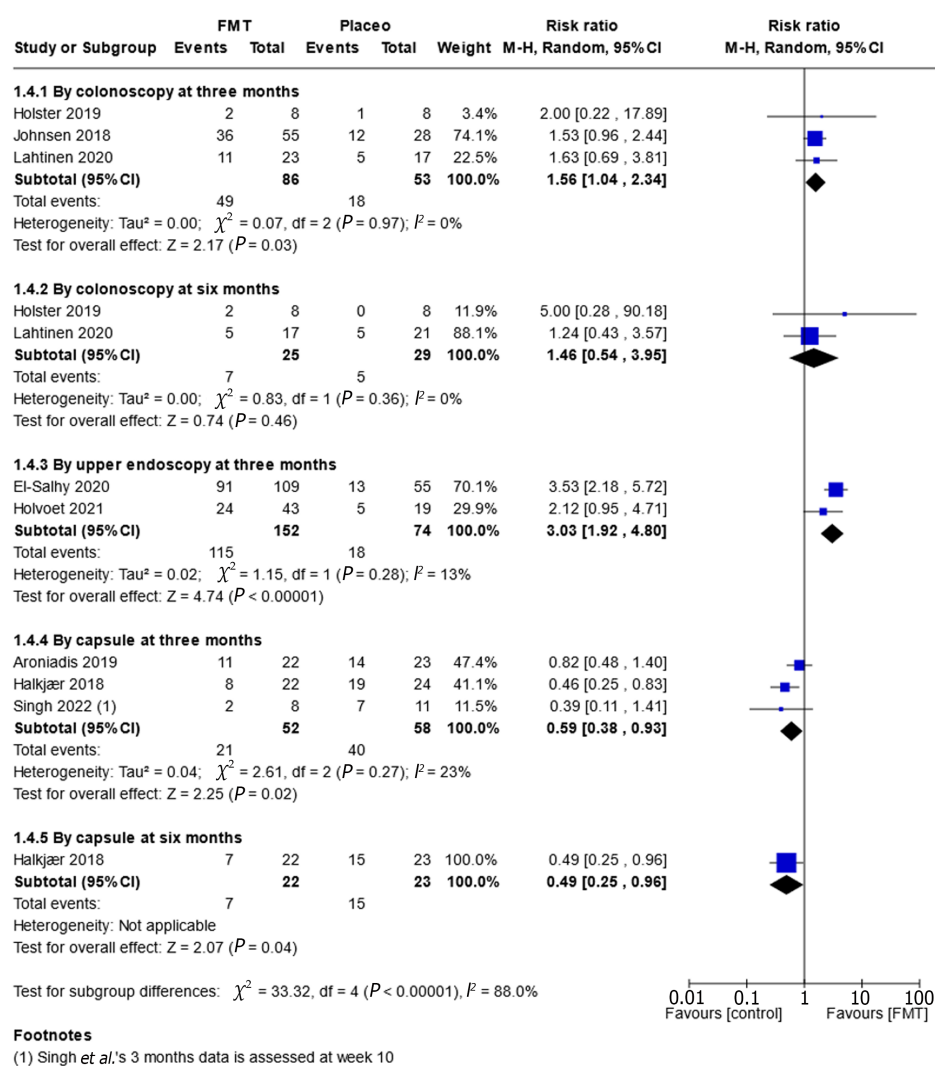


Figure 6 Forest plot of randomised controlled trials of fecal microbiota transplantation for treating irritable bowel syndrome: Improvement of symptoms after three and six months (route of administration subgroup analysis). FMT: Fecal microbiota transplantation.

In general, the results from the trials used for this review were highly heterogeneous. Therefore, it is possible that the absence of a positive overall effect is simply the result of how different the trials were from one another. The trials had pronounced differences in their selection processes for participants and donors, the routes of administration, the transplant quantities, and the frequency of administration. These differences make it difficult to draw conclusions about FMT as a treatment for IBS.

There is scientific evidence to support the hypothesis that FMT may be beneficial for patients with IBS. Observational trials have reported that IBS patients have reduced diversity or aberrant microbiota composition when compared to healthy controls[74]. Altered gut microbiota is also referred to as 'microbiota dysbiosis' and has been connected with disturbances in the microbiota gut-brain axis signaling[75]. Furthermore, other modulating agents targeting the microbiota, such as specific probiotic strains and antibiotics, have had demonstrable effects in IBS patients[76]. However, the underlying causes and mechanisms of dysbiosis in IBS and other diseases remain largely unknown. It has yet to be determined whether dysbiosis is a cause or a consequence of IBS, and even a 'healthy' microbiome has yet to be satisfactorily defined.

All eight trials included in this review reported on changes in gut microbiota after FMT. Aroniadis *et al*[59], El-Salhy *et al*[60], Halkjær *et al*[43], Lahtinen *et al*[58] and Singh *et al*[63] reported that participants receiving FMT saw changes in their gut microbiota that made their profiles more like the donors, when compared to placebo participants. Johnsen *et al*[62] reported these data in a later publication with the same outcome[77]. Holster *et al*[61] reported that microbiota diversity was not significantly affected by either FMT or placebo (autologous FMT). Holvoet *et al*[44] reported that responders to FMT had a higher baseline microbial diversity compared to those whose FMT treatment failed.

The possible effects, both positive and negative, of autologous FMT as placebo should be borne in mind.

In the treatment of recurrent CDI, the highest cure rates have been reported with repeated treatments delivered through lower endoscopy, but delivery through capsules is also highly effective[35,78]. In contrast, in IBS, FMT administered *via* upper or lower endoscopy, rather than capsules, has resulted in significant improvements in IBS-SSS. While much research has focused on FMT capsules[79], it is possible that the engraftment of the donor microbiota is better accomplished through endoscopic methods in IBS patients. Future RCTs in IBS patients that examines the combination of different routes of delivery for strain engraftment could be very interesting. Such studies would also contribute towards a more comprehensive understanding of microbial engraftment dynamics, which is currently lacking. A recent, systematic meta-analysis with shotgun metagenomic results showed that receiving FMT from multiple routes (for example, both *via* colonoscopy and capsules during the same treatment) resulted in increased engraftment[80]. Likewise, El-Salhy *et al*[81] present additional data from their trial and argue for using super donors since the efficacy of FMT appears to be donor-dependent. This argument needs further corroboration. Finally, data about patient and donor diets could prove relevant when determining the optimal patient-donor match[82].

The findings of this review have limited applicability and generalisability. More trials are needed to investigate whether FMT is a beneficial treatment strategy for IBS. Several aspects of the methods used in these trials could have influenced the effect of FMT, such as the route of administration, duration and interval between treatments, and the quantity of faecal microbiota transplanted to the patient. Despite the subgroup analyses we conducted as part of this review, firm conclusions cannot be drawn due to the small number of events and participants in the trials. Nonetheless, the results do suggest a possible beneficial effect in delivering FMT by endoscopy (colonoscopy or gastroscopy) over other routes.

Most of the patients in the trials we reviewed had moderate-to-severe IBS and were diagnosed according to the Rome III criteria. The newest, Rome IV criteria are more rigorous and it is not clear whether the greater homogeneity of IBS study populations they encourage will affect the efficacy of FMT. We recommend that future trials use the Rome IV criteria.

Additional investigations of microbiota, both when selecting patients of interest and after interventions, are needed in order to establish the precise mechanism of action of FMT as a potential treatment for IBS.

CONCLUSION

We did not find evidence to support the use of FMT for IBS patients outside of clinical trials in this systematic review and meta-analysis. We report a possible beneficial effect when delivering FMT by endoscopy (colonoscopy or gastroscopy). FMT appears to be safe, when compared to placebo, in patients with IBS, regardless of route of administration. Further randomised clinical trials are necessary in order to determine the effect of FMT in IBS.

ARTICLE HIGHLIGHTS

Research background

Irritable bowel syndrome (IBS) is a widespread gastrointestinal disorder accompanied by chronic abdominal pain and altered bowel habits. Gut microbiota disturbances have been linked to the pathophysiology of IBS, with fecal microbiota transplantation (FMT) emerging as a potential treatment strategy.

Research motivation

Manipulating gut microbiota composition *via* FMT could offer a promising avenue for IBS treatment, warranting further investigation into its efficacy and safety.

Research objectives

This review and meta-analysis aimed to evaluate the effectiveness and safety of FMT for treating IBS.

Research methods

A comprehensive search of Cochrane Central, MEDLINE, EMBASE, and Web of Science to identify randomised controlled trials (RCT) comparing FMT to placebo or autologous FMT in IBS patients. Primary outcome was improvement of symptoms, while secondary outcomes were quality-of-life scores and adverse events.

Research results

Our analysis incorporated data from eight RCTs with 484 participants. FMT did not result in significant improvement of symptoms when compared to placebo after three months, and no significant

improvement in quality of life was observed. Subgroup analysis indicated that endoscopic FMT delivery led to symptom improvement, whereas FMT capsules did not. FMT was found to be safe.

Research conclusions

This systematic review and meta-analysis do not support FMT as a treatment for IBS outside of clinical trials. Nevertheless, FMT was found to be safe.

Research perspectives

Large-scale, RCTs are needed to confirm or refute these findings. Investigating the potential significance of combining different FMT delivery routes for strain engraftment could provide a more comprehensive understanding of microbial engraftment dynamics in IBS patients.

FOOTNOTES

Author contributions: Halkjær SI, Gluud LL and Petersen AM conceived the review; Halkjær SI, Lo B, Cold F, Højer Christensen A, Gluud LL and Petersen AM wrote the protocol for the review; Halkjær SI and Lo B searched and selected studies for the review; Halkjær SI, Lo B, Holster S, König J, Brummer RJ, Aroniadis OC, Holvoet T and Lahtinen P collected data for the review; Lo B, Cold F and Gluud LL assessed the risk of bias in the studies used; Halkjær SI, Lo B, Gluud LL and Petersen AM assessed the certainty of the evidence; Halkjær SI and Lo B interpreted the data; Halkjær SI and Lo B wrote the review; Halkjær SI, Lo B, Cold F, Højer Christensen A, Petersen AM, Holster S, König J, Brummer RJ, Aroniadis OC, Holvoet T, Lahtinen P and Gluud LL commented on the review. All authors have read and approved the final manuscript. None of the authors have extracted data from, or assessed the risk of bias in, trials they carried out themselves.

Conflict-of-interest statement: None of the authors report relevant conflicts of interest for this article.

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