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Review Article

Faecal Microbiota Transplantation [FMT] in the Treatment of Chronic Refractory Pouchitis: A Systematic Review and Meta-analysis

Shafquat Zaman,[a] Akinfemi Akingboye,[b] Ali Yasen Y. Mohamedahmed,[c] Elizabeth Peterknecht,[d] Pratik Bhattacharya,[d] Mohammed E. El-Asrag,[a,e] Tariq H. Iqbal,[f,g] Mohammed Nabil Quraishi,[a,g] Andrew D. Beggs[a,g]

[a]Institute of Cancer and Genomic Science, College of Medical and Dental Science, University of Birmingham, Birmingham, UK
[b]Department of General Surgery, Russells Hall Hospital, Dudley, UK
[c]Department of Colorectal Surgery, Royal Wolverhampton NHS Trust, Wolverhampton, UK
[d]Department of General Surgery, Sandwell and West Birmingham Hospitals, Birmingham, UK
[e]Faculty of Science, Benha University, Benha, Egypt
[f]Institute of Microbiology and Infection, College of Medical and Dental Science, University of Birmingham, Birmingham, UK
[g]Microbiome Treatment Centre, University of Birmingham, Birmingham, UK

Corresponding author: Ali Yasen Y. Mohamedahmed, Royal Wolverhampton NHS Trust, Wolverhampton WV10 0QP, West Midlands, UK. Email: dr.aliyasen1@gmail.com

Abstract

Background: The aim of this systematic review and meta-analysis is to assess the efficacy and safety of faecal microbiota transplantation [FMT] in the treatment of chronic pouchitis.

Methods: A PRISMA-compliant systematic review and meta-analysis was conducted using the following databases and clinical trial registers: Medline, Embase, Scopus, Cochrane Database of Systematic Reviews [CENTRAL], clinical trials.gov, ScienceDirect, and VHL [virtual health library]. The primary outcome was clinical response/remission in patients treated with FMT. Secondary outcomes included safety profile, quality of life, and changes in the gut microbiome.

Results: Seven observational cohort studies/case series and two randomised, controlled trials with a total of 103 patients were included. The route, preparation, and quantity of FMT administered varied among the included studies. Clinical response rate of 42.6% with a remission rate of 29.8% was estimated in our cohort following FMT therapy. Minor, self-limiting, adverse events were reported, and the treatment was well tolerated with good short- and long-term safety profiles. Successful FMT engraftment in recipients varied and, on average, microbial richness and diversity was lower in patients with pouchitis. In some instances, shifts with specific changes towards abundance of species, suggestive of a 'healthier' pouch microbiota, were observed following treatment with FMT.

Conclusion: The evidence for FMT in the treatment of chronic pouchitis is sparse, which limits any recommendations being made for its use in clinical practice. Current evidence from low-quality studies suggests a variable clinical response and remission rate, but the treatment is well tolerated, with a good safety profile. This review emphasises the need for rationally designed, well-powered, randomised, placebo-controlled trials to understand the efficacy of FMT for the treatment of pouchitis.

Key Words: Chronic pouchitis; dysbiosis; microbiome; faecal microbiota transplantation; FMT

1. Introduction

Ileal pouch-anal anastomosis [IPAA] is a surgical procedure performed following a pan-proctocolectomy for medically resistant ulcerative colitis [UC].[1] Other indications include familial adenomatous polyposis [FAP],[2] other polyposis syndromes or conditions with multiple synchronous cancers involving the rectum,[2] and carefully selected cases of Crohn's disease.[3] Also known as an ileo-anal pouch, ileal-anal pull-through, restorative proctocolectomy, or an internal pouch [with various configurations], it allows restoration/retention of anal function and serves as an alternative to a permanent ileostomy. Various techniques for anastomosing ileum to the anus have been described in the literature[2]; Parks and Nicholls pioneered the procedure in the 1970s by combining the idea of an ileal reservoir with ileo-anal anastomosis.[4]

The J-shaped pouch[5] is technically easier to construct and confers an excellent long-term quality of life, demonstrating superior function over the S- and W-shaped configurations.[6] In addition, concurrent improvements and advancements in surgical technology have led to the increased use of stapling devices over hand-sewn anastomosis and laparoscopic approaches, robotic techniques, single incision laparoscopic surgery [SILS], trans-anal total mesorectal excision [TaTME], and natural orifice techniques, which all promise to refine further and improve pouch surgery outcomes.[2]

Although IPAA surgery offers removal of disease burden, providing adequate continence and avoiding the need for a permanent stoma, all of which may translate into improved quality of life, it is not without associated morbidity and mortality. Mortality rates are low, but early post-operative complications associated with pouch surgery include haemorrhage [staple line bleeding, pouch ischaemia], acute pelvic sepsis [anastomotic leak, infected haematoma], and portal vein thrombosis.[2]

Late complications include chronic pelvic sepsis manifesting as anastomotic strictures, fistula formation, poor pouch compliance, pouch failure, small bowel obstruction, and pouchitis.[2] The last is a complication following IPAA in both acute and chronic settings. It has a reported cumulative incidence rate of 45% at 5 years[7] and is characterised by abdominal cramping, fever, increased bowel frequency, bloody stools, urgency, tenesmus, extraintestinal manifestations, and general malaise.[8]

Chronic pouchitis develops in 10–15% of patients with acute pouchitis and can be divided into 'antibiotic-responsive' and 'antibiotic-refractory'.[9] However, studies on pouchitis are complicated by the lack of a universally accepted definition. Chronic 'antibiotic-refractory' pouchitis is considered in patients with persistent symptoms despite a 4-week course of antibiotic treatment.[10] Alternatively, patients not improving after a 2-week course of antibiotics [usually ciprofloxacin or metronidazole], and symptoms persisting beyond 4 weeks, may be diagnosed with 'chronic' pouchitis.[11]

The combination of clinical symptoms and endoscopic and histological assessment is pooled to assess the severity of pouchitis through a variety of scoring systems such as the 'Pouchitis Disease Activity Index' [PDAI].[12] To standardise definition for comparative purposes, the PDAI brought together the Mayo clinic definition and the St Marks pouchitis triad/histopathological index. Composite score ranges from 0 to 18, with a total score of ≥7 equating with a diagnosis of pouchitis.

More recently the Heidelberg Pouchitis Activity Score [PAS], introduced in 2002,[13] also generates a composite score by combining clinical, endoscopic, and histological features and ranges from 0 to 36 [score of ≥ 13 indicating pouchitis]. PAS differs from the PDAI index with omission of clinical features such as fever and the presence of chronic inflammation.

The exact aetiology of pouchitis remains unclear, and treatment options include often repeated courses of antibiotics, probiotics, and disease-modifying agents.[9] More recently and through increasing interest in correcting bacterial dysbiosis for various conditions, faecal microbiota transplantation [FMT] has been used in the treatment of chronic pouchitis. Also known as stool transplantation or bacteriotherapy, the procedure involves transplanting minimally treated, whole, faecal samples, collected from carefully screened healthy donors, into the patients' gastrointestinal [GI] tract.

Gut microbiota in health is predominantly composed of the Bacteroidetes and Firmicutes phyla[14] with smaller proportions of Proteobacteria, Actinobacteria, Verrucomicrobia, Eucarya, and various phages.[15] Imbalances, or changes in the composition and function of intestinal microbes [dysbiosis] is associated with wide-ranging disorders; both gastrointestinal [GI] and non-GI.[15] Patients with pouchitis have decreased bacterial diversity, or richness, with reduced levels of Bacteroidetes, Ruminococcaceae, Lachnospiraceae, Streptococci, and Faecalibacterium and higher levels of more pathogenic species including members of Enterobacteriaceae and Fusobacterium.[16] Ruminococcaceae and Lachnospiraceae are particularly important in the production of butyrate and other short-chain fatty acids [SCFAs], nutrients considered crucial in maintaining colonic health. Lower levels of these fatty acids have been observed in pouch inflammation.[16] Additionally, reduced production of secondary bile acids and higher levels of sulphate-reducing bacteria secondary to gut microbiota dysbiosis may all be implicated in the pathogenesis of pouchitis.[16] Consequently, modifying the pouch microbiome and reversing altered gut microbiota towards a 'healthier' composition through faecal transplantation may be a viable therapeutic option.

Our aim was to determine the efficacy, safety profile, and microbial changes associated with FMT use in treating patients with chronic pouchitis. FMT is an established treatment, supported by national guidelines, for recurrent/refractory *Clostridium difficile* infection [CDI].[17,18] However, although largely favourable,[19–24] it has shown conflicting evidence as an emerging therapy in patients with active UC.[25,26]

Recent systematic reviews have assessed the safety and efficacy of FMT in the treatment of pouchitis.[27,28] This review builds on these, adding information from the first, completed, randomised, controlled trial [RCT] assessing the effect of FMT in treating chronic pouchitis.[29]

2. Methods

2.1. Data sources and search strategy

An online search in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[30] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA][31] guidelines was conducted using the following databases and clinical trial registers: Medline, Embase, Scopus, Cochrane Database of Systematic Reviews [CENTRAL], clinical trials.gov, ScienceDirect, and VHL [virtual health library]. The search was performed by two independent reviewers using the following search terms 'faecal microbiota transplantation, fecal microbiota transplantation, faecal microbiota transplant, fecal microbiota transplant, FMT, faecal transplantation, fecal transplant, stool transplantation, or stool transplant' and 'pouchitis, chronic pouchitis, antibiotic resistant pouchitis, antibiotic dependent pouchitis, ileal pouches, ileal pouch, J pouch, J-pouch, ileal pouch anal anastomosis, ileal pouch-anal anastomosis, or IPAA'. Comprehensive search criteria are outlined in Supplementary File 1.

Furthermore, a manual search of reference lists and bibliographies in previous reviews was performed to identify additional studies.

2.2. Selection criteria

Papers included in this review were based on the following: Population, Intervention, Comparison, and Outcome[s] [PICO] framework.

2.2.1. Population

Individuals with 'chronic pouchitis' [recurrent or antibiotic-refractory], treated with FMT in all study types [RCTs, non-randomised clinical trials, observational/cohort studies, pilot studies, and case series] were included. Case reports were

excluded. Participants of all ages were included, and no date or language filters were applied. Data presented as conference abstracts and available online were also considered.

2.2.2. Intervention

Interventions included any preparation or formulation of FMT administered into the GI tract through any means [orally/capsules, nasogastric tube, endoscopy, pouchoscopy, colonoscopy].

2.2.3. Comparison

In RCTs, accepted comparators were either no treatment or placebo.

2.2.4. Outcomes

The primary outcome was clinical response/clinical remission in patients with chronic pouchitis treated with FMT. Clinical response and/or remission were defined through the PDAI or where necessary, its variations including the modified PDAI [mPDAI] or clinical PDAI [cPDAI].

The PDAI incorporating clinical, endoscopic, and histological features establishes a cut-off of 7 for differentiating between pouchitis [≥7 points] and no pouchitis [<7 points]. Clinical response to FMT was defined as a reduction in PDAI of ≥3. Clinical remission following FMT treatment was defined as a reduction in PDAI of ≥3 and an overall PDAI score of <7.

Secondary outcomes included safety of FMT treatment, adverse events, and microbiome changes.

2.3. Exclusion criteria

Any studies where FMT was used to treat conditions other than chronic pouchitis, such as UC or *Clostridioides difficile* infection, were excluded.

2.4. Design and study selection

Titles, abstracts, or full texts of selected articles were screened independently by two reviewers [SZ and MNQ] to identify potentially eligible studies. All human studies investigating the effects of FMT treatment on chronic pouchitis, in any gender and including all ages, were considered. Any disagreement between the reviewers during this process was resolved through discussion and consensus.

2.5. Data extraction and collection

Data extracted from included studies [where available] comprised:

- study-related data [author details, year of publication, study country of origin, study design, study size];
- baseline demographic and clinical information [details of intervention and methodology employed, clinical outcomes, donor characteristics];
- bioinformatic methodology and taxonomic changes post FMT treatment;
- safety profile and adverse events.

Extracted data were entered into a pre-generated standard Microsoft® Excel [Microsoft Corporation, Redmond, WA] file, pilot tested and adjusted accordingly. Two reviewers independently performed the data extraction, resolving any disagreements through discussion and consensus.

2.6. Risk of bias and quality assessment

The Cochrane risk of bias tool was used to appraise the risk of bias for RCTs.[32] Two investigators independently reviewed all studies and graded the risk of bias as 'high', 'low', or 'unclear'. This was done for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Methodological quality and risk of bias assessment for observational studies can be performed through various tools, including the Newcastle–Ottawa scale [NOS].[33] The NOS is a star-based scoring system [maximum score 9] enabling reviewers to evaluate an observational study in the following: selection of the study groups, comparability of the groups, and the ascertainment of the outcome of interest. A study with a total score of 9 is deemed to be at low risk of bias, 7/8 at medium risk, and those that score ≤6 are judged to be at high risk. Due to the single-arm design of our remaining studies, we were unable to assess methodological quality and risk of bias using a validated tool.

2.7. Statistical analysis

For the primary outcome, pooled estimates of relative risk from the RCTs, and response rates from case series, were estimated with a random effects model using the method of DerSimonian and Laird.[34,35] Exact confidence intervals were calculated for the individual studies. Heterogeneity was assessed using the I^2 statistic and calculation of 95% prediction intervals for the response proportion, ie, low heterogeneity: >25%; moderate heterogeneity 25–75%; high heterogeneity >75%.[36] Confidence intervals for relative risks from individual RCTs were calculated assuming that the sampling distributions of the log-relative risk were normally distributed. All analyses were performed in R version 4.2.1 using the meta package [Texas, USA].

3. Results

A total of 199 studies was identified after the systematic search of the above-mentioned electronic databases. Review of titlesand abstracts and exclusion of any duplicates [n = 49] meant the full manuscripts of the remaining 150 articles were reviewed and assessed against the eligibility criteria. This identified nine relevant studies[29,37–44] that were included in our final data synthesis. The PRISMA flow chart is shown in Figure 1.

3.1. Study characteristics

The selected studies included two cohort/observational studies,[42,44] four prospective, open-label pilot studies,[37,38,41,43] one open-label case series,[39] one single-centre, double-blind, parallel group trial,[29] and one prospective, placebo-controlled, double-blind [proof of concept] trial.[40]

A total of 103 patients [range 3–26] was included, with a male proportion ranging between 27.3% and 66.7%. Six studies[38–41,43,44] reported the median age of their included patients; two studies[29,37] reported mean age; and one study[42] did not provide this information. Characteristics of the included studies, together with FMT preparation and treatment protocol and baseline disease severity indices, are highlighted in Table 1. Risk of bias assessment for the included RCTs is shown in Supplementary File 2.

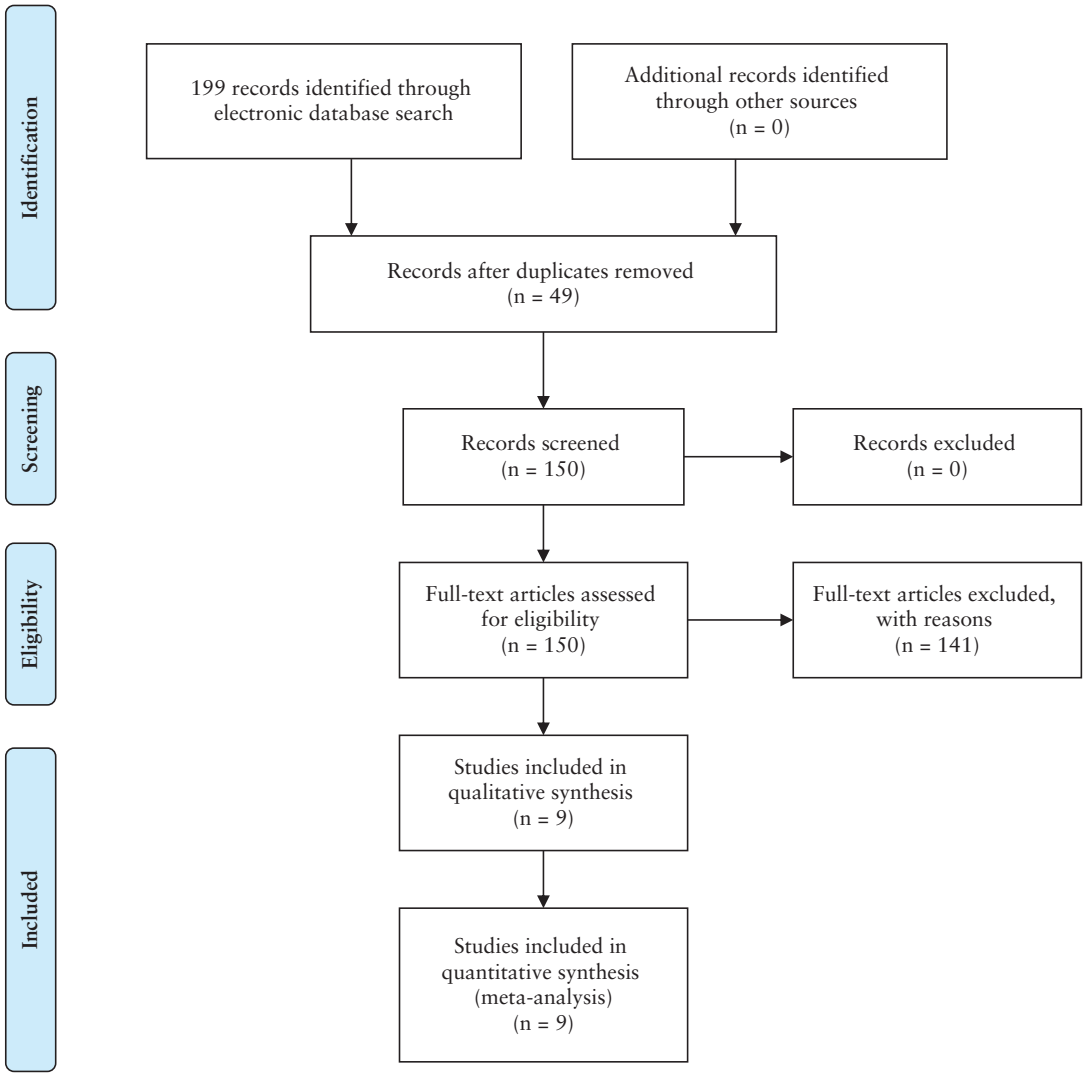

Figure 1. PRISMA flow chart

There was a lack of consensus on the definition of chronic pouchitis among the included studies, but this often centred on the PDAI or a modified version [mPDAI] of this scoring system. Other studies focused more on the duration of typical pouchitis symptoms or the need for recurrent antibacterial therapy. Moreover, there was variation in concurrent therapies permitted during the different studies, such as probiotic use.[29,38,41]

3.2. Baseline disease characteristics

There was variable reporting of baseline PDAI score [pre-FMT treatment] between the studies [Table 1]. Two studies[38,39] reported on the use of advanced therapy in the form of biologics prior to FMT treatment, and severe, refractory UC was the main reason given for performing colectomies.

3.3. FMT treatment protocol

The method and route of FMT delivery into the GI tract varied among our included studies. The upper GI tract was used to deliver FMT in four studies and included nasogastric infusion[44] or insertion endoscopically [OGD] into the jejunum,[42,43] and a further study[40] transplanted FMT endoscopically but with the exact site not specified.

Methods using the lower GI tract included colonoscopic administration,[39] pouchoscopy/trans-anal catheter,[29] pouchoscopy alone[38,41] and self-administered enemas.[37] There was also heterogeneity in the FMT treatment protocol used between studies. A single [once only] FMT treatment was given in three studies via a nasogastric tube,[44] pouchoscopy[41] and colonoscopy.[39] The remainder included two FMT treatments given 4 weeks apart[29,38]; single endoscopic delivery followed by daily oral capsules for 14 consecutive days[40]; once daily self-administered enema for 14 consecutive days[37]; 2–4 FMTs given every 4 weeks depending on therapeutic outcome[42]; and 1–7 FMTs with an interval of 3–4 weeks.[43] In one study,[29] loperamide was given to patients half an hour before each FMT infusion, and in another a proton pump inhibitor was given the night before and the morning of FMT treatment.[44]

In five studies, 20–30g of donor faecal material suspended in various volumes of saline was infused into the recipient.[29,37,38,40,44] In one study, ~150–200g of stool dissolved in 500 ml saline was used as treatment.[39]

In one of the two double-blinded trials included in our analysis, frozen FMT containing food colourant to replicate the faecal colour, and matching placebo capsules, were used.[40] In

Table 1. Characteristics of included studies

Reference	Study type	No. of subjects	Control/ comparator	Treatment protocol & FMT preparation	Bowel cleansing	Age [years] median [range]/ mean [SD]	Gender [% male]	Average disease severity indices at baseline	Treatment duration	Relevant study characteristics
Landy *et al.* 2015	Cohort [pilot study]	8	Nil	Once-only nasogastric infusion of faecal-saline solution [30 g stool homogenised with 50 mls of 0.9% normal saline; 30 mls administered and flushed with 50 mls normal saline] FMT prepared from related/ un-related donor stool provided within 6 h prior to transplantation	NR	46 [24–63]	37.5%	PDAI: 11.5 [10–14]	Once-only FMT	Patients with chronic pouchitis defined as current PDAI ≥7 of more than 4 weeks duration not responsive to one or more Abx Chronic ADP defined as symptoms only controlled while on Abx and chronic ARP defined as pouchitis no longer responding to a single Abx FMT offered to patients ADP or ARP and failed to respond to or declined immunosuppressives and/ or de-functioning ileostomy Exclusion: Abx or NSAID use within 2 weeks of study participation
Stallmach *et al.* 2016	Prospective, open-label, pilot study	5	Nil	1–7 FMTs given over intervals of 3–4 weeks through endoscopic infusion into the jejunum [150 g stool homogenised with 400 mls isotonic sodium chloride] FMT prepared from two, unrelated, healthy donor stools collected on day of transplantation Single donor to patient [fresh or frozen]	NR	32 [26–40]	40%	PDAI: 10.8 ± 1.94	1–7 FMTs with intervals of 3–4 weeks	Patients with ARP [not defined] Previous Abx therapy: ciprofloxacin, metronidazole, rifaximin Third FMT donor used and initiated clinical remission in non-responder
El-Nachef *et al.* 2017	Prospective, open-label, pilot study	11	Nil	Once-only FMT by pouchoscopy FMT prepared from single, healthy, screened donor	NR	47 [27–77]	27.3%	PDAI: 8.5 ± 2.7 ePDAI: 4 ± 1.95 hPDAI: 2.5 ± 1.5	Once only FMT	Adult patients with pouchitis [not defined] confirmed by endoscopy and pathology included Concurrent therapies permitted with exception of antibiotics/probiotics
Steube *et al.* 2017	Cohort study	16	Nil	FMT encapsulated, cryopreserved microbiota [for 5 consecutive days] or a one-time endoscopic jejunal application FMT prepared from unrelated, healthy, screened donors	NR	NR	NR	PDAI: NR	2–4 FMTs Delivered every 4 weeks according to therapeutic outcome	Safety and effectiveness of encapsulated FMT or endoscopic application to patients with chronic ARP [not defined]. Clinical response and mucosal inflammation assessed by FCP levels

Table 1. Continued

Reference	Study type	No. of subjects	Control/ comparator	Treatment protocol & FMT preparation	Bowel cleansing	Age [years] median [range]/ mean [SD]	Gender [% male]	Average disease severity indices at baseline	Treatment duration	Relevant study characteristics
Selvig *et al.* 2019	Prospective, open-label, single-centre, pilot study	18 [19 enrolled, 1 lost to follow-up]	Nil	Initial pouchoscopy infusion into proximal pouch with optional second administration 4 weeks later [*n* = 11]. 250 mls donor faecal suspension [25 g of stool] FMT prepared from 13 donors, single [non-pooled] donor to patient	Day before FMT, bowel purge with 10 oz of magnesium citrate Morning of FMT, sodium phosphate enema	45 [34–56]	33%	PDAI: median [IQR] 7 [6–8] *n* = 11 ePDAI: 3.36 ± 1.37; *n* = 11 hPDAI: 1.09 ± 0.67; *n* = 11	1 or 2 FMTs Single or optional re-treatment after 4 weeks	Chronic pouchitis defined as prior endoscopic evaluation confirming inflammation and over 4 weeks of symptoms such as increased stool frequency, urgency, tenesmus, or bleeding Exclusion criteria: severe immunosuppression, Crohn's disease, untreated enteric infection, fistulising disease, and pregnancy Concurrent therapies permitted except Abx
Herfarth *et al.* 2019	Prospective, placebo-controlled, double-blind, trial with open-label follow-up [proof of concept study]	6 FMT: 4 Placebo: 2 OLE: 5	Placebo group	Frozen eFMT and matching placebo containing food colourant to replicate faecal matter; oFMT and matching placebo capsules eFMT [2* 30 ml, total 24 g donor stool] or placebo oFMT [6 G3 capsules, total 4.2 g donor stool] or placebo capsules for 14 days OLE: patients experiencing relapse during first 4 weeks after endoscopic transplant offered open label active eFMT followed by 14 days daily active oFMT FMT prepared from a single, screened stool donor	NR	34.5 [22–60]	66.7%	PDAI: NR	Single endoscopic FMT [active/ placebo] followed by daily oral encapsulated FMT [active/ placebo] for 14 days	Patients with ADP defined by: the need for continuous Abx therapy [>4 weeks] to maintain clinical remission and at least two attempts in past 2 years to stop Abx resulting in pouchitis episodes; or by active pouchitis with a mPDAI ≥5 and ≥4 Abx therapies for pouchitis in past 12 months Clinical remission [mPDAI <4 with corresponding clinical sub-scores for patient reported outcomes of bowel frequency and urgency of ≤1] induced in all patients with Abx, stopped at least 24 h prior to FMT Trial stopped prematurely—lower than expected clinical remission rate and low FMT engraftment
Nishida *et al.* 2019	Open-label case series	3	Nil	Single colonoscopic infusion proximal to the pouch [~150–200 g freshly obtained donor stool dissolved in 500 ml saline and filtered] FMT prepared from healthy adult relatives	Standard bowel preparation with polyethylene glycol solution prior to FMT	45 [24–52]	66.6%	PDAI: 12 ± 2.45	Once-only FMT	Patients with pouchitis defined as current PDAI ≥7 Exclusion criteria: intestinal CMV infection, pregnancy, current serious disease, participating in other studies

Table 1. Continued

Reference	Study type	No. of subjects	Control/ comparator	Treatment protocol & FMT preparation	Bowel cleansing	Age [years] median [range]/ mean [SD]	Gender [% male]	Average disease severity indices at baseline	Treatment duration	Relevant study characteristics
Kousgaard *et al.* 2020	Prospective, open-label, single-centre, cohort pilot study	9	Nil	Once daily enema for 14 consecutive days [100ml suspended faecal material per enema bottle]; first dose under physician supervision and remainder self-administered FMT prepared from 5 different faecal donors in total [2–3 enema bottles from each donor] but single donor to patient	NR	51.5 ± 13.9	33.3%	PDAI: 8.6 ± 3.4 cPDAI: 3.7 ± 0.7 ePDAI: 3.2 ± 2 hPDAI: 1.7 ± 1.4	Once-daily enema for 14 consecutive days	Adult patients with chronic pouchitis defined as ≥3 episodes of pouchitis based on clinical symptoms, endoscopic and histological inflammation within the past 12 months Inclusion criteria: ≥18 years of age with IPAA >1 year, cPDAI ≥3, treatment with ciprofloxacin and/ or metronidazole for pouchitis [≥1 treatment during the past year] Exclusion criteria: immunosuppression, planned or current pregnancy, breastfeeding, enteric bacterial infection
Karjalainen *et al.* 2021	Single-centre, double-blinded, parallel group trial	26 FMT: 13 placebo: 13	Autologous FMT	Two faecal transplantations on Weeks 0 and 4, first through pouchoscopy and second via trans-anal catheter [170 ml of faecal transplant containing 30 g of stool infused into the afferent limb] FMT group: frozen donor faecal material Placebo group: autologous FMT prepared from own fresh stool FMT prepared from single, healthy, screened donor	Bowel preparation not done prior to FMT	FMT: 42.7 ± 10.2 Placebo: 45.5 ± 11.7	FMT: 53.8% Placebo: 61.5%	FMT PDAI: 5.6 ± 2.7 Placebo PDAI: 5.1 ± 3.3	Two faecal transplantations into the pouch on Weeks 0 and 4	Chronic pouchitis defined as duration of symptoms longer than 4 weeks Frequent use of Abx defined as need for Abx treatment more than once within 1 year Inclusion criteria: IPAA for UC, endoscopically and histologically diagnosed pouchitis within 6 months before FMT use, frequent/ continuous use of Abx for chronic pouchitis Exclusion criteria: <18 or >75 years of age, immunosuppressive/ immunomodulatory medication, pregnancy, suspicion, or established Crohn's disease Abx discontinued at least 36 h before first FMT, probiotics permitted to continue

NR, not recorded; FMT, faecal microbiota transplantation; PDAI, Pouchitis Disease Activity Index; cPDAI, clinical Pouchitis Disease Activity Index; ePDAI, endoscopic Pouchitis Disease Activity Index; hPDAI, histological Pouchitis Disease Activity Index; mPDAI, modified Pouchitis Disease Activity Index; Abx, antibiotics; NSAID, non-steroidal anti-inflammatory drugs; FCP, faecal calprotectin; OLE, open-label extension; eFMT, endoscopic FMT; oFMT, oral FMT; ADP, antibiotic-dependent pouchitis; ARP, antibiotic-refractory pouchitis; CMV, cytomegalovirus; IPAA, ileal pouch-anal anastomosis.

Table 2. Characteristics of included studies and clinical outcomes

Reference	Time since RPC [median/ mean, years]	Previous advanced therapy	Pre-FMT treatment	Primary outcome definition	Clinical response [reduction in PDAI 3]	Clinical remission [reduction in PDAI ≥3 and total score <7]	Clinical response [not specified]	PDAI score post-FMT	ePDAI post-FMT	hPDAI post-FMT	Quality of life assessment	Adverse events	Follow-up
Landy *et al.* 2015	10 [4–22]	NR	Recipient treated with PPI night before and morning of FMT treatment	Clinical end-points number of patients in clinical remission [cPDAI = 0/ PDAI ≤ 7] or clinical response [reduction in PDAI ≥3] 4 weeks after FMT and number demonstrating changes in pouch faecal bacterial sensitivities	4weeks: 2/8	4weeks: 0/8	NR	4weeks: 10.5 [9-14]	NR	NR	CGQoL Pre-FMT: 0.41 [0.2-0.7] 4weeks: 0.47 [0.2-0.7]	Nausea: 3/8 Vomiting: 1/8 Bloating: 2/8 Fever: 1/8 All transient [<24 h]	4 weeks
Stallmach *et al.* 2016	3 [1.3–8]	NR	NR	NR	5/5	4/5	NR	3.8 ± 1.94	NR	NR	NR	Mild transient fever and moderate CRP increase: 1/5	3 months [$n = 3$] 4 months [$n = 1$] 12 months [$n = 1$]
El-Nachef *et al.* 2017	13 [3–27]	NR	NR	Composite safety endpoint [NIH grade ≥2 adverse event or escalation of therapy] at Week 4	7/11	6/11	NR	5.4 ± 3	Post-FMT: 1.8 ± 1.99	Post-FMT: 1.6 ± 1.28	NR	0: NIH grade ≥2 adverse event or escalation of therapy	NR
Steube *et al.* 2017	NR	NR	NR	NR	NR	NR	Improvement: 7/16 No improvement: 5/16 Clinical deterioration: 4/16	NR	NR	NR	NR	NR	NR
Selvig *et al.* 2019	6.5 [IQR 4–13]	Biologics [17%]	7/18 pretreated with rifaximin	Clinical improvement in pouchitis at 4 weeks post FMT assessed by patient surveys	1/11	1/11	Symptom sub-score Pre-FMT: 1.94 ± 1.08 Post-FMT: 1.72 ± 1.33	Median [IQR] 6 [5.5–7.5] $n = 11$	4weeks: 3.36 ± 1.55	4weeks: 1.36 ± 0.88	NR	SBO [not related to FMT]: 1 Abdominal pain/discomfort: 4 Flatulence: 4 Bloating/ cramping: 3 Fatigue: 3 Nausea: 2	12 months

Table 2. Continued

Reference	Time since RPC [median/ mean, years]	Previous advanced therapy	Pre-FMT treatment	Primary outcome definition	Clinical response [reduction in PDAI 3]	Clinical remission [reduction in PDAI ≥3 and total score <7]	Clinical response [not specified]	PDAI score post-FMT	ePDAI post-FMT	hPDAI post-FMT	Quality of life assessment	Adverse events	Follow-up
Herfarth *et al.* 2019	5 [1–10]	NR	Abx stopped at least 24h before FMT	Safety of the combined eFMT and oFMT approach	NR	NR	1/6 clinical response and remission [off Abx at Week 16]	NR	NR	NR	NR	Nil	16 weeks
Nishida *et al.* 2019	8 [4.5–9]	Biologics	NR	Clinical response at 8 weeks after FMT	1/3	0/3	NR	9.3 ± 3.3	NR	NR	NR	Nil	8 weeks
Kousgaard *et al.* 2020	17.6 ± 6.7	NR	Ciprofloxacin and/or metronidazole stopped 7 days prior to FMT	Significant reduction of the PDAI score at 30 days follow-up compared with baseline at inclusion or PDAI <7	30-day follow-up: 4/9	6-month follow-up: 3/9	NR	30-day follow-up: PDAI: 5.2 ± 4.5 cPDAI: 14 days: 1.6 ± 1.7 30 days: 2 ± 1.7 6 months: 0.7 ± 0.6	4weeks: 2.2 ± 1.8	4weeks: 1 ± 1.2	NR	Minor adverse events [abdominal pain, nausea, fatigue, bloating]: 7/9	6 months
Karjalainen *et al.* 2021	FMT: 9.8 [1.6–21.9] Placebo: 8.3 [3–26.6]	NR	Abx stopped at least 36h before first FMT Loperamide [2 mg] half an hour before each FMT	Remission defined as a PDAI score <7 and no Abx treatment of pouchitis during follow-up period	NR	NR	FMT: 9/13 relapsed during 52-week follow-up Placebo: 8/13 relapsed during 52-week follow-up	52 weeks FMT PDAI: 4.8 ± 2.7 Placebo PDAI: 5.5 ± 3.1	NR	NR	15days from Baseline: FMT: 20.3 ± 3.1 Placebo: 20.3 ± 4 26-weeks FMT: 22.7 ± 2.7 Placebo: 20 ± 2.4	FMT [3/13]: fever, abdominal pain, faecal urgency, nausea Placebo [1/13]: fever	52 weeks

NR, not recorded; NIH: National Institute of Health; FMT, faecal microbiota transplantation; PDAI, Pouchitis Disease Activity Index; cPDAI, clinical Pouchitis Disease Activity Index; ePDAI, endoscopic Pouchitis Disease Activity Index; hPDAI, histological Pouchitis Disease Activity Index; Abx, antibiotics; CGQoL, Cleveland Global Quality of Life; PPI, proton pump inhibitor; SBO, small bowel obstruction; RPC, restorative proctocolectomy; CRP, C-reactive protein; eFMT, endoscopic FMT; oFMT, oral FMT; IQR, interquartile range.£

the other trial, autologous FMT [patient's own fresh stool] was transplanted in the placebo arm.[29]

3.4. Donor characteristics

FMT donor information was provided in all nine studies.[29,37–44] These ranged from a single donor in three studies[29,40,41] to two,[43] five,[37] 13,[38] and number not specified in the remainder.[39,42,44] Gender-specific breakdown of donors was not provided in our studies and, due to insufficient information, we were unable to determine a median age.

In one study, donor stool samples were derived from screened healthy relatives.[39] Three studies[29,42,43] used healthy unrelated donors, and one used a combination of both related and unrelated donors for their FMT preparation.[44] This information was not clearly stated in the remaining studies.[37,38,40,41] In six studies, FMT from a single donor only was used as treatment.[29,37,38,40,41,43] Follow-up of patients in our included studies ranged from 4 weeks to 12 months. Only one patient was lost to follow-up [Table 2].

3.5. Clinical outcomes

As outlined in Table 2 the primary outcome differed between our studies. Some focused on composite safety endpoints, clinical improvement/response, and others were more objective, taking into account changes in disease severity indices [PDAI score].

3.5.1. Efficacy of FMT: meta-analysis

There were two RCTs[29,40] that compared FMT with a non-FMT intervention, of which one RCT did not demonstrate clinical response in either of the arms.[40] The pooled odds ratio [OR] of treatment success was 0.52 against placebo [95% CI 0.10-2.58] [Figure 2].As only one study[29] reported a positive outcome in either of the arms, heterogeneity was not calculated.

The mean pooled overall response [as variably defined by individual studies] for FMT in chronic pouchitis, based on all the included nine studies,[29,37–44] was 38% [95% CI 23%-54%] with likely moderate heterogeneity [I^2 = 42%] [Figure 3].

3.5.2. Clinical response

Clinical response following FMT treatment, based on a strict definition as a reduction in PDAI score of 3, was reported in a total of 42.6% [20/47; CI 20.1%-71.7%] patients from six studies.[37–39,41,43,44] In the studies by Landy *et al.*[44] and Kousgaard *et al.*,[37] 25% [2/8] and 44.4% [4/9] of participants achieved clinical response at 4 weeks, respectively. However, only 9% responded clinically in the study by Selvig *et al.*[38]

In the study by Stallmach *et al.*,[43] all participants [n = 5] achieved a clinical response with mean PDAI scores reducing from 10.8 ± 1.94 at baseline to 3.8 ± 1.94 post-FMT. In the open-label study by Kousgaard *et al.*,[37] mean PDAI scores reduced from 8.6 ± 3.4 [baseline] to 5.2 ± 4.5 [30-day follow-up].

3.5.3. Clinical remission

Clinical remission was defined as a reduction in PDAI score of ≥3 with a total PDAI score of <7. This outcome was reported in six of the nine studies[37–39,41,43,44] and was estimated as 29.8% of the total cohort. High rates of remission were reported by Stallmach *et al.*[43] and El-Nachef *et al.*[41] [80% and 55%, respectively]. However, Landy *et al.*[44] and Nishida *et al.*[39] had no cases of clinical remission.

In the recent placebo-controlled trial of FMT, at 52 weeks, nine of 13 [69.2%] patients in the treatment arm and eight of 13 [61.5%] in the placebo arm experienced relapse of pouchitis.[29] This was defined by a PDAI score ≥7 or antibiotic treatment to control symptoms of pouchitis. In the treatment arm, interestingly, five of nine patients relapsed before the administration of a second FMT but none in the placebo group during this period.

Moreover, the use of continuous antibacterial therapy prior to FMT was associated with a significantly greater hazard for relapse following FMT treatment compared with placebo (hazard ratio [HR]: 13.08; 95% CI 1.47-116.6).[29]

3.6. Endoscopic outcomes

Three of the nine studies[37,38,41] reported endoscopic sub-scores [ePDAI] pre- and post-FMT treatment. The endoscopic element of the scoring system ranges from 0 to 6 points and includes findings of pouch oedema [1], granularity [1], friability [1], loss of vascular pattern [1], mucous exudates [1], and ulcerations [1]. These scores were taken at baseline and 1 month after FMT treatment. Mean ePDAI at baseline was 3.5 and this reduced to 2.5 post-FMT.

3.7. Histological outcomes

Three studies[37,38,41] reported histological sub-scores [hPDAI] before and after FMT transplantation. This sub-component ranges from 0 to 6 points, based on acute histological inflammation and scored as follows: polymorphonuclear leukocyte infiltration [none—0; mild—1; moderate and crypt abscess—2; severe and crypt abscess—3] and ulceration per low field [mean] [none—0; <25%—1; 25% to 50%—2; 50%—3]. Mean hPDAI score at baseline was 1.8 reducing to 1.3 at 30-day follow-up.

3.8. Inflammatory biomarkers

Table 3 shows levels of inflammatory biomarkers and patient-reported outcomes in patients treated with FMT for chronic pouchitis.

Faecal calprotectin [FCP] levels were reported in five studies[29,37,38,42,43] and generally showed a downward trend following FMT. Mean levels reported in Kousgaard *et al.*[37] reduced from a baseline of 732 µg/g to 152 µg/g. Median levels reported in Stallmach *et al.*[43] reduced from a baseline of 566 [units not provided] to 47 [units not provided]. Steube *et al.*[42] and Selvig *et al.*[38] showed a similar trend: from 536 and 344 to 150 and 240, respectively. No significant differences were reported in the FCP levels at any time point [4, 12, 26, and 52 weeks] between the FMT and placebo groups in Karjalainen *et al.*[29] Selvig *et al.*[38] also reported a moderate median reduction in erythrocyte sedimentation rate [ESR] levels from 27 mm/h to 23 mm/h.

3.9. Patient-reported outcomes

Stool frequency was reported in four studies.[29,37,38,41] Selvig *et al.*[38] and Kousgaard *et al.*[37] reported modest reductions from 9.25/day and 11.2/day to 7.25/day and 9.7/day, respectively. Abdominal pain scores [using a 10-point scale] and rectal bleeding were also reported by Selvig *et al.*[38] Abdominal pain scores reduced from 4.5 to 3 and the number of participants with rectal bleeding reduced from 4/18 to 2/18 after

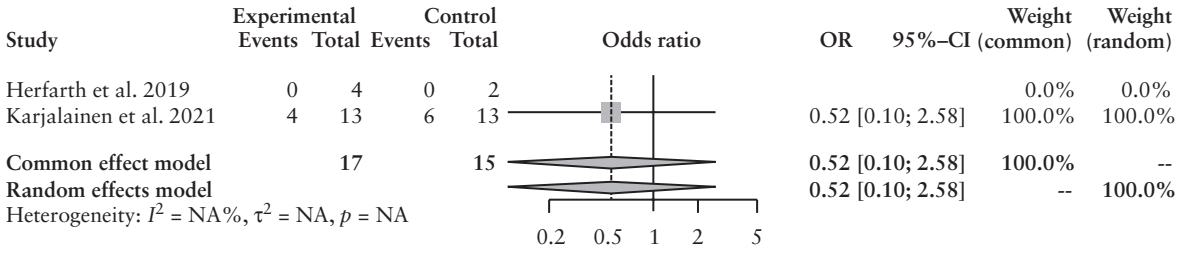

Figure 2. Randomised, controlled trial [RCT] forest plot.

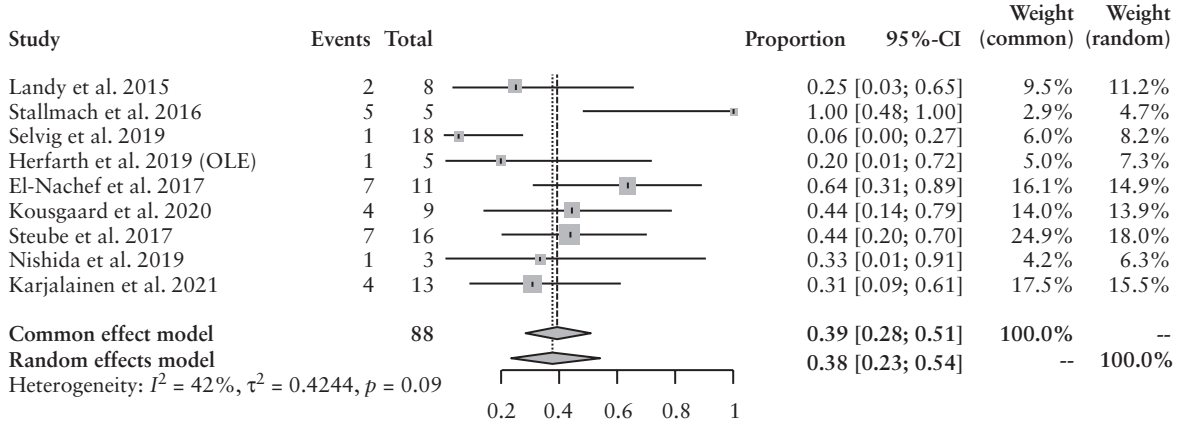

Figure 3. Forest plot of mean pooled overall response to faecal microbiota transplantation [FMT] in chronic pouchitis.

treatment. Improvement in bleeding per rectum was also reported by El-Nachef *et al.*[41] No significant differences were reported between the FMT and placebo arms for stool frequency, rectal bleeding, and faecal urgency in Karjalainen *et al.*[29]

3.10. Adverse events following FMT

The occurrence of adverse events [Table 2] in relation to FMT treatment was documented in all but one of the included studies. In the RCT,[29] 3 of 13 [23.1%] patients in the FMT arm reported minor, self-limiting effects within 1 week after treatment and included fever, abdominal pain, nausea, and faecal urgency. In the placebo arm, one patient reported fever. No major adverse events or deaths were reported in any of the other included studies, and FMT was considered to have good short- and long-term safety profiles and was tolerated well.

3.11. Microbiota analysis

Tables 4 and 5 provide details of changes in microbial diversity and taxonomy following treatment with FMT.

3.11.1. Changes in microbial diversity

Four studies,[37,39,42,44] reported on changes in microbial diversity in patients following FMT. The results were inconsistent, with two studies[39,44] reporting no overall changes and the other two studies[37,42] demonstrating differences.

In the study by Landy *et al.*,[44] prior to FMT, patient stool samples were characterised by low bacterial richness and diversity as measured by various indices [Shannon, inverse Simpson, and Chao 1 estimate] compared with donor stool. FMT infusion resulted in no overall changes in bacterial richness or diversity of either the faecal or the mucosal microbiota. However, non-metric multidimensional scaling [NMDS] analysis did suggest a shift in the microbiota composition towards a greater similarity to donor stool.

Similarly, Nishida *et al.*[39] reported no significant change in either the Shannon diversity index or the Bray–Curtis dissimilarity index at 4 and 8 weeks after FMT. Of note, both studies used a once-only FMT regimen and neither study reported a significant beneficial clinical response.

In the pilot study by Kousgaard *et al.*,[37] baseline patient samples had significantly lower microbial diversity and richness compared with donor stool. Following FMT treatment, there was a significantly increased microbial richness and marginally increased diversity at 30-day follow-up, with a transition towards donor microbial composition. This effect was retained in two out of the three patients completing 6-month follow-up.

Steube *et al.*[42] also reported a significant increase in bacterial diversity in clinical responders versus a lower microbial diversity in patients with chronic antibiotic-resistant pouchitis. Importantly, both studies used regimens of multiple dose FMT. Clinical response was seen in 44% and clinical remission in 33.3% at 6 months, in Steube *et al.*[42] and Kousgaard *et al.*,[37] respectively. Interestingly, before FMT the average microbial richness and diversity were lower in samples from relapsed patients, compared with those from patients in clinical remission.[37]

3.11.2. Taxonomic changes

Four studies[37,38,43,44] detailed microbial taxonomic changes following FMT therapy through analysis of 16S ribosomal ribonucleic acid [rRNA] gene profiles. Stallmach *et al.*[43] found

Table 3. Inflammatory biomarkers and patient-reported outcomes in patients treated with FMT for chronic pouchitis

Reference	FCP	CRP	ESR	Abdominal pain	Stool frequency	Rectal bleeding	Urgency	Subjective GI symptom improvement
Landy *et al.* 2015	NR	NR	NR	NR	NR	NR	NR	NR
Stallmach *et al.* 2016	[*n* = 3] Pre-FMT: 566 [479–849] Post-FMT: 47 [<15–150]	NR	NR	NR	NR	NR	NR	NR
El-Nachef *et al.* 2017	NR	NR	NR	Decrease: 9/11	Decrease: 6/11	Improvement: 2/3	Improvement: 3/11	Yes: 6/11
Steube *et al.* 2017	Responders: 536 [116–3000] mg/kg stool to 150 [191—1409] mg/kg Non-responders: 1005 [529–1579] mg/kg to 1450 [1221–1778] mg/kg	NR	NR	NR	NR	NR	NR	NR
Selvig *et al.* 2019	[*n* = 4] Pre-FMT median [IQR]: 344 [192–489] Post-FMT median [IQR]: 240 [152–468]	[*n* = 9] Pre-FMT median [IQR]: 5.1 [5–7.4] Post-FMT median [IQR]: 8.8 [5–9.4]	[*n* = 9] Pre-FMT median [IQR]: 27 [5–33] Post-FMT median [IQR]: 23 [8–40]	Pre-FMT median: 4.5 [2–5.75] 4 weeks post-FMT median: 3 [1.25–4] [10-point scale]	Pre-FMT median: 9.25 [6.6–14]/ day 4 weeks post-FMT median: 7.25 [6–10]/ day	Pre-FMT: 4 [22%] 4 weeks post-FMT: 2 [11%]	Pre-FMT median [IQR]: 1 [1–2] 4 weeks post-FMT median [IQR]: 1 [1–1] [0–2 scale]	Yes: 9/18
Herfarth *et al.* 2019	?	NR	NR	NR	NR	NR	NR	NR
Nishida *et al.* 2019	NR	NR	NR	NR	NR	NR	NR	NR
Kousgaard *et al.* 2020	Inclusion: 732.1 µg/g ± 1019.1 30-day follow-up: 152 µg/g ± 235.9	Inclusion: 2.9 mg/L ± 2.2 30-day follow-up: 8.5 mg/L ± 11.9	NR	NR	Inclusion: 11.2 ± 4.9 14 days: 10.1 ± 2.9 30 days: 10.4 ± 3.2 6months: 9.7 ± 3.5	NR	NR	NR
Karjalainen *et al.* 2021	FCP change 4 weeks FMT: -17 [-236–144] Placebo: -23 [-166–100] 12 weeks FMT: 158 [-266–1054] Placebo: 112 [-521–584] 26 weeks FMT: 200 [-113–450] Placebo: 60 [-374–380] 52 weeks FMT: 120 [-235–755] Placebo: 236 [-588–782]	NR	NR	NR	Median [0–2 scale] Baseline: FMT: 0 Placebo: 0 4 weeks FMT: 1 Placebo: 0 12-weeks FMT: 0 Placebo: 0 26 weeks FMT: 0 Placebo: 0 52 weeks FMT: 0 Placebo: 1	Baseline: FMT: 1 Placebo: 2 4 weeks FMT: 1 Placebo: 2 12 weeks FMT: 0 Placebo: 2 26 weeks FMT: 1 Placebo: 3 52 weeks FMT: 2 Placebo: 3	Median [0–-2 scale] Baseline: FMT: 0 Placebo: 0 weeks FMT: 0 Placebo: 0 12 weeks FMT: 1 Placebo: 0 26 weeks FMT: 0 Placebo: 0 weeks FMT: 0 Placebo: 1	4 weeks FMT: 3 Placebo: 3 12 weeks FMT: 2 Placebo: 5 26 weeks FMT: 1 Placebo: 0 52 weeks FMT: 0 Placebo: 1

NR, not recorded; FMT, faecal microbiota transplantation; FCP, faecal calprotectin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; GI, gastrointestinal.

a transition in the stool community of clinical responders, to a composition like that of unrelated donors.

Kousgaard *et al.*[37] reported that patient microbial diversity and richness were significantly lower than those of donor stool before FMT, with members of Ruminococcus, Bacteroides, and Firmicutes more prevalent in donor material than in patient samples. This reversed after FMT treatment, with Bacteroides mainly responsible for the shift in microbial composition towards the donor's.

Bacterial communities found to be significantly enriched in pre-FMT samples in Selvig *et al.*[38] included Erysipelotrichaceae, Lachnoclostridium, and Flavonifractor, compared with donor stool. These changes were consistent between both the probiotic and non-probiotic groups. However, no consistent change in bacterial taxa was observed following FMT treatment.

In the pilot study by Landy *et al.*[44] post-FMT stool samples showed a reduction in proportional abundance of *Escherichia coli/Shigella* spp. and *Ruminococcus gnavus,* with a relative increase in abundance of *Sutterella stercoricanis*, *Dorea longicatena,* and *Faecalibacterium prauznitzii*. Although these general trends were observed, none of these was significant and no consistent compositional change or engraftment was reported.

3.12. Quality of life

In addition to clinical efficacy and safety profile, quality of life following any intervention remains an important consideration [Table 2]. We found mixed results following FMT treatment.

Landy et al.[44] reported no significant changes in Cleveland global quality of life [CGQoL] scores before and after FMT therapy. However, in the RCT by Karjalainen *et al.*,[29] although the treatment was not considered effective clinically in treating patients with chronic pouchitis, the FMT group reported significant improvement in QoL indicators at 26 weeks compared with the placebo arm [$p = 0.036$].

4. Discussion

Interest in the therapeutic potential of correcting dysbiotic microbiota by FMT, to treat both acute and chronic disorders, has been growing in recent years. Several small studies have investigated the role of FMT in the treatment of chronic pouchitis. Although the pathogenesis remains unclear, dysbiosis of the gut microbiota has been proposed. Altered anatomy as a result of ileal pouch formation, promoting faecal stasis, abnormal immune response, and a pro-inflammatory environment, has been suggested.[45]

We conducted a systematic review and meta-analysis to examine existing evidence on the clinical efficacy, safety profile, and microbial changes associated with FMT use as a potential treatment option for patients with chronic pouchitis.

Two recent reviews on managing chronic pouchitis with FMT have been published.[27,28] Cold *et al.*[27] included nine studies, with one RCT and a total of 65 patients reporting a total clinical response after FMT in 31.8% of evaluated patients, and clinical remission in 22.7%. They concluded that although FMT showed promising results, its effects on symptom control were limited. The review of Kayal *et al.*,[28] including only four studies [$n = 38$], similarly deemed FMT to be safe but clinically limited.

We build on this existing knowledge base by providing an up-to-date review, and include nine studies with a total of 103 patients, including the latest RCT.[29] In agreement with previous literature, the evidence suggests that FMT is safe and well tolerated, with only minor adverse events reported. No infectious complications or hospitalisations linked to FMT treatment were observed. This was seen across all studies, including the two placebo-controlled trials with a 16- and 52-week follow-up period, respectively.[29,40] We estimated a clinical response rate of 42.6% with a remission rate of 29.8%. Moreover, limited evidence suggests an improvement in quality-of-life parameters.[29] However, these data are limited by several factors, including study design and between-study heterogeneity.

Presently a lack of high-quality evidence means that although FMT may be an option in chronic pouchitis, the true treatment effects and safety profile remain unclear. Some studies noted objective symptomatic improvement using disease activity indices, and others reported reduction in sensitive biomarkers of gut inflammation, such as FCP levels, following treatment. However, placebo-controlled data regarding the efficacy of FMT for chronic pouchitis are currently limited. The double-blind, proof-of-concept study in patients with antibiotic-dependent pouchitis, receiving a single endoscopic FMT followed by daily oral encapsulated FMT for 2 weeks, was ended prematurely due to failure of response.[40] High rates of pouchitis recurrence and low rates of FMT engraftment were reported. Clinical response and remission were achieved in only one of six patients, with microbiome analysis demonstrating successful donor engraftment in this case.

FMT or placebo was administered through pouchoscopy [Week 0] and a repeat through transanal catheter [Week 4] in the study by Karjalainen *et al.*[29] At 52 weeks, nine of 13 patients in the FMT arm compared with eight of 13 in the placebo group experienced relapse of pouchitis. Moreover, five of nine relapses in the FMT group compared with none in the placebo occurred prior to the administration of the second FMT. This was an interesting observation and thought to be due either to an adverse host response to donor microbiota or to a clinical effect of autologous FMT. Analysis of the gut microbiota and results of the associated microbial changes are awaited. This will help to determine whether the poor response rate correlated with failure of donor microbiota engraftment.

In an open-label study of nine patients with chronic pouchitis, once-daily FMT enemas were administered for 14 consecutive days.[37] Unlike the two trials where FMT was prepared from a single, healthy, screened donor, in this study FMT was prepared from multiple donors. Clinical response was achieved in four of nine patients at 30-day follow-up and clinical remission in three of nine at 6 months.

Stallmach *et al.*[43] prepared FMT from two, unrelated, healthy donors and administered multiple doses to patients with chronic pouchitis. They reported a clinical response in five of five patients with remission being achieved in four of five. These results suggest that successful donor microbiota engraftment is better achieved with multiple, frequent, faecal transplantations. Moreover, the concept of a 'super-donor' may also be important, as pre-selection of donors, based on characteristics of their microbiota, may have an effect on clinical response. However, optimal donor-stool selection and processing methods, storage, intensity/duration of therapy,

Table 4. Gastro-intestinal tract microbial diversity and profile changes following FMT treatment in patients with chronic pouchitis

Reference	Bioinformatic methodology	Alterations in Abx sensitivity	Stool microbiota content and diversity [pre-FMT]		α + β diversity [after FMT]		Taxonomic changes [after FMT]	
			Patients	Donor	Responders	Non-responders	Responders	Non-responders
Landy *et al.* 2015	16S rRNA gene pyrosequencing and H NMR spectroscopy	4/8: ciprofloxacin-resistant coliforms in stool pre-FMT 3/8: ESBL-coliforms pre-FMT 2/4: coliforms regained sensitivity to ciprofloxacin after FMT treatment	Phylum level: higher proportion of *Proteobacteria* [$p = 0.0047$] compared with donors Family level: significantly lower proportion of obligate anaerobes Ruminococcaceae, Coriobacteriaceae, Porphyromonadaceae, Rikenellaceae, and higher proportion of Enterobacteriaceae and Clostridiaceae Genus level: significantly lower abundances of anaerobes including *Faecalibacterium prausnitzii* and higher proportions of *Escherichia/Shigella* spp. and *Ruminococcus gnavus* Low bacterial richness and diversity compared with donor stool [Shannon & inverse Simpson indices and Chao 1 estimate]	Higher bacterial richness and diversity compared with donor stool	No overall change in bacterial richness or diversity of faecal/mucosal microbiota However, NMDS analysis [Bray–Curtis calculator] indicated shift in both stool and mucosal microbiota with greater similarity to donor stool ANOVA analysis [Yue/Clayton calculator] also suggested greater similarity to donor stool	NR	Reductions in *Escherichia coli/Shigella* spp. and *Ruminococcus gnavus* in patient stool and increase in *Sutterella stercoricanis*, *Dorea longicatena* and *Faecalibacterium prauznitzii* However no significant taxonomic changes in stool Patient biopsy samples: reduction in proportional abundance of *Enterococcus*	NR
Stallmach *et al.* 2016	16S rRNA gene sequencing [V1-V2 regions]	NR	NR	NR	NR	NR	Patients 1 and 3: stool composition similar to that of donor	Patient 2: unique pattern distinct from the microbiome of donor
El-Nachef *et al.* 2017	NR	NR	NR	NR	NR	NR	NR	NR
Steube *et al.* 2017	16S rRNA gene sequencing [V1-V2 regions]	NR	Lower diversity in patients compared with donors [total phylotype number, Shannon diversity and Pielou´s evenness]	Higher diversity compared with pouchitis patients	Significant increase in diversity	NR	NR	NR

Table 4. Continued

Reference	Bioinformatic methodology	Alterations in Abx sensitivity	Stool microbiota content and diversity [pre-FMT]		α + β diversity [after FMT]		Taxonomic changes [after FMT]	
			Patients	Donor	Responders	Non-responders	Responders	Non-responders
Selvig *et al.* 2019	16S rRNA gene sequencing [V4-region]	NR	Pouch control and pouchitis patients stool pre- and post-FMT had significantly lower bacterial diversity [Faith's metric] regardless of rifaximin intake Ruminococcaceae [Flavonifractor] significantly more abundant in pouchitis compared with pouch control Lachnospiraceae, Erysipelotrichaceae, Lachnoclostridium, and Flavonifractor significantly more abundant compared with donor stool	Higher stool bacterial diversity [Faith's metric] compared with patients Members of Ruminococcaceae [for instance *Faecalibacterium*] and Lachnospiraceae [for instance *Agathobacter*] higher in donor stool compared with patients *Faecalibacterium* significantly more abundant in donors compared with pouch control	NR	NR	No consistent change in bacterial taxa Single patient showing clinical response had microbiota composition similar to donor stool	NR
Herfarth *et al.* 2019	Metagenomic 16S rRNA gene sequencing [V4 region]	NR	NR	NR	NR	NR	NR	NR
Nishida *et al.* 2019	PCR and terminal restriction fragment length polymorphism analysis	NR	NR	NR	No significant change in either Shannon diversity index or Bray–Curtis dissimilarity index at 4 and 8 weeks post-FMT	No significant change in either the Shannon diversity index or Bray–Curtis dissimilarity index at 4 and 8 weeks post-FMT	NR	NR
Kousgaard *et al.* 2020	16S rRNA gene sequencing [V4-region]	NR	Significantly lower microbial diversity and richness compared with donor Highly heterogeneic microbial composition Members of Bacteroides, Ruminococcus and Firmicutes genera less abundant compared to donor material	Members of Ruminococcus and Bacteroides more prevalent than in patient samples	Significantly increased richness and marginally increased diversity at 30-day follow-up Significantly higher similarity to donors after FMT—effect retained in 2 out of 3 patients completing 6-month follow up Patients in remission more resilient microbiota as measured by higher community similarity pre- and post-FMT compared with relapsing patients	NR	Highly heterogeneic, some post-FMT samples enriched for members of Bacteroides genera	NR
Karjalainen *et al.* 2021	NR	NR	NR	NR	NR	NR	NR	NR

NR, not recorded; FMT, faecal microbiota transplantation; rRNA, ribosomal ribonucleic acid; V-region, hypervariable region; NMDS, non-metric multidimensional scaling; Abx, antibiotics; PCR, polymerase chain reaction.

Table 5. Summary of the relationship between patients' and donors' microbiota post-FMT in patients with chronic pouchitis

Reference	Donor relationship [after FMT]		Stool metabonomic analysis
	Responders	Non-responders	
Landy *et al.* 2015	Shift in both stool and mucosal microbiota towards a greater resemblance with donor stool but not significant	NR	Significantly higher levels of tyrosine, alanine, formate, phenylalanine, leucine, and histamine compared with donors In donors, significantly higher levels of valerate, uracil, fumarate, and higher levels of acetate and butyrate compared with patients
Stallmach *et al.* 2016	Patients 1 and 3: stool composition similar to that of donor	Patient 2: unique pattern distinct from the microbiome of donor	NR
El-Nachef *et al.* 2017	NR	NR	NR
Steube *et al.* 2017	NR	NR	NR
Selvig *et al.* 2019	NR	NR	NR
Herfarth *et al.* 2019	NR	NR	NR
Nishida et al. 2019	NR	NR	NR
Kousgaard et al. 2020	Significantly higher similarity to donors after FMT with the effect retained in 2 out of 3 patients completing 6-month follow up	NR	NR
Karjalainen et al. 2021	NR	NR	NR

NR, not recorded; FMT, faecal microbiota transplantation.

and FMT administration protocols all require further assessment in large, well-designed trials to answer many unresolved issues. Moreover, future studies assessing successful donor engraftment will potentially allow for identification of specific microbial communities associated with clinical response.

FMT appears to be safe and well tolerated in chronic pouchitis patients. Only minor, self-limiting, adverse events were noted, and this is in keeping with literature from other conditions. Thorough screening of donor material by biobanks and microbiome treatment centres is essential, and studies investigating long-term safety profiles are warranted.

Microbiota analysis was assessed using 16S rRNA gene sequencing in some studies. Lower microbial richness and diversity was noted in patients compared with healthy donors. Whether this observation is a cause or secondary consequence of the disease remains unknown. This is also complicated further by chronic pouchitis patients receiving multiple courses of antibiotics throughout the course of their illness, resulting in drastic changes to host gut flora.

Interestingly, some studies reported an increase in microbial diversity and a shift towards donor microbiota after FMT treatment, correlating with beneficial clinical effect. More specifically, members of Bacteroides, Ruminococcus and Firmicutes taxa, SCFA-producing and generally considered as 'healthy', were less abundant in pouchitis patients compared with donor material.

At the genus level, significantly lower levels of anaerobes including *Faecalibacterium prausnitzii*, and higher proportions of *Escherichia/Shigella* spp. and *Ruminococcus gnavus,* were found in patients. Following FMT treatment, reductions in *Escherichia coli/Shigella* spp. and *Ruminococcus gnavus,* and increases in *Faecalibacterium prauznitzii* [may confer anti-inflammatory properties] were demonstrated.

However, conclusions drawn from this review need to be interpreted with caution. Although we aim to bring all published data together to assess the effect of FMT in treating chronic pouchitis, these studies are mainly observational cohort studies/case series with small patient numbers. This makes it difficult to draw robust conclusions on the tolerability of FMT. Moreover, varying definitions and interpretations of chronic pouchitis and clinical remission between studies add further complexity.

Like most clinical studies with FMT across various indications, the FMT preparation and administration protocols are highly variable in studies exploring its use in the treatment of pouchitis. Attempting to identify possible optimum protocols towards designing a Phase 2 RCT based on outcomes from these studies is hindered by being significantly underpowered and are likely to lead to unreliable conclusions. However, based on data extrapolated from better powered UC RCTs[46] it can be deduced that intensive treatment regimens [for example at least once a week treatment for at least 8 weeks for induction] as well as direct administration of FMT into the pouch via an enema or pouchoscopy may be more likely to increase chances of remission. These protocols must nevertheless be balanced against patient acceptability and tolerability which highlights the importance of patient collaborations in research design such as seen through patient and public involvement and engagement [PPIE].'

Additionally, there were differences in assessing pouchitis disease activity prior to and after FMT treatment, using varying time points and methods. Not all our included

studies assessed patients using the full 18-point composite PDAI scale. The use of modified versions, including mPDAI and cPDAI, means that pooling results and estimating true effect becomes challenging. Therefore, standardising definitions of 'chronic pouchitis' [symptoms >4 weeks despite antibiotics], 'clinical response' [reduction in PDAI score of ≥3], 'clinical remission' [reduction in PDAI score of ≥3 and total PDAI score <7], and using the full PDAI or pouchitis activity score [PAS], will allow improved data synthesis. In addition, grading pouch inflammation [mild, moderate, and severe] is necessary, as FMT may only be effective in certain patients.

Differences also existed in the preparation, delivery [upper GI vs colonoscopically], and duration of FMT treatment given between our studies, as well as the use of single versus multiple faecal donors who may or may not have been related to the patient. Interpretation is further complicated by permitting concurrent therapies in some studies, pre-treating patients with antibiotics prior to FMT, and the use of bowel preparation. Large, well-designed, clinical trials are needed to answer many of these unresolved issues, including consensus on methodology of obtaining, storing, preparing, and delivering FMT to patients with chronic pouchitis. Additionally, longer follow-up using objective assessment tools will allow a more comprehensive assessment of clinical response, relapse/remission rates, adverse effects, and safety profile of faecal transplantation.

In conclusion, meta-analysis of the best available evidence for FMT in the treatment of chronic pouchitis is sparse, which limits any recommendations being made for its use in clinical practice. Present evidence from mainly low-quality studies suggests a variable clinical response and remission rate, but the treatment is well tolerated with a good safety profile. Well-designed, robust, and rigorously conducted RCTs are needed to answer many unresolved issues regarding FMT efficacy, including optimal delivery methods and duration of treatment and the identification of specific donor microbial characteristics associated with clinical response and remission.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Study concept and design: SZ, MNQ, ADB. Acquisition of data: SZ, MNQ, EP, PB, AYYM. Analysis and interpretation of data: AYYM, MEE, MNQ. Drafting of manuscript: SZ, AA. Critical revision of manuscript: AA, THI, MNQ, ADB. Final approval: all authors.

Data Availability

All data relevant to this study are included in the article. Additional data are available on request from the corresponding author.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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