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Adverse events in Faecal Microbiota Transplant (FMT) a review of the literature

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Adverse events in Faecal Microbiota Transplant (FMT) a review of the literature

Running title: Adverse events in faecal transplant.

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Background

Faecal microbiota transplant (FMT) is the infusion of donor faeces into the gut aiming to improve microbial diversity. The procedure has gained significant interest recently in the treatment of recurrent *Clostridium difficile* infection (CDI). The literature is currently dominated by small case series and isolated case reports. There is no standardisation of methods and recording of outcomes.

Aim

The aim of this review is to present the adverse events that have been associated with the use of FMT as reported in the English literature to date.

Methods

A database search of Medline and Embase identified publications where FMT has been administered. Review articles were excluded. 109 publications were identified that describing the use of FMT in 1555 individuals.

Findings

Other than three small randomised controlled studies, the data consisted of small series and case reports. CDI was the most common indication for FMT (n=1190) with the majority of the remaining cases receiving FMT for inflammatory bowel disease. Its use had also been applied to irritable bowel syndrome, metabolic syndrome and constipation in small numbers.

Adverse events appear to be uncommon, often mild and self-limiting; however serious adverse events including bacteraemia, perforations and death have been reported.

Conclusion

We find the vast majority of adverse events to be mild, self-limiting and gastrointestinal in nature. In some a credible association is not established, due to the lack of controlled data. There is a need for standardised, randomised controlled trials both to qualify and quantify the risks associated with FMT.

Keywords: Faecal microbiota transplant, complications, adverse events, *Clostridium difficile* infection, inflammatory bowel disease.

Adverse events in Faecal Microbiota Transplant (FMT) a review of the literature

Background

The recurrence rate of a conventionally treated first episode of *Clostridium difficile* infection (CDI), with vancomycin or metronidazole is up to 30%. [1,2] Should relapse occur the risk of further recurrence then rises to 40-50%. [3] In addition CDI has increased in both incidence and severity globally. [4,5]

The suboptimal nature of CDI management has driven the search for alternative therapies. This includes the licensing of the macrolide fidaxomicin, found in phase 3 clinical trials to be non-inferior to vancomycin for acute diarrhea but with a 45% relative reduction in recurrence rates, possibly due to less disruption of the intestinal microbiome.[5] Faecal microbiota transplant (FMT) that is, the infusion of donor stool into the gut with the aim of improving microbial diversity, has also been the subject of significant interest in recent years. FMT has successfully been used in the treatment of recurrent *Clostridium difficile* infection (CDI). [1,2]

Faecal microbiota transplant was first described in 1958 as a treatment of "Staphylococcal pseudomembranous enterocolitis". [6] In the last 5 years there has been an explosion of interest (Figure 1), and it has become an accepted treatment option for CDI. There is also interest in the application of FMT in a variety of other conditions including inflammatory bowel disease. [7]

The literature is currently dominated by small case series and isolated case reports. There is no standardisation of methods and recording of outcomes. There has only been one randomised control trial of FMT in the treatment of CDI to date [8] finding FMT superior to vancomycin in efficacy. The emergent body of published evidence finds FMT efficacious with low rates of adverse events [4,7] but these are as yet to be adequately quantified. The aim of this review is to present the adverse events as reported in the English literature to date.

Materials and Methods

Medline and Embase were individually searched using the terms f(a)ecal transplant, f(a)ecal transplantation, f(a)eces transplant, f(a)eces transplantation, f(a)ecal bacteriotherapy, f(a)ecal microbiota transplant, f(a)ecal microbiota transplantation, f(a)ecal microbiota transplanted, f(a)ecal bacteria therapy, stool infusion, stool infused, f(a)eces infused, f(a)eces infusion, f(a)ecal infusion, f(a)ecal infused, f(a)eces within 2 words of infusion or infused, f(a)eces enema, f(a)ecal enema (Figure 2). This yielded 5579 citations for which the abstracts and keywords were searched for terms pertaining to faecal transplant. After duplicates were removed 383 publications relevant to faecal microbiota FMT were identified. Papers and abstracts that described first-hand experience of the use of faecal transplant were identified for inclusion, and review and discussion articles were excluded. After further removal of papers which essentially described previously published cohorts of cases, 109 publications were identified that described the use and outcomes of FMT. Three further publications were identified from trawling bibliographies. All published papers were obtained in full.

Results

The 109 publications described the use of FMT in 1555 patients. This included individual cases, uncontrolled series and three randomised controlled trials. For 1190 individuals the indication was given as *Clostridium difficile* infection (Table I).

Randomised Control Trials

There have been three published RCTs using FMT to date. [8–10] A double blinded RCT assessing FMT as an intervention for metabolic syndrome [9] randomised patients to duodenal infusion of autologous faeces (n=9) or donor faeces (n=9) and observed no adverse events in either arm. A trial in Ulcerative Colitis (UC) randomised patients to receive donor faeces (n=27) or placebo (water) (n=26) as 50ml retention enemas once weekly for 6 weeks [10] and also reported no adverse events. The only RCT to date assessing FMT specifically for CDI[8] involved randomising participants to one of three therapies 1) vancomycin followed by bowel lavage and subsequent infusion of donor faeces via nasoduodenal tube (n=16). 2) Vancomycin treatment for 14 days with bowel lavage on day 4-5 (n=13) or 3) Vancomycin for 14 days alone (n=13). The adverse events from this study are listed in Table II.

Non-controlled studies

FMT to treat *Clostridium difficile* (n=1174)

The reports on 1174 patients describe FMT primarily for CDI without controls. Publications comprised 30 single case reports [11–40] and case series [1,3,41–83] ranging from 2 cases [41,43,44,46,48] to the largest series of 146 cases. [68] In 32 cases undergoing FMT primarily for CDI inflammatory bowel disease was also present. [15,21,25,29,32,36,38,44,45,56,63,80]

Modes of delivery

Methods of administration were specified in 946 cases, comprising nasogastric tube (n=133); [1,15,21,23,37,42,49,65,79,80] naso-jejunal / nasoduodenal tube (n=2); [20,48] Gastroscopy/ endoscopy/ enteroscopy (n=64); [28,35,40,50,62,65,73] rectal enema (n=156) [11–13,24,41,57,72,77,79] which was repeated again 3 days later in once case; [11] Colonoscopy (n=530). [1,3,14,16–19,22,25–27,29,32,38,43–48,50,51,54,56,58,60,62,63,66–69,80–82] Simultaneous jejunal (via enteroscopy) and colonoscopic infusion was administered in 40 cases. [53,55,71] Two case series comprising six [59] and seven cases [52] described patients receiving faecal enema at home, self-administered or by a family member. One patient had both enteroscopic and colonoscopic FMT.[62] FMT instilled through a previously placed gastric tube was described in 5 cases. [31,65] One patient refusing invasive procedures had FMT administered trans-rectally over 10 minutes having had the solution drawn and instilled into 20 5ml syringes. [33] Another underwent FMT twice in 10 days firstly via an 'intestinal tube' and then by colonoscopy. [39] Only in one paper was FMT administered intentionally to manage both for CDI and concurrent inflammatory bowel disease, Crohn's (n=7) and Ulcerative Colitis (UC) (n=6). [84]

In 132 of 1190 CDI cases, one or more FMT additional procedures were administered. [1,8,27,32,42,48,50,54,56,59–61,63,64,66–68,72,75–78,82] One patient was finally successfully treated with a bacterial suspension enema following failed enema of faeces. [41]

Adverse events as a result of FMT given for *C.difficile* infection

Procedural Complications

In only four cases was an adverse event directly attributable to the FMT procedure itself. These comprised: 'microperforation', described as following biopsy of an area of 'presumed ischaemic small bowel injury' during the FMT procedure. This resolved with conservative management. [63] Caecal perforation at FMT necessitating colectomy. [64] 'Minor mucosal tear' during colonoscopy to deliver FMT. [51] One FMT procedure was abandoned after the discovery of chronic graft versus host disease of the terminal ileum in a stem cell transplant recipient patient that had been persistently PCR positive for the *C.difficile* toxin gene. [78]

Infective Complications

Norovirus transmission possibly associated with FMT has been reported in 2 cases [46] both cases testing positive for norovirus by PCR. One presented day 2 post FMT with diarrhoea but the donor was asymptomatic and tested negative and the second case presented with vomiting and diarrhoea 12 days post FMT, again with an asymptomatic donor who was not tested.

A patient diagnosed with influenza B 3 days post FMT was not thought to be infected through the FMT as the donor remained asymptomatic throughout the 12 week follow up period. [76] Gram negative bacteraemia occurred in four cases after FMT. [28,31,38,85] two of whom died as a result of the procedure. [31,85] *Escherichia coli* bacteraemia occurred 24 hours after colonoscopic FMT in a 61 year old man with concomitant Crohn's disease and diverticulitis who had had 6 prior *Escherichia coli* bacteraemias in the preceding 3 and half years – leading the authors to postulate that altered intestinal permeability was the cause. The

case responded to antibiotics. [38] Another case involving *Serratia spp* bacteraemia occurred 12 days following jejunal- placed FMT – the patient dying more than 30 days after the procedure from recurrent ventilator-associated pneumonia. A CT scan prior to death showed no evidence of colitis, and stool cultures remained negative for culture and toxin 14, 20 and 30 days post-transplant. [28] The remaining two cases were bacteraemia are described in the section on deaths associated with FMT.

Inflammatory Complications

Fever of unknown cause

Fever in the absence of an identified infectious agent was reported in 11 cases, [1,69,71,73,76] with only one specifying the temperature reading, at 38.8 degrees 2 days post FMT. This resolved spontaneously. [1] Fever was described by authors as 'mild and transient' in 2 cases, [69] 'low grade' in 5 (resolving spontaneously within 12-24 hours). [71] One case reported spontaneous resolution of fever with negative blood cultures. [73] Fever, diarrhoea, encephalopathy and pancytopenia 4 days post FMT were described in a patient with cirrhosis and non-Hodgkin's lymphoma (the management and outcome were not discussed), [76] fever was also recorded post FMT in a solid organ transplant recipient. [76]

Exacerbation of Inflammatory Bowel disease

In patients with concomitant inflammatory bowel disease and CDI (where FMT was administered primarily for CDI) clinical deterioration occurred in six cases [25,76] Four out of five cases in one series [76] were hospitalised with a flare of IBD within the 12 week follow up period. Colectomy within 1 month of FMT was necessary in one case due to worsening ulcerative colitis, whilst another two underwent colectomy 105 and 293 days after FMT respectively. A patient with UC described as 'quiescent' for 20 years presented 9 days post

colonoscopic FMT with abdominal cramping and loose bloody stools with mucus. Repeat colonoscopy showed new features consistent with UC when compared to the previous appearance on colonoscopy to deliver FMT and biopsy confirmed inflammatory colitis. [25]

In the only paper describing colonoscopic FMT for concomitant IBD (Crohns n=7 and UC n=6) and CDI omitted to mention whether any adverse events occurred, but did report that of the 11 clearing their CDI infection, 46% required escalation of their IBD management. [84]

Gastrointestinal Complications

Gastrointestinal side effects were the most commonly reported although terms were inconsistent and imprecise. Symptoms included flatulence (n=25); [56,77,80] diarrhoea (n=18); [51,58,75,76,80] irregular bowel movements (n=14); [56] post infectious inflammatory bowel syndrome (n=13); [52,68,74] abdominal distension/bloating (n=12); [1,71,76,80] abdominal pain/tenderness (n=11); [75,76,78,80] constipation (n=10); [14,77] cramping (n=9); [73,80] nausea (n=7) (the route of administration was not recorded); [75,76] blood in stools (n=2) (both cases had concomitant inflammatory bowel disease); [80] microscopic colitis (n=2). [68] Other miscellaneous comments included 'intermittent obstipation'; [24] mucoid stools; [80] 'visceral hypersensitivity' [68] and 'a few patients developed temporary constipation'. [72]

The outcomes of these symptoms were often not recorded but largely the terminology used to describe them gave the impression they were not deemed to be significant adverse events with descriptions as mild, [86] short lived, [80] transient [73,77] and self limiting, [8,71] though in one paper over the counter fibre preparations had been used to manage side effects. [58] There were very few descriptions of longer term symptomatic cases, these included 5 cases of post-

infectious IBS remained symptomatic at the end of the study follow up period at 16-35 months [74] and constipation that persisted 'for months'. [14]

Deaths Potentially Attributable to FMT

Three deaths have been described in patients undergoing FMT. [31,76,85] One patient, after an uncomplicated FMT delivered via a pre-existing gastric tube, developed septic shock 3 days later with decompensated toxic megacolon, and blood cultures yielded *Pseudomonas aeruginosa*, *Escherichia coli*, *Lactobacillus casei.* The patient died of septic shock 4 days after colonic resection. The authors conclusion was that the link to FMT was unclear. [31] A second patient died of respiratory failure one day after aspirating during sedation to deliver a colonoscopic FMT. [76] We have also reported a case of regurgitation of faeculent material during endoscopic FMT under general anaesthetic followed by aspiration pneumonia and septic shock. The patient died 48 days later. [85]

Other deaths in the follow up period

Other deaths which occurred in patients that had undergone FMT for CDI were reported in 41 cases [1,3,49,50,54,60,63,64,68,76] summarised in Table III. Of these, seven were attributable to *C.difficile* infection. [50,60,68] In one case series 3 deaths occurred within 1.5 to 3 months of FMT all having severe diarrhoea pre-transplantation associated with the hypervirulent ribotype 027. [60] Another described 3 patients who failed to respond to FMT and died within 3 weeks to 2 months of the procedure, two of whom were described as 'seriously weakened after long lasting diarrhoeal disease' and another died of complications related to subtotal colectomy after developing fulminant colitis. [50] Another death was attributed to complicated CDI without further detail. [68]

Other reported events

Events that do not fall into the above categories are tabulated in table IV. These include reports from publications listing any untoward event without necessarily ascribing them directly to the FMT procedure. Table V shows crude rates for the commonest reported symptoms and adverse events following FMT. As there is no standard for classifying and reporting these adverse events following FMT, we expect that there is likely to be significant underattainment.

FMT to treat Inflammatory Bowel Disease

Excluding the RCT for UC previously discussed, [9] 226 of the 1555 ascertained underwent FMT primarily for inflammatory bowel disease. Amongst these were 159 procedures for ulcerative colitis [83,87–100] and 67 for Crohn's. [92,100–107] In addition eight patients underwent FMT for pouchitis following restorative proctocolectomy for ulcerative colitis, [108] three for mixed UC/Crohns [109] or IBD unspecified. [110] Concomitant CDI was present in 6 patients. [90,93] Publications ranged from four single case reports [99,106,107,110] to series ranging from 3 [97,109] to 62 patients. [89]

Modes of delivery

Methods of administration of FMT in these cohorts were highly variable, including nasogastric tube (n=18); [104,108] naso-duodenal tube (n=10); [95] endoscopy (n=31) [102,106] and colonoscopy (n=31), [90,91,96,100,103,110] the latter repeated at 4 and 12 weeks for one patient. [110] Rectal enema was described using a variety of regimens in 17 cases. [94,98,109] Training in self-administration of FMT allowed one patient to complete 69 procedures in total, initially daily then weekly. [109] A plethora of other methods of administration combine different routes in largely inconsistent regimens, including 25 cases of initial colonoscopic FMT [90,93,97,105,109] and one case of initial naso-jejunal infusion [93] followed by a variable number of rectal enemas. The remaining 21 were described as 'self-administered faecal enemas in a tapered then maintenance schedule'. [90,93] Another approach involved daily administration of combined nasojejunal infusion and rectal enemas (n=5). [88] In 16 patients using home- based faecal transplant, the authors did not specify their methods further. [87] Four patients had ileo-

colonoscopy and biopsies followed directly instillation of FMT via NJ tube which was repeated twice the following day. [101]

Adverse events of FMT given for Inflammatory Bowel Disease

Procedural

Inability to tolerate retention of a faecal enema with immediate leakage on 3 consecutive days and secondly low back pain [94] were each reported, both in children. This uncommon side effect probably resulted from the complex positioning for the procedure adopted. Patients were rotated 180 degrees left lateral to right lateral over a 10 minute period, in the left lateral decubitus position with elevated hips, then received four retention enemas in 60ml aliquots every 15 minutes.

Fever and raised inflammatory markers

As with CDI, fever was the most frequently encountered inflammatory adverse events in 14 cases, [88,91,94,100–102] this was quantified in two as greater than 38 degrees Centigrade with negative blood cultures; [88] up to 39 degrees in one case, self limiting after 3 days which the authors concluded this was non-significant and interpreted as an 'immunological reaction to the applied bacteria to the inflamed colon'; [91] 'transient' in three cases; [101] 'mild' in one case; [100] one episode of fever was accompanied by 'chills' responding to acetaminophen and antihistamines and did not recur with further FMTs. [94] In a further two cases of fever these were considered doubtful adverse events as the patients had fever after colonoscopy under general anaesthesia before FMT. [102]

Deterioration in IBD was also described in 6 cases; [88,90,94,96] of which one was described as 'disabling haematochezia' three weeks after FMT; [94] other reports include increased CRP (n=6). [88,91] Only one of which was quantified at 31.5 mg/L, this patient also had a raised interleukin-6. [91] Itchiness [88] and erythema [88] were described in individual cases but these were not described further. A case of 'hives' occurred in a patient with history of medication allergies during the 7 day follow up period following colonoscopic FMT of anonymous donor faeces. [100]

Gastrointestinal

Again gastrointestinal adverse effects predominated (Table VII) with; diarrhoea (n=28); [88,91,94,100,102,104] abdominal distension/bloating (n=24); [92–94,100,104] abdominal pain/cramping/tenderness (n=20); [94,100,101,104] flatulence (n=10); [88,94] vomiting (n=3); [88,104] Constipation (n=5) [100] bloody stool (n=4) [94,98] (one following withdrawal of prednisolone) [98] and 'mild-moderate diarrhoea observed and self-limiting' without specifying the number affected described. [95]

Other reported events

Other reported adverse events of uncertain/ if any relation to faecal transplant are shown in table VI.

FMT to treat Irritable Bowel Syndrome (IBS)

FMT was used in attempt to treat IBS in 18 cases. [105,111] The first study [111] described a total of 13 patients, 11 undergoing one FMT, one having two and one having three procedures. The time course, method and necessity for further FMTs were not specified. The second case series [105] involved colonoscopic infusion of faeces followed by various regimes comprising

4 enemas (n=2), 9 enemas, 4 nasojejunal infusions then 5 enemas and 5 combined nasojejunal infusions and enemas. There were no adverse events described in either study.

FMT to treat Constipation

FMT as a treatment for constipation has been described in 7 patients. [105,112] The route of administration was described in 4 cases and included two cases that had their FMT as a colonoscopic procedure followed by 9 enemas. One patient had 15 enemas as daily infusions, and another had a regimen that consisted of colonoscopic FMT followed by 5 combined nasojejunal infusions and enemas followed by a further 5 enemas. [105] In the remaining 3 cases it was noted only that two had 5 FMTs with the method not recorded and a third had 10 days of FMT infusions. [112] There were no reported adverse events in any of these studies.

FMT used in other conditions

Several cases of Pseudomembranous colitis unattributed to *C.difficile* infection have been treated with FMT (n = 21). [6,113,114] However it is noteworthy that these papers were published either before [6,113] or shortly after [114] the association of *C.difficile* and pseudomembranous colitis being first reported in 1978[115]. Various methods of administration were described; 'a long enteral tube' in one case, [114] 15 patients had retention enemas given twice daily 'in almost all circumstances'. [114] The remaining five were given as retention enemas once, [113,114] twice (n=2) [6] and three times (n=1). [6] Despite no directly attributable adverse events being reported, overall three patients died (duration of follow up was not recorded). [114] Of these, one had no pseudomembrane noted at autopsy, the second had no endoscopic evidence of the disease and died of pneumonia, whilst the third failed to

respond to faecal enema clinically and was found to have pseudomembranes involving most of the small bowel at autopsy. Another case series of 9 patients treated with FMT for antibiotic associated diarrhoea (not specifying whether *C.difficile* related) [(116)] suffered no reported adverse events on 18 month follow- up.

Discussion

We have comprehensively reviewed the available literature on FMT published before November 2014 to determine what adverse events may be encountered. The literature surrounding FMT is largely of poor quality in that it is dominated by anecdotal case reports and small series without comparators or controls. There are only three small randomised controlled trials [8–10] reporting only 52 of the 1555 patients covered by the literature.

We found that there was wide variation in all areas of methodology, such as in patient and donor selection; preparation and administration of the transplant; number of procedures per patient; follow up and reporting of outcome data. In many of the reports no information on adverse events was included. Without any standardisation or structure it is not possible to provide a robust assessment of the range and incidence of significant adverse events. In addition the follow up period was highly variable from about 1 week [100] to 15 years. [112]

FMT has been applied beyond the treatment of CDI where its use is well established, to ulcerative colitis [10,83,84,87–99] Crohn's disease [92,100–107] and mixed IBD. [109] Pioneering application in patients with constipation, [105,112] metabolic syndrome [9] and IBS [105,111] has been reported, raising questions as to the exact pathophysiology of these conditions. FMT has also been given to paediatric patients suffering CDI [17,18,21,76,80] and ulcerative colitis. [94,97,104] Non-IBD immune-compromised patients receiving therapy range from those chronic medical conditions to solid organ (n=23) [30,35,48] and haematology transplant patients[20] have also been described. Use of FMT has been reported in four cases with HIV, [39,76] and seven patients with concomitant use of 'antineoplastic agents'. [75] In addition to these patients some of whom were severely immunocompromised individuals,

FMT as a salvage therapy has also been employed in intensive care unit patients for unresponsive fulminant CDI. [13,28,37] Comparison between patients with such a heterogeneous range of conditions risks confounding true adverse effects with conditions that are part of the natural progression of disease.

The literature esteems the use of FMT in CDI[2] where the FMT replenishes the defective diverse range of non-pathogenic colonic flora that act to prevent proliferation of *Clostridium difficile*.[3] Because of the extent of case reports in CDI it is possible to summarize the emerging themes of adverse events. The procedure is generally safe, and side effects experienced mild and self-limiting (Table V). Nevertheless there are limited reports of serious adverse events, bacteraemia, inflammatory bowel disease flares, and death. Without proper comparators it is not possible to be certain that these are significant risks in a condition which itself has a high morbidity and mortality. [117]

In IBD, where the interplay of microbiota, host resistance and inflammatory mediators is more poorly understood, [98,102] the role and outcomes of FMT is less well defined. Use in all forms IBD is the second most commonly reported indication for FMT, though the numbers of patients are small, 278 (17.8%). Some authors reporting successful outcomes [89,98,99,102,103,106,107,109,110] while others are more guarded, reporting more variable results or no discernible improvement.[10,91,93,101,104] In a relapsing and remitting condition the significance of adverse events such as flares and deteriorations are difficult to delineate the natural history of the disease.

The long term effects and outcomes of FMT are yet to be established. This may be of concern as the gut microbiome becomes increasingly implicated in disease states. [35] The majority of patients with CDI are elderly often with other serious conditions, but many other recipients of FMT are likely to be much younger. For them the long term consequences of manipulation of the gut microbiome must be understood. For example are anecdotal reports of changes that have occurred after FMT. These include improvements in comorbid conditions; reversal of immune thrombocytopenic purpura [99] and neurological symptom reversal in three patients with multiple sclerosis. [112] In two patients, the resistant coliforms present prior to FMT were supplanted by ciprofloxacin sensitive coliforms post FMT. [108] FMT for refractory CDI resulted in an apparent improvement in the associated urinary organisms exhibiting 'significantly decreased drug resistance"[48] a principle further supported by two case reports using FMT to decolonise patients with multi-drug resistant carbapenemase producing strains of *Klebsiella pneumoniae.* [118,119] Others have noted improvement in pre-existing allergic sinusitis [54] arthritis [54] In one series treating Crohns with FMT 8/11 of the patients noted relief of concomitant 'skin lesions'[102] a phenomenon also seen in another group using FMT to treat UC where three cases had improvement in 'skin problems' as well as reduced insulin requirements in a diabetic patient [95] Since undertaking our recent search there has also been a case report published linking FMT to the development of obesity.[120]

On the whole adverse events largely appear to be gastrointestinal in nature, and some have very nebulous association with the procedure. Most are mild and self-limiting, but there were deaths directly attributable to the procedure. We noted relatively higher rates of adverse

events in the IBD groups than the CDI group which may indicate the underlying condition itself predisposing to the risk of adverse events.

Limitations

We have presented those adverse events reported to date. Important limitations are

1. the search was limited to reports in the English language
2. every effort has been made to remove the duplicate reports but it is possible that some patients have been included in more than one publication
3. there is a global lack of standardisation around the practice of FMT
4. there is an absence of structured follow up and reporting of outcome data including adverse events
5. given the dominance of case reports and case series in the literature there is likely to be reporting bias that may affect the prevalence of adverse events
6. there is a lack of high quality randomised trials on FMT, especially for applications other than CDI

Conclusion

On reviewing the adverse events reported in association with FMT, we find the vast majority are generally mild, self-limiting and gastrointestinal in nature. In some a credible association is not established, due to the lack of controlled data. There have however been a few reports of serious adverse events. From the limited data we have collected, it may appear that rates of adverse events appear to be higher in IBD than CDI. However there is a need for standardised, randomised controlled trials both to qualify and quantify the risks of faecal transplant – which may of course change with time as the function of the microbiome is further defined.

Potential recipients of FMT can only give informed consent if they understand the potential for adverse outcomes. Whereas we feel this may be possible for CDI, the quality of data available for other indications is so poor that the information required is not available.

It is important to establish standardised and where possible evidence based procedures for FMT. These should cover both the procedural aspects of FMT, but recording of outcomes in a standardised and comprehensive format. In view of the potential for long term effects following a procedure such as FMT there is a need to establish national registries.

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Table I

Indication for FMT

Indication for FMT	Number of patients *(n=1555)*
C.difficile infection	1190
Ulcerative colitis	186
Crohns disease	67
Antibiotic associated diarrhoea*	32
Pseudomembranous colitis**	21
IBS	18
Concurrent IBD/CDI	13
Metabolic syndrome	9
UC pouchitis	8
Constipation	7
IBD mixed or unspecified	4

* Unspecified whether related to CDI

**Not as a result of CDI but these include publications prior to or shortly after the association between *C.difficile* and pseudomembranous colitis being made

Table II

Adverse events reported from the randomised controlled trial for FMT in CDI

Adverse events from the RCT for FMT in CDI (8)		
Vancomycin & bowel lavage & FMT *(n=16)**	Vancomycin & bowel lavage *(n=13)*	Vancomycin only *(n=13)*
Diarrhoea *(n=15)*	Constipation *(n=2)*	Death *(n=1)* ***
Abdominal Cramps *(n=5)*	Diarrhoea** *(n=1)*	Diarrhoea *(n=1)*
Belching *(n=3)*	'Excessive gas' *(n=1)*	Constipation *(n=1)*
Constipation (n=3)	Urinary tract infection *(n=1)*	Pain (RA) *(n=1)*
Abdominal pain *(n=2)*		
Nausea *(n=1)*		
Fever during dialysis *(n=1)*		
Urinary tract infection *(n=1)*		
Dizziness & diarrhoea *(n=1)*		
Choledocholithiasis *(n=1)*		

* Diarrhoea, abdominal pain/cramps and belching all resolved within 3 hours of FMT. Events during follow up – fever on dialysis was treated with antibiotics, blood cultures were negative, the UTI case had a history of recurrent UTIs. The case with dizziness and diarrhoea had a history of autonomic dysfunction.

** Subsequently diagnosed with Crohns disease.

*** Death was deemed unrelated to study drug.

Table III

Deaths reported following FMT that were not attributed to FMT by the authors.

Cause of Death (Time after FMT)	Reference
Pulmonary disease (n=6)	(1,3,49,54,64,76)
CDI related (n=7)	(50,60,68)
Malignancy (n=5)	(1,3,54,60,63)
Co-morbid conditions unspecified/unrelated (n=17)	(50,60,68,76)
Superior mesenteric vein thrombosis (5 months)	(3)
Sepsis in a Crohn's patient (5 months)	(54)
Cerebrovascular event	(54)
Myocardial infarction	(54)
Unknown	(54)
PD peritonitis (day 3)	(49)

Table IV

Other reported events following FMT for CDI.

Adverse event (Time after FMT)	Reference
Proteus spp UTI (day 33)	(45)
Herpes zoster (8 weeks)	(60)
Pneumococcal meningitis	(60)
Pertussis	(76)
Line infection (n=2)	(26,39)
Fall, hip fracture	(76)
Upper GI Haemorrhage	(42)
Hip pain	(76)
Cerebrovascular accident (day 21)	(76)
Anxiety (n=6)	(75)
Oesophageal carcinoma	(1)
Fournier's gangrene	(1)

Table V

Overall rates of the commonest adverse events with the denominator as the total number of cases receiving FMT for CDI.

Effect	Number of patients	Overall % *(n=1190)*
Abdo distension/bloating/cramping	28	2.35%
Flatulence	25	2.1%
Diarrhoea	23	1.93%
'irregularity of bowel movements'	14	1.18%
IBS Symptoms	13	1.09%
Constipation	13	1.09%
Abdominal pain/tenderness	11	0.92%
Fever	11	0.92%
Nausea	7	0.59%
IBD flare/deterioration	5	0.42%
Gram Negative Bacteraemia	4	0.34%
Perforation/tear	3	0.25%
Belching	3	0.25%
Attributable death*	3	0.25%
Blood in stools	2	0.17%

* This includes a case report [85] we have published since the search – therefore this one case is not represented in the overall denominator figure (the percentage rate however remains unchanged by this addition)

Table VI

Other reported events following FMT for IBD.

Adverse event (Time after FMT)	Reference
Hip paraesthesia	(88)
Collapse	(88)
Blisters on tongue	(88)
Fatigue (n=3)	(94)
Cervical lymphadenopathy (post URTI)	(94)
Headache, nausea and vomiting*	(94)
Self-limiting headache	(97)
'Severe cold' (3 weeks)	(106)
'common cold' (n=3)	(88)
'mild stuffy nose/sore throat/drippy nose' (n=4)	(104)
Headache	(100)

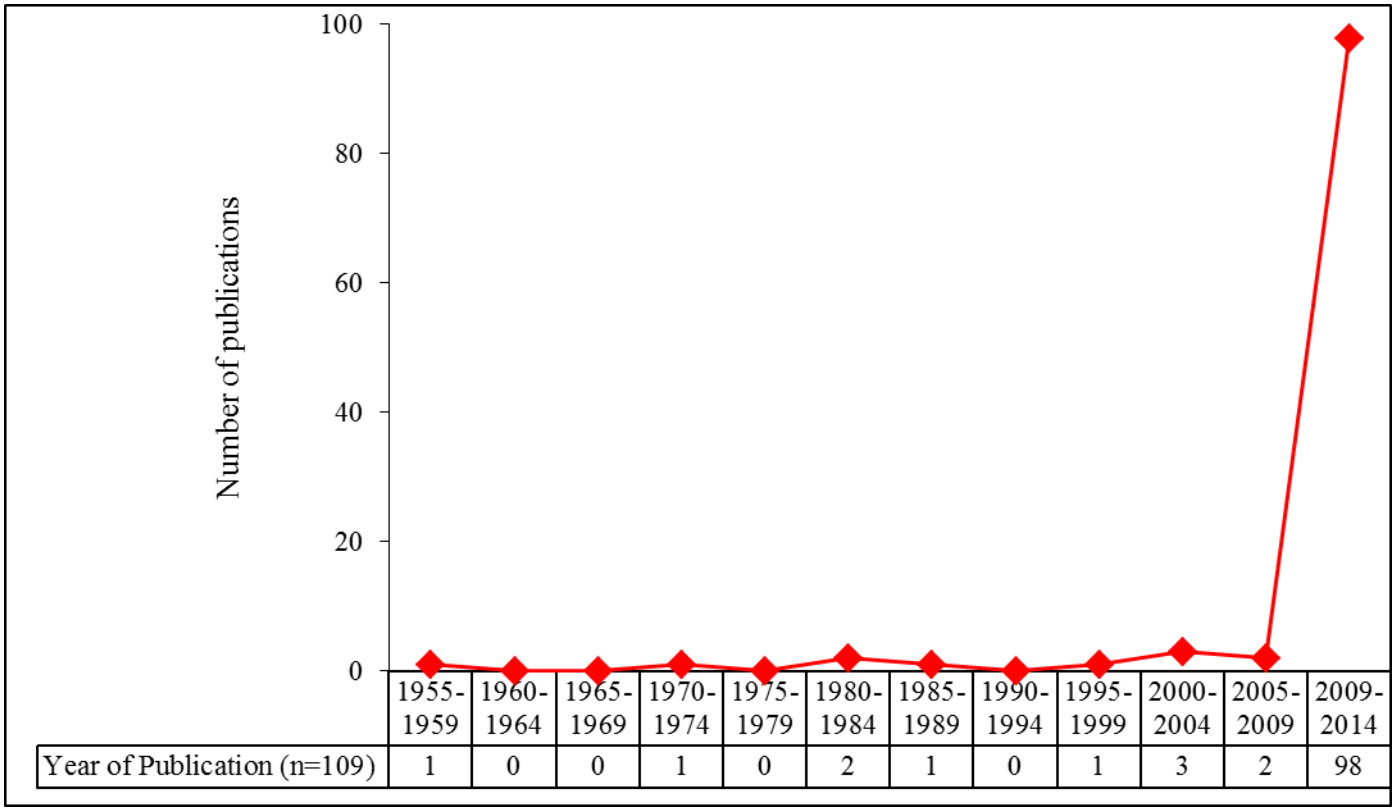
* Described by the authors as baseline symptoms from concurrent medication use and not attributed to FMT.

Table VII

Overall rates of the commonest adverse events using the denominator as the total number of cases receiving FMT for IBD.

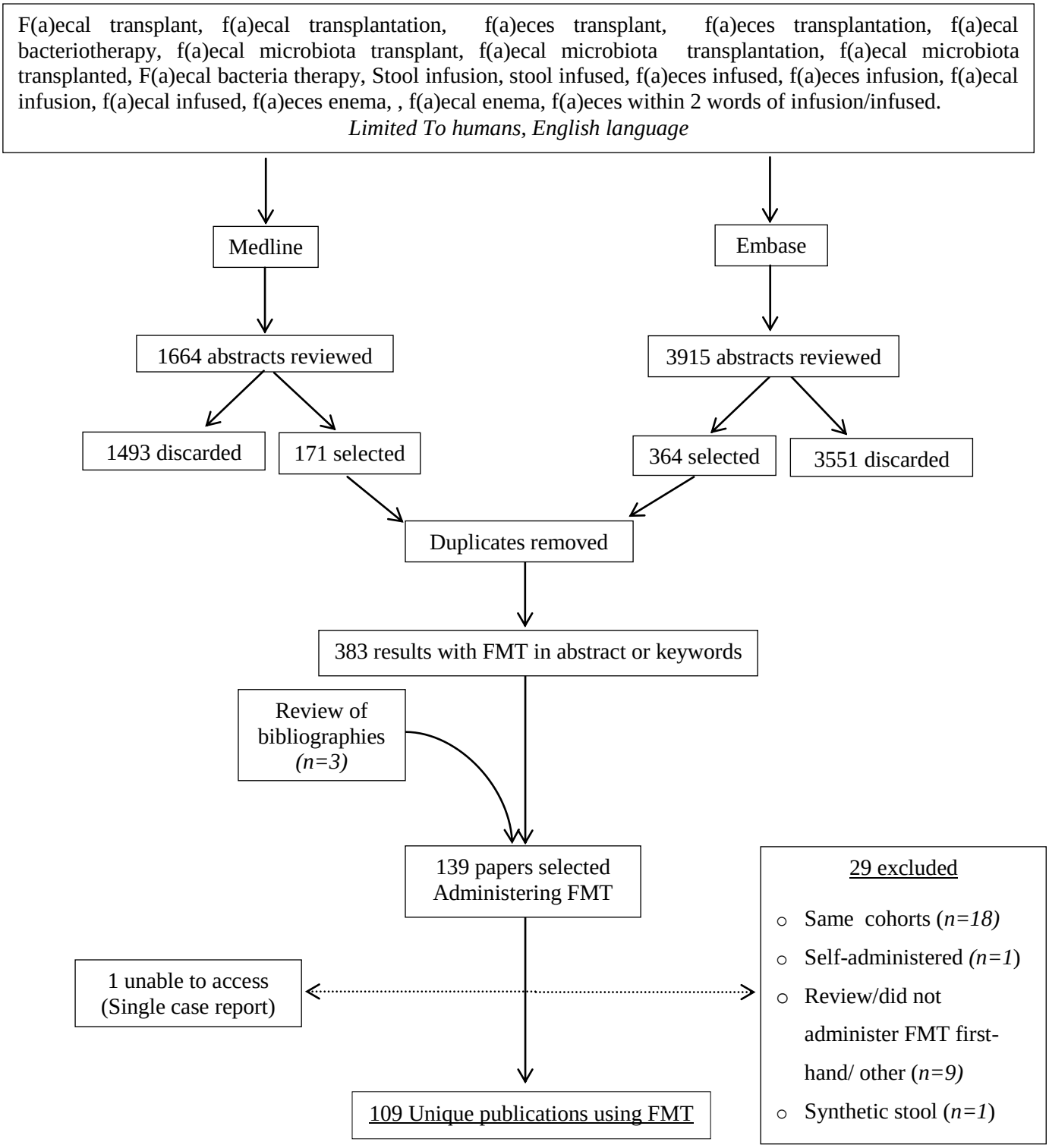
Effect	Number of patients	Overall % *(n=265)*
Diarrhoea	28	10.57%
Abdominal distension/bloating	24	9.06%
Abdominal pain/cramping/tenderness	20	7.55%
Fever	14	5.28%
Flatulence	10	3.77%
Deterioration of IBD	6	2.26%
Raised CRP	6	2.26%
Constipation	5	1.88%
Blood in stools	4	1.50%
Vomiting	3	1.32%

Figure 1



Publications of FMT use arranged by year of publication from first description in 1958 to 2014, demonstrating the surge of FMT use in the preceding 5 years.

Figure 2



Overview of search strategy