

Fecal microbiota transplantation in ulcerative colitis

C. Blanchaert¹, Dr. B. Strubbe², H. Peeters²

(1) University of Ghent, Ghent, Belgium ; (2) Department of Gastroenterology, AZ Sint-Lucas, Ghent, Belgium.

Abstract

Background/study aims: Fecal microbiota transplantation (FMT), a treatment aiming to restore dysbiosis by transferring stool from a healthy donor into the patient, has cure rates up to 90% in the management of recurrent *Clostridium difficile* (C. difficile) diarrhea. This paper tries to determine whether FMT is safe and effective in the treatment of ulcerative colitis, and what the potential characteristics could be of a 'super donor'.

Methods: The PubMed database was searched using the term fecal microbiota transplantation inflammatory bowel disease. Only articles discussing the use of FMT in the treatment of ulcerative colitis were withheld. Finally, 31 original studies (10 case reports, 17 open label trials, 4 randomized controlled trials (RCTs)) and 1 meta-analysis were included.

Results: So far 4 RCTs have investigated the effectiveness of FMT in treating UC. Three RCTs reported a significant difference between FMT and a control group, achieving clinical remission in 24 to 44% of patients (vs. 5 to 20% of patients in control groups). The meta-analysis confirms that significantly more patients in the FMT-group achieve clinical remission in comparison to patients in the control group ($p=0,01$): 42,1% vs. 22,6%. The composition of the gut microbiota plays an important role in the success of FMT-treatment.

Conclusion: FMT seems to be a promising and safe therapy in the management of UC. Further research, with larger cohorts, will be needed to confirm this and to determine the optimal FMT procedure. (*Acta gastroenterol. belg.*, 2019, 82, 519-528).

Keywords: fecal microbiota transplantation, ulcerative colitis, inflammatory bowel disease.

Introduction

To date the pathogenesis of ulcerative colitis (UC) is not fully understood. The current hypothesis states that an overactivation of the immune system to an altered composition of the gut microbiota (better known as dysbiosis) causes an inflammatory bowel reaction in genetically susceptible people (1-7). Present treatments, such as 5-aminosalicylates (5-ASA), corticosteroids, immunosuppressants and biologicals, target this overactivation of the immune system (8). In recent years however, there has been more interest in the role of the microbiota (3,9-12). The microbiota plays a vital role in the development of disease. Diversion of the fecal stream induces inflammatory remission and mucosal healing in the excluded intestinal segment (10,12,13). A genetically susceptible mouse raised in a germ-free environment will not develop colitis, unless commensal gut bacteria are introduced (9,11).

Fecal microbiota transplantation (FMT) is a treatment aiming to restore dysbiosis, by transferring stool from a healthy donor into the patient (2,7,14). FMT has proven its worth in the management of recurrent *Clostridium*

difficile (C. difficile) diarrhea, with cure rates up to 90% (12,14-17). Because of the success in treating C. difficile, whose proliferation is mostly dependent on an alteration in the microbiota composition, FMT has been suggested as a potential treatment in other gastrointestinal diseases linked to dysbiosis. Possible candidates for this treatment are metabolic syndrome, irritable bowel syndrome and inflammatory bowel disease (IBD) (16,18). This paper tries to determine if FMT is safe and effective in the treatment of ulcerative colitis, and what the potential characteristics could be of a 'super donor'.

Methods

The PubMed database was searched using the term fecal microbiota transplantation inflammatory bowel disease. Since this only produced 336 search results, no additional search limitations were added. Based on title and abstract many articles could be excluded given they treated topics not relevant to the topic discussed in this paper. Fifty-eight articles discussing FMT in the treatment of UC were retained and more thoroughly studied. Only original studies were included, with the exception of 1 meta-analysis. Articles had to be written in English. Studies discussing patients with C. difficile surinfections were excluded. Finally 31 original studies (10 case reports, 17 open label trials, 4 randomized controlled trials (RCTs)) and 1 meta-analysis were withheld for this article.

Results

Is FMT an effective UC-treatment?

Case reports

See Table 1 for an overview. The first to report positive results about the use of FMT in the treatment of IBD were Bennet and Borody in 1989 (19,20). Bennet, who suffered from UC, transplanted himself with stool from a healthy donor. Half a year later Bennet was still

Correspondence to: Prof. Dr. Harald Peeters, Department of Gastroenterology AZ Sint-Lucas, Groenebriel 1, 9000 Gent. Fax: 00329 224 64 88. Tel: 00329 224 64 80.
E-mail: Harald.Peeters@azstlucas.be

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Table 1. — Overview case reports

Ref., year of publication	N	Concomitant medication	Route of administration	Freq	Donor	Results
Borody et al, 1989 (20)	1	Unknown	Unknown	Unknown	Unknown	Clinical remission after 3 months without additional medication
Bennet et al, 1989 (19)	1	Tocopherylquinone <i>As a protocol to 'sterilise' the bowel*</i>	Enema	1	Bennet himself	Clinical remission after 6 months, without concomitant medication
Borody et al, 2003 (21)	6	Prednisolone, azathioprine, esalazine, olsalazine <i>Vancomycine, metronidazole, rifampicine 7-10 days before FMT Polyethylene glycol*</i>	Enema	5	Relative	Clinical and endoscopic remission 1-13 years, all medication discontinued
Vandenplas et al, 2015 (23)	1	Unknown	Colonoscopy and naso-duodenal tube	7	Relative	Longer remission period after every infusion, 6 months after final FMT in clinical and endoscopic remission
Kellermayer et al, 2015 (24) Ped.	3	Unknown	Colonoscopy and enema	22-30	No relative	30 FMT: 261 days in remission 25 FMT: 159 days in remission 22 FMT: 105 days in remission
Ni et al, 2016 (2) Fecal microbiota transplantation (FMT)	1	Mesalazine	Percutaneous endoscopic cecostomy	1/day for a month, 2/week for 3 months	Relative	Clinical and endoscopic remission 3 months after FMT, sustained clinical remission at 12 months
Seth et al, 2016 (22)	1	5-ASA, corticosteroids, azathioprine <i>Polyethylene glycol, Loperamide*</i>	Colonoscopy	3	No relative	Sustained clinical and endoscopic remission 10 months after FMT, with discontinuation of medication
Shimizu et al, 2016 (26) Ped.	1	Corticosteroids <i>Magnesium citrate day before FMT*</i>	Colonoscopy and enema	16	Relative	In clinical remission during study with 1,5 mg corticosteroids as maintenance therapy
Kumagai et al, 2016 (25) Ped.	1	Unknown	Enema and nasoduodenal tube	6	Relative	No clinical response
Wang et al, 2018 (4) We report the first case of a UC patient with allergy to 5-aminosalicylic acid (5-ASA)	1	Immunosuppressants, anti-TNF, corticosteroids	Colonoscopy	2	No relative	Sustained clinical and endoscopic remission 9 months after FMT

Freq = Frequency, number of FMT administrations; Ped. = pediatric study population ; N = number of patients *medication printed in italic was administered as part of the investigation.

in clinical and endoscopic remission (19). That same year Borody published a case report in which 2 patients, 1 with UC and 1 with Crohn's disease (CD), were successfully treated with FMT. After 3 and 4 months respectively, both patients were in clinical remission with no endoscopic signs of active inflammation (20). Out of the 10 case reports included in this review Kumagai et al is the only study failing to report a clinical response (2,4,19-25).

Both Vandenplas and Kellermayer reported that, as more transplants were administered, the period of remission increased and side effects decreased (23,24). In the study of Vandenplas et al an 18 months old child received 7 transplants and was in sustained clinical and endoscopic remission 6 months after the final transplant (23). Kellermayer et al reported 105 days of remission after 22 fecal transplants. The remission period lengthened to 261 days after administering 30 transplants (24). Several studies reported both clinical and endoscopic remission after FMT, with the ability to discontinue all therapy (2,4,21,22). Borody et al, in 2003, reported the

longest period of remission, with one patient still in remission after 13 years (21). Wang, Seth and Ni saw a remission period of 9, 10 and 12 months respectively (2,4,22). Shimizu et al reported clinical remission after FMT in an 11 year old patient. Endoscopically there was visible improvement in the sigmoid colon, however inflammation persisted in the transverse colon. The patient was kept on 1,5mg prednisone a day (26).

Open label studies

Where case reports show mainly positive results, open label studies give a more nuanced image of FMT-effectiveness in treating UC. See Table 2 for an overview. Damman et al managed to obtain clinical remission after 4 weeks in 1 of 5 UC-patients. All 5 patients experienced a clinical exacerbation after 3 months (27). In the study of Cui et al 8 out of 14 patients (57,1%) were able to discontinue steroids following FMT-treatment. Four patients (28,6%) were in long-term remission (3-18 months) at follow-up (28). Kunde et al reported similar

Table 2. — Overview open label trials

Ref., year of publication	N	Concomitant medication	Route of administration	Freq	Donor	Results
Angelberger et al, 2013 (31) which is an effective alternative for treatment of Clostridium difficile-associated disease, is being considered for several disorders such as inflammatory bowel disease, irritable bowel syndrome, and metabolic syndrome. Disease remission upon FMT is thought to be facilitated by an efficient colonization of healthy donor microbiota, but knowledge of the composition and temporal stability of patient microbiota after FMT is lacking. METHODS: Five patients with moderately to severely active ulcerative colitis (Mayo score >= 6) have been postulated to contribute to intestinal inflammation. Fecal microbiota transplantation (FMT)	5	5-ASA Mesalazine 5-10 days before FMT Polyethylene glycol Pantoprazole Loperamide*	Nasogastric tube + enema	3	No relative	No clinical remission, 1 patient with clinical and slight endoscopic response at week 12, 2 patients deteriorated at week 4
Kump et al, 2013 (30) alterations of the intestinal microbiota, termed dysbiosis, have been postulated to contribute to intestinal inflammation. Fecal microbiota transplantation (FMT)	6	Adalimumab, 5-ASA, prednisolone Polyethylene glycol, Loperamide*	Colonoscopy	1	No relative	No clinical remission, each patient had a temporary improvement of symptoms after 2 weeks, 33,3% had a sustained improvement after 3 months
Kunde et al, 2013 (29) Ped.	10	5-ASA, 6-mercaptopurine, corticosteroids	Enema	5	Relative	67% clinical response, 33% in clinical remission after 1 month
Suskind et al, 2015 (33) Ped.	4	Probiotics, Mesalamine, azathioprine Rifaximin 3 days before FMT Omeprazole evening and morning before FMT Polyethylene glycol*	Nasogastric tube	1	Unknown	No clinical response, 3 patients started additional therapy before ending the study, 1 patient started a restrictive diet
Damman et al, 2015 (27) possibly due to changes in the microbiota. We measured the degree to which the transplanted microbiota engraft following FMT in patients with UC using a donor similarity index (DSI)	5	5-ASA Polyethylene glycol*	Colonoscopy	1	(no) relative	1 patient in clinical remission after 4 weeks, other patients showed no response, all patients deteriorated after 3 months
Cui et al, 2015 (28) and treated with step-up FMT strategy. Follow-up clinical data was collected for a minimum of 3 months. Fecal microbiota composition before and post FMT of patients and related donors were analyzed by 16S rRNA sequencing. RESULTS: Eight of fourteen (57.1 %)	14	Corticosteroids Mesalamine before and after FMT during follow-up Metoclopramide Esomeprazole Mg*	Gastroscopy	1-2	(no) relative	57,1% clinical response and stop corticosteroids, 28,6% in long-term remission (3-18 months), 42,9% no response
Zhang et al, 2016 (34)	19	Complete suction of the stomach fluid before FMT, Metoclopramide, Esomeprazole*	Gastroduodenoscopy	1	Unknown	47,4% clinical response after 3 months, 10,5% clinical remission
Wei et al 2016 (36)	20	5-ASA, prednisone, FMT followed with 5 consecutive days of pectin (FMTP) Vancomycin 3 days before FMT Polyethylene glycol*	Colonoscopy	1	No relative	FMT: 70% clinical response, 30% clinical remission after 12 weeks FMTP: 60% clinical response, 40% clinical remission after 12 weeks
Vermeire et al, 2016 (18) given the role of the intestinal microbiota in this disease. We assessed the impact of faecal microbiota transplantation in patients with inflammatory bowel disease and studied predictors of clinical (non-	8	5-ASA, Corticosteroids, azathioprine, infliximab Polyethylene glycol*	Nasogastric tube and colonoscopy	2	(no) relative	2 patients in clinical and endoscopic remission up to 2,5-3y after FMT
Karolewska-Bochenek et al, 2017 (1)	8	5-ASA, corticosteroids, immunosuppressants, biologicals Proton pump inhibitor and ondansetron the morning of FMT	Naso-duodenal tube and gastroscopy	8	Unknown	87,5% clinical response and 37,5% clinical remission after 2 weeks

Table 2. — Overview open label trials (continuation)

Ref., year of publication	N	Concomitant medication	Route of administration	Freq	Donor	Results
Nishida et al, 2017 (14)	41	5-ASA, corticosteroids, immunosuppressants, anti-TNF <i>Polyethylene glycol*</i>	Colonoscopy	1	Relative	No clinical remission, 34.1% clinical response after 4 weeks, 26.8% response after 8 weeks, 21.9% response after 12 weeks
Mizuno et al, 2017 (32) its safety and efficacy have not been confirmed. This single-arm, open-label, non-randomized study aimed to evaluate the safety and efficacy of FMT for Japanese patients with UC as the first registered clinical trial in Japan. METHODS We enrolled 10 patients with active UC despite medical therapy. The donors were the patients' relatives and were carefully screened for infectious diseases. Fecal material was administered via colonoscopy, and the primary endpoint was the presence or absence of serious adverse events related to FMT. The secondary endpoint was a change in partial Mayo score at 12 weeks post-FMT. Scores ≤ 2 were considered a clinical response. Fecal samples were collected to follow changes in gut microbiota, while extracted complementary DNA were analyzed by a next-generation sequencer. We obtained written informed consent from all patients and donors. This study was approved by our Institutional Review Board and is registered in the University hospital Medical Information Network (UMIN)	10	5-ASA, thiopurine, biologicals, tacrolimus <i>Polyethylene glycol*</i>	Colonoscopy	1	Relative	60% exacerbation 30% increase in inflammation 10% clinical remission
Ishikawa et al, 2017 (35) which is associated with dysbiosis; however, treatment efficacy remains unclear. Hence, we studied the impact of antibiotic pretreatment with amoxicillin, fosfomycin, and metronidazole (AFM) therapy	36	5-ASA, anti-TNF, corticosteroids, immunosuppressants, tacrolimus <i>patients got treated 2 weeks until 2 days before FMT with amoxicillin, metronidazole, phosphomycine (AFM)</i> <i>Polyethylene glycol</i> <i>Scopolamine*</i>	Colonoscopy	1	Relative	AFM + FMT: 82.3% clinical response after 4 weeks, 52.9% clinical remission after 4 weeks AFM only: 68.4% clinical response after 4 weeks, 15.8% clinical remission after 4 weeks
Uygun et al 2017 (3)	30	Mesalazine <i>Sennoside, Loperamide*</i>	Colonoscopy	1	(no) relative	70% clinical response after 12 weeks, 43.3% clinical and endoscopic remission after 12 weeks
Jacob et al, 2017 (6) open-label pilot study to assess the safety, clinical efficacy, and microbial engraftment of single FMT delivery by colonoscopy for active ulcerative colitis using a 2-donor fecal microbiota preparation (FMP)	20	Mesalazine, corticosteroids, thiopurine, vedolizumab, anti-TNF <i>Polyethylene glycol, Loperamide*</i>	Colonoscopy	1	No relative	35% clinical response after 4 weeks, 15% clinical remission, 15% of patients needed an escalation of care
Kump et al, 2018 (7)	27	Mesalazine, corticosteroids, immunosuppressants, anti-TNF <i>patients were treated with vancomycin, paromomycin and nystatin during 10 days until 36h before FMT.</i> <i>Polyethylene glycol*</i>	Colonoscopy	5	(no) relative	AB only: was poorly tolerated, 50% needed additional therapy AB+FMT: 59% clinical response after 90 days, 24% in clinical and endoscopic remission
Goyal et al, 2018 (17) Ped.	14	Mesalazine, corticosteroids, immunosuppressants, biologicals <i>Metronidazole or vancomycine starting 7 days before FMT until 2 days before.</i> <i>Omeprazole 5 days before and 2 days after FMT. Loperamide*</i>	Upper endoscopy and colonoscopy	1	(no) relative	No clinical remission, 50% clinical response after 1 month and 21.4% after 6 months

Freq = Frequency, number of FMT administrations; Ped. = pediatric study population; N = number of patients *medication printed in italic was administered as part of the investigation

results in their study. Six out of 9 (67%) children had an improvement of symptoms. After 1 month, 3 patients were in clinical remission (29). Kump et al, in their 2013 study, reported a temporary improvement of symptoms 2 weeks post-FMT in all 6 of their patients. Two of them had a sustained clinical response, none went into remission (30). In the study of Angelberger et al, 1 out of 5 patients showed clinical and slight endoscopic response following 3 consecutive days of FMT-treatment, 2 patients deteriorated (31). Mizuno et al reported 1 out of 10 patients responding to treatment (32). Nishida et al failed to reach clinical remission in a study population of 41 UC-patients. At week 4, 14 patients (34,1%) had clinical improvement. This number declined to 9 patients (21,9%) at week 12 (14). In the study of Goyal et al, none of the 12 UC-patients and 2 patients with indeterminate colitis (IC) achieved clinical remission. At follow-up 7 patients (50%) showed symptom improvement, 3 patients (21,4%) maintained this response after 6 months (17). Finally, Suskind et al reported that 3 out of 4 pediatric patients had to start additional therapy (33).

Contrary to the previous 9 studies, the following were able to obtain clinical remission. Vermeire et al reported on 2 UC-patients (25%) still in clinical and endoscopic remission 2,5 and 3 years after stool transplantation (18).

Karolewska-Bochenek achieved a clinical response in 7 out of 8 (87,5%) pediatric patients following a 2-week course of fecal transplants. Three patients were in clinical remission at the end of the course (1). In the study of Uygun et al, 21 patients (70%) showed clinical response at week 12. Thirteen patients (43,3%) were in clinical and endoscopic remission (3). Zhang et al described 9 patients (47,4%) experiencing symptom improvement after 3 months, 2 of them additionally achieved clinical remission (34). In the study of Jacob et al a clinical response of 35% (7/20) and remission rate of 15% (3/20) was observed after 4 weeks. Three patients needed an escalation of care (6).

Ishikawa and Kump, compared a treatment of only antibiotics to a combination therapy of antibiotics and FMT. Both observed better results when combining antibiotics and FMT (7,35). Ishikawa et al described a clinical response of 82,3% and a remission rate of 52,9% after 4 weeks, in the combination-therapy group vs. 68,4% and 15,8% in the monotherapy-group respectively ($p=0,33$ and $p=0,18$ respectively) (35). Kump et al, in their 2018 study, reported a clinical response of 59% and a remission rate of 24% after 90 days, following combination therapy. The antibiotic course on its own was very poorly tolerated. Five out of 10 patients needed

Table 3. — Overview RCTs and meta-analysis

Ref., year of publication	N	Concomitant medication	Route of administration	Freq	Donor	Results
Moayyedi et al, 2015 (37)	75	Mesalamine, corticosteroids, immunosuppressants, anti-TNF	Enema	6	No relative	FMT: 24% in clinical and endoscopic remission after 7 weeks Sham: 5% in clinical and endoscopic remission after 7 weeks
Rossen et al, 2015 (40)	37	Mesalamine, corticosteroids, immunosuppressants <i>Polyethylene glycol</i> <i>Loperamide*</i>	Nasoduodenal tube	2	No relative	FMT: 47,8% clinical response, 30,4% in clinical remission after 12 weeks Autologous: 52% clinical response, 32% in clinical remission after 12 weeks
Costello et al, 2015 (39)	73	Oral corticosteroids	Colonoscopy and enema	3	No relative	FMT: 32% in steroid-free remission, 55% in endoscopic remission after 8 weeks Autologous: 9% in steroid-free remission, 17% in endoscopic remission after 8 weeks
Paramsothy et al, 2017 (38)	81	5-ASA, thiopurine, methotrexate, corticosteroids	Colonoscopy and enema	41	No relative	FMT: 44% in clinical remission, 54% clinical response, 32% endoscopic response, 12% endoscopic remission after 8 weeks Sham: 20% in clinical remission, 23% clinical response, 10% endoscopic response, 8% endoscopic remission after 8 weeks
Narula et al, 2017 (41) endoscopic remission, and serious adverse events. Odds ratios with 95% confidence intervals (CIs) META-ANALYSE	277	See above	See above	Idem	No relative	FMT: 27,9% in clinical and endoscopic remission, 42,1% in clinical remission, 26,4% in endoscopic remission after 7 to 12 weeks Placebo: 9,5% in clinical and endoscopic remission, 22,6% in clinical remission, 10,2% in endoscopic remission after 7 to 12 weeks

Freq = Frequency, number of FMT administrations; Ped. = pediatric study population; N = number of patients *medication printed in italic was administered as part of the investigation

additional therapy due to *C. difficile* diarrhea, antibiotic-associated diarrhea or aggravation of UC (7). Finally Wei et al compared a treatment of only FMT to FMT followed by 5 consecutive days of pectin. The pectin-group displayed a response rate of 60% after 12 weeks and a remission rate of 40%. In comparison to 70% and 30% respectively in the FMT only-group ($p=0,042$ and $p=0,042$ respectively) (36).

Randomized controlled trials (RCTs) and meta-analysis

So far there have been 4 RCTs investigating the effectiveness of FMT in the treatment of UC (37-40). See Table 3 for an overview. Moayyedi et al (2015) reported a statistically significant difference ($p=0,03$) in the capability to induce remission in UC, between FMT and placebo. After 7 weeks, 9 out of 38 (24%) patients in the FMT-group went into clinical remission. Seven patients achieved both clinical and endoscopic remission. Clinical remission was maintained in 8 patients after 1 year. In the control group patients were given a retention enema with water. Two out of 37 patients (5%) went into remission, 1 patient achieved both clinical and endoscopic remission (37).

Paramsothy (2017) was the second author to describe a significant difference between FMT and placebo in inducing remission in UC ($p=0,021$), using a RCT design. An initial fecal or watery suspension was infused via colonoscopy. Subsequently patients administered enemas 5 times a week for 8 weeks to themselves. After 8 weeks of FMT-treatment 18 out of 41 patients (44%) were in clinical remission, 22 patients (54%) showed clinical response, this in comparison to 8 (20%) and 9 patients out of 40 (23%) receiving placebo. Endoscopic response was seen in respectively 13 (32%) and 4 (10%) patients in the FMT- and placebo-group. Endoscopic remission did not differ between both groups. Patients that initially received placebo, were given the opportunity to switch to FMT-treatment, once the results of the first part of the study were in. Out of 40 patients that formed the original control group, 37 participated in the open-label part of the trial. Seventeen patients (46%) went into remission after 8 weeks, 8 patients (22%) were also in endoscopic remission (38).

Both Costello and Rossen compared FMT to autologous stool transplantation. The autologous group functioned as a control group. In the study of Costello et al (2015) 73 UC-patients were randomized: 38 patients received donor stool, 35 patients received their own stool. FMT proved to be significantly better ($p=0,02$) in inducing steroid-free remission in UC-patients in comparison to autologous FMT: 32% (12/38) vs 9% (3/35) after 8 weeks (39). Endoscopic remission was achieved in 55% (21/38) vs 17% (6/35) in respectively the FMT- and autologous-group. Rossen et al (2015) were the only ones not reporting a statistically significant difference between FMT and a control group. At week 12, 7 out of 23 patients (30,4%) in the FMT-group were

in clinical remission, vs. 8 out of 25 patients (32%) in the control group (40).

In the meta-analysis of Narula et al (2017) the results of the 4 RCTs were pooled together. It was confirmed that significantly more patients in the FMT-group achieved clinical remission in comparison to patients in the control group ($p=0,01$): 42,1% vs. 22,6% respectively (Figure 1) (41).

FMT preparation and administration

The exact mixing protocol varies in each study, the basic principle however is the same in all studies. Donor material is mixed with a sterile saline solution to form a liquid suspension, which is then filtered (1-4,7,14,17,18,22,23,25-32,34-37,41). To administer this fecal suspension several possible routes exist: enema, percutaneous endoscopic cecostomy (PEC), colonoscopy, nasoduodenal/-jejunal/-gastric tube and gastroscopy (Table 1-3).

Moayyedi et al stated that the best approach to administer FMT might be via retention enema (37). Several studies however, favoured the colonoscopic approach (2,25,41). When administering FMT via enema or colonoscopy issues with holding up the suspension for long enough could occur (28). With this in mind, loperamide was given in some studies to reduce intestinal peristalsis (3,6,17,22,30,31,40). With colonoscopy, larger quantities of stool can be dispensed more proximal into the colon (2,41). An enema only reaches up to the splenic flexure (1,2). Additionally in colonoscopy, the extent and severity of UC can be assessed whilst therapy is given. However, colonoscopy also has a higher risk for severe complications (haemorrhage, intestinal perforation) when performing it in a patient with significant colonic distention or severe colitis (2). Nasogastric or nasoduodenal tubes have the disadvantage that the gastric and bile acidity could have a negative influence on some of the bacterial species, which in turn effects the efficacy of FMT-treatment (1,3,22,25,33). In the study of Zhang et al stomach fluid was completely drained before administering FMT, in order to prevent this issue (34). Vermeire et al reports on one patient suffering an aspiration pneumonia after having a nasojejunal tube (18). A review study discussing 325 *C. difficile*-cases treated with FMT, reported superior results using an enema or colonoscopy vs. using a nasoduodenal tube: there was a successful outcome in 95%, 89% and 76% of the cases respectively (26). Ni et al were the only ones to use percutaneous endoscopic cecostomy. In this method stool transplants are given antegradely via a temporary stoma at the level of the caecum. No side effects were reported (2).

Composition of the gut microbiota – is there such a thing as a ‘super donor’?

The composition of the donor's gut microbiota is an important factor in the success of FMT-treatment.

Several studies established a link between the resemblance of the patient's microbiota post-FMT to that of the donor, and the clinical response this patient had (5,14,17,18,27,28,31,37,40). IBD-dysbiosis in the past, has been characterized by a decreased amount of Firmicutes and Bacteroidetes, and an increased amount of Actinobacteria and Proteobacteria (3,10-12,22). In the review of Allegretti et al the 'super donor phenomenon', linking certain donors to successful FMT-treatments, was mentioned (15). Moayyedi et al also reported on such a phenomenon. Most patients showing clinical response post-FMT received stool material of a specific donor, donor B (37). In the study of Shimizu et al the donor had a similar composition to this donor B and the patient went in to remission. The microbiota mainly consisted of Bacteroides (Bacteroidetes), Faecalibacterium, Blautia and Ruminococcus (Firmicutes) (26). Adversely, in the analysis of Fuentes et al, based on the RCT of Rossen, Ruminococcus gnavus was found at higher levels in donors of failed FMT (5). Paramsothy et al also described one donor having more successful transplants. Patients treated with a sample containing fecal material of this donor reached clinical remission in 37%, relative to 18% receiving a sample to which this donor did not contribute (38). Nishida et al did not mention super donors, however they did report that the proportion of Bifidobacterium (Actinobacteria) was significantly higher in donor feces used in responders than in donor feces used in non-responders. Conversely the proportion of Lactobacillales (Firmicutes) and Clostridium cluster XI and IV (Firmicutes) were significantly higher in donor feces used in non-responders (14).

One of the most consistent findings in the pathogenesis of IBD, is the reduced bacterial diversity (10-13). Frequently there was a (temporary) increase in bacterial diversity post-FMT (6,7,17,24,27,29,30,32,35-37,39). Some studies found that responders tend to have a higher bacterial diversity post-FMT than non-responders (17,18,38,40). The same applies to donor samples. Kump and Vermeire reported an association between donor microbiotas with higher bacterial richness, and remission (7,18). According to the study of Wei et al, in which a treatment with only FMT was compared to FMT-treatment followed by a course of pectin, pectin could help delay the loss of diversity in the fecal microbiota. Pectin is a polysaccharide that can be fermented into short chain fatty acids (SCFAs) by commensal bacteria (36).

Some bacterial species in the patient's microbiota are associated with disease activity. Angelberger et al saw a positive and negative correlation between respectively, the amount of Enterobacteriaceae (Proteobacteria) and Lachnospiraceae (Firmicutes), and the Mayo score (31). Consistently Kump et al reported that a partial response was associated with decreased Enterobacteriaceae loads and increased Streptococcaceae (Firmicutes) (7). Multiple studies confirm the idea of Lachnospiraceae positively influencing UC disease activity (24). Several

studies saw an increase in Bacteroidetes post-FMT (26-28,30,35,38). Ishikawa et al reported a significantly larger increase in Bacteroidetes between responders and non-responders. Restoration of the amount of Bacteroidetes post-FMT correlated with clinical response. Additionally a strong negative correlation between Bacteroidetes and endoscopic severity of the disease existed (35). Fuentes et al partly contradicts these findings. In their study, a microbial ecosystem rich in Bacteroidetes and Proteobacteria and low in Clostridium clusters IV and XIVa (Firmicutes), observed in UC-patients post-FMT, predicted a poor sustained response (5).

In the past, UC has been linked to a decrease in production of SCFAs, such as butyrate and propionate. Butyrate, known for downregulating proinflammatory responses in intestinal epithelial cells, is mainly produced by species within the Firmicutes (5,7). Nishida and Fuentes define UC dysbiosis by a decrease in abundance of Roseburia hominis and Faecalibacterium prausnitzii (F. prausnitzii), both known butyrate producers within the Firmicutes (5,14). In the analysis of Fuentes et al, sustained remission was associated with an increase of butyrate producers and overall butyrate production capacity (5). Angelberger et al reported that Roseburia was one of 4 bacterial species still present in the microbiota of the only patient showing clinical response to FMT after 12 weeks (31). Similarly Vermeire et al described that Roseburia, together with Oscillibacter (Firmicutes), was transplanted only in the 2 UC-patients successfully responding to FMT-treatment (18).

Paramsothy reported that Fusobacterium and Suterella (Proteobacteria) were consistently associated with not going into remission (38). Adversely Goyal found that pre-FMT samples from responders were characterized by a significant increase in Fusobacterium amount (17).

The number of administrations

Some studies state that multiple FMT sessions might be more efficacious than a single dose in treating UC (1,3,15,17,29,31). Kellermayer et al showed a significant correlation ($p=0,04$) between the number of FMT-applications and the immunomodulator-free period. Following 22 transplants clinical remission lasted 105 days. This period lengthened to 159 and 261 days, with 25 and 30 transplants respectively (24). Similarly the patient of Vandenplas et al remained in clinical remission for longer and had fewer side effects as more transplants were given. The first 4 stool transplants each induced temporary improvement of 1 to 2 weeks. The 5th transplant provided a remission period of 1 month. The last 2 transplants resulted in an increasingly longer period of remission: first 2 months, then 6 months (23). Out of the 4 RCTs, the Rossen study scores the lowest in terms of effectiveness. FMT was administered twice in this study (40). Paramsothy and Moayyedi respectively performed 41 and 6 fecal transplants and achieved a considerably higher response rate. Costello et al administered FMT

only 3 times and saw better results than Rossen (Table 3) (39).

Is FMT safe to use in patients suffering from UC?

Hypothetically, the 2 main potential side effects of FMT are: transmission of infections (29,38) and bacteraemia (25). Therefore, in most studies, blood and stool samples of donors are screened to exclude infection risks. Blood samples are examined for the presence of viruses such as hepatitis A, B, C, cytomegalovirus, Epstein-Barr, Herpes Simplex, Varicella zoster, Treponema pallidum, HIV (1-3,17,27,29-31,33,35-37,40). Stool samples are screened for the presence of enteric pathogens such as Yersinia, Salmonella, Shigella, Campylobacter, C. difficile, Helicobacter pylori, Escherichia coli, Vibrio, Listeria, Giardia, Aeromonas and parasites (1-3,17,18,21,25,27-32,35-37,40).

In the RCT of Rossen et al 1 patient was surprisingly diagnosed with systemic CMV-infection following an autologous stool transplant. The patient fully recovered after a ganciclovir treatment (40). Suskind et al reported 2 patients with C. difficile post-FMT. Presumably these infections were not related to FMT-treatment, given they appeared 3 and 4 months after transplantation (33). Moayyedi et al also described a patient with increasing abdominal pain who was diagnosed with C. difficile (37).

As for the risk of bacteraemia, patients with fever shortly after FMT were frequently reported. Fever episodes were short-lived and self-limiting (3,6,17,18,23,25,28-31,36,40). Some studies used blood cultures to exclude bacteraemia. None came back positive (25,29,31).

There were no serious adverse events reported – leading to hospitalization or potentially death (29) – that could be directly linked to FMT (1-3,6,17,18,21,23,25-37,39,40). Some patients experienced worsening of symptoms (6,28,32,37,39). Temporary gastrointestinal discomfort was frequently reported post-FMT: diarrhea (17,28,29,34,35), abdominal cramps/pain (17,25,27,29,40), increased stool frequency (27,34,40), bloating, flatulence (17,29,33), nausea (1,17,35), vomiting (1,17,18,23,33,40), borborygmus (34,35,40). Other complaints mentioned are: testicular pain (28), rectal abscess (37), blood in the stool (2,17,29), fatigue (29), skin pruritus (34).

Some complications are due to the FMT-procedure itself. On an abdominal X-ray of a patient with persistent abdominal pain, free air could be seen, suggesting the patient had a microperforation, possible a complication of colonoscopy. The patient was managed non-operatively and without the need for antibiotics (27). Wei et al reported leakage of donor material within 30 minutes after administering FMT by colonoscopy (36). Following the use of a nasogastric tube, a patient complained about nasal stuffiness (33). One patient developed aspiration pneumonia after vomiting on a nasojejunal tube (18).

Discussion

Fecal microbiota transplantation seems to be a promising treatment in the management of UC. To date, there are 4 RCTs available examining the effect of FMT in UC. Three RCTs reported a significant difference between FMT and a control group, achieving clinical remission in 24 to 44% of patients (vs. 5 to 20% of patients in control groups). The meta-analysis of Narula et al confirms that significantly more patients receiving donor FMT achieve clinical remission compared to those receiving control interventions: 42,1% vs. 22,6% (p=0,01) (41). Rossen et al was the only RCT unable to confirm this significant difference (Figure 1) (40). It was also the only RCT using a proximal route of administration (Table 3).

Stool material is best administered via colonoscopy. Larger quantities of stool can be dispensed more proximal into the colon in comparison to retention enemas. Additionally the severity and extent of mucosal damage can be assessed whilst the procedure is being performed. When administering FMT via gastroscopy or nasogastric tube, bile and gastric acids have their effect on the bacterial species, potentially rendering them ineffective by the time they pass through the colon. A newer method is percutaneous endoscopic cecostomy. The possible advantage of this method is that fecal suspensions pass through the colon in a way that conforms to human physiology. This could be beneficial to flora reconstruction. However, it is an invasive method (2).

The composition of the gut microbiota, both of the donor and the patient, plays an important role in the success of FMT-treatment. There appears to be a

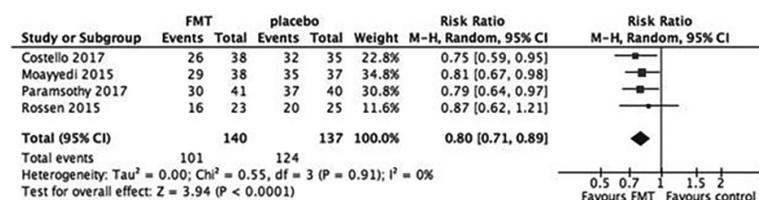


Figure 1. — Forrest plot combined clinical remission and endoscopic response
Forrest plot of all RCTs, reporting combined clinical remission with endoscopic remission or response. Adopted from “Systematic Review and Meta-analysis: Fecal Microbiota Transplantation for Treatment of Active Ulcerative Colitis”. With courtesy of the author Narula N.

relationship between the resemblance post-FMT of a patient's microbiota to that of its donor, and the clinical response. Several studies mention the 'super donor phenomenon', linking certain donors to more successful FMT-treatments (15,37,38). The specific characteristics these donors possess are not yet clear, and require further research. There are, however, a few trends that can be seen. First, dysbiosis in IBD has been defined as a decreased amount of Firmicutes and Bacteroidetes, and an increased amount of Actinobacteria and Proteobacteria. It seems that when FMT succeeds in reversing this dysbiosis, by either adding Firmicutes and Bacteroidetes or decreasing the amount of Actinobacteria and Proteobacteria, clinical response follows. However, not all study findings are consistent with this hypothesis. Nishida et al found that the proportion of Bifidobacterium (Actinobacteria) was significantly higher in donor feces used in responders in comparison to feces used in non-responders. Additionally Nishida reported that Lactobacillales and Clostridium clusters XI and IV (both part of the Firmicutes phylum) were more present in donor feces used in non-responders (14). Fuentes et al reported that a microbial ecosystem rich in Bacteroidetes and Proteobacteria and low in Clostridium clusters IV and XIVa (Firmicutes), observed in UC-patients post-FMT, predicted a poor sustained response (5). Secondly, the bacterial diversity of a donor sample and of the patient's microbiota post-FMT seems to be an important predictor of treatment success. One study described that pectin could help delay the loss of bacterial diversity. Finally, UC has been linked to a decrease in production of SCFAs, such as butyrate and propionate. Butyrate, with its anti-inflammatory qualities, is mainly produced by species within the Firmicutes. Increasing the butyrate production capacity seems to be associated with clinical response. It should be mentioned that some of the changes in the microbiota could be induced by bowel preparation given before colonoscopy (most studies used polyethylene glycol) (27,30,35). However it is very unlikely that bowel preparation has a significant long-term effect on the microbiota composition. One study for example mentions that after the use of polyethylene glycol they observed an increase in Proteobacteria and a decrease in bacterial richness and diversity, which is opposite to the changes observed after FMT administration (30).

One of the most consistent findings in the pathogenesis of IBD is an increased instability of the patient's microbiota. Following temporary shifts in the composition, the microbiota is less inclined to return to its original composition, unlike the microbiota of a healthy individual (10-13). This could explain why clinical responses post-FMT tend to decrease over time, and why changes in the microbiota post-FMT are commonly not sustained a few months later. Potentially multiple transplants are needed to treat active inflammation (37,38), which brings forth the idea to use FMT as a maintenance therapy. In the study of Ni et al, for instance, 1 patient received FMT in the hospital via percutaneous

endoscopic cecostomy (PEC), once a day for a month. After discharge from the hospital, FMT via PEC was given twice a week for 3 months. In the following 12 months the patient reported no return of symptoms (2). So far, no large controlled study examining FMT as a maintenance therapy has been released.

There seems to be a consensus that, in the short-term, FMT is a safe treatment option in UC-management (1,3,14,29,31,32,38,40,41). Narula et al, in their meta-analysis, reported no significant difference in adverse events between the FMT and control group (41). About the long-term safety no statements can be made yet, due to short follow-up periods. However, long-term experience in the use of FMT in patients with recurrent *C. difficile* diarrhea seems reassuring (41).

The studies reported in this paper had relatively small study populations, the largest consisted of 81 patients. This makes it difficult to draw statistically significant and/or definite conclusions from the obtained results. These studies are very heterogeneous in terms of study structure (route of administration, number of administrations, etc.) and design (randomization, control, comparison,...), making it more difficult to compare or merge results. Moreover, as mentioned before, follow-up periods were relatively short, so very little is known about long-term results or side effects.

Future studies, ideally RCTs with larger study populations and a longer follow-up, should offer an answer to the following questions: is there a place for FMT in UC-treatment, possibly in the form of maintenance therapy? What makes a good stool donor, which bacterial species should be present in order to obtain a successful response? A quick search on clinicaltrials.gov shows us that in the following 3 to 4 years FMT in the treatment of UC will remain a hot topic. In May 2018 the first Belgian stool bank was established. The RESTORE study (NCT03110289) – a multicentre Belgian trial comparing the effect of 'super donor' FMT to autologous FMT – is currently ongoing.

In conclusion, FMT seems to be a promising and safe therapy in the management of UC. Further research, with larger cohorts, will be needed to confirm this and to determine the optimal FMT procedure (donor selection, route of administration, number of transplants).

Conflict of interest

None.

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