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Fecal Microbiota Transplantation (Fecal Transplant) for Adults With Inflammatory Bowel Disease



Image courtesy of OpenBiome.

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Summary

- Inflammatory bowel disease (IBD) includes Crohn’s disease and ulcerative colitis — lifelong conditions that can cause disabling symptoms, serious complications, and increased risk of death.
- People with IBD have reduced diversity of naturally occurring bacteria and other micro-organisms, and this may be a key aspect of the disease.
- Fecal microbiota transplantation (FMT) is the transfer of filtered fecal material from a healthy donor. Because FMT has been successful in treating some cases of *Clostridium difficile* (*C. difficile*) infection, it is being explored for the treatment of IBD.
- The evidence for FMT in IBD includes two recent systematic reviews and six subsequent studies, including two randomized controlled trials (RCTs). Several other trials are underway.
- Experts agree that, although FMT shows promise, current clinical evidence does not support its use for the treatment of IBD.

The Technology

IBD includes Crohn’s disease and ulcerative colitis. These chronic relapsing conditions are caused by inflammatory reactions that can damage the gastrointestinal tract.¹ The symptoms experienced during relapses depend on the segment of the intestinal tract involved, and range from mild to severe.² Ulcerative colitis is generally limited to the superficial layers of the large bowel; if untreated, it can lead to frequent bloody stools, toxic megacolon, and colorectal cancer.³ Crohn’s disease can involve any part of the gastrointestinal tract and can cause diarrhea, abdominal pain, fatigue, and malnutrition.³ Crohn’s disease can also have extraintestinal manifestations such as arthritis, liver disease, and growth impairment in children.⁴

The gastrointestinal tract is exposed to countless antigens, including both safe and disease-causing micro-organisms, and the immune system must discriminate among them.⁵ The micro-organisms (“microbiota”) include more than 1,000 species of bacteria plus fungi, parasites, and viruses that play a key role in nutrition, energy metabolism, host defense, and immune system development.⁶⁻⁹ Compared with healthy people, patients with IBD have reduced microbiota diversity, and some researchers feel that this may make the gut less adaptable to environmental changes and natural disturbances.^{1,10-12}

Manipulation of the microbiota has emerged as a possible treatment for IBD, including interventions such as diet, prebiotics, probiotics, antibiotics, and FMT.¹ An older therapy that has recently been rediscovered, FMT aims to restore a

healthy intestinal microbial community in a patient via the infusion of a filtrate of feces from a healthy donor.^{8,13} Donor feces are diluted with a liquid such as water or saline and strained to remove large particles. The resulting suspension is introduced into the recipient's gut via an upper gastrointestinal route (e.g., nasogastric tube or endoscope) or via a lower gastrointestinal route (e.g., rectal enema or working channel of a colonoscope).^{12,14}

FMT has shown very high cure rates for recurrent *C. difficile* infection, regardless of the recipient, donor, or delivery method.^{7,15,16} This may be due to correction of the relatively depleted, homogeneous intestinal microbiota that facilitated the growth of toxic organisms.¹¹ FMT may therefore be a promising approach for the management of other gastrointestinal diseases such as IBD.^{1,8,10,12,16}

IBD is common in Western industrialized countries, generally affecting about 0.4% of the population.¹¹

Regulatory Status

Health Canada considers FMT to be an “investigational new biologic drug”. For all indications other than the treatment of *C. difficile* infection, FMT must be used within a clinical trial that is authorized by Health Canada. A clinical trial application is not required if FMT is used for the treatment of unresponsive *C. difficile* infection, although sponsors must submit a notification to Health Canada's Biologics and Genetic Therapies Directorate, including informed consent of the patients.¹⁷

The US Food and Drug Administration (FDA) classifies human feces as a biological agent and has determined that its use in FMT therapy and other research should be regulated to ensure patient safety. The FDA is in the process of developing policy for the study and use of FMT therapy, primarily for *C. difficile*.¹⁸ The use of FMT is not regulated in the European Union, including the United Kingdom.^{15,19,20}

Patient Group

IBD is common in Western industrialized countries, generally affecting about 0.4% of the population.¹¹ Its incidence is

increasing in developing countries, possibly due to changing dietary habits and the related effects on microbiome composition.^{1,2} In 2012 there were an estimated 233,000 people with IBD in Canada (129,000 with Crohn's disease and 104,000 with ulcerative colitis) with an average incidence of 16.3 new cases of Crohn's disease and 12.9 new cases of ulcerative colitis per 100,000 people, or an estimated 10,200 new cases of IBD annually.²¹

Both diseases are thought to result from a combination of genetics, environment, and a dysfunctional host immune system.^{1,8,22} Concordance rates in monozygotic twins of 16% for ulcerative colitis and 35% for Crohn's disease suggest factors beyond genetics, in particular, the environment, may contribute significantly to the natural history of disease.^{1,22,23} Studies in different ethnic groups show an interaction between genetics and environment; for example, if a child moves from a low-incidence population in a developing country to a developed country where incidence rates are higher, the likelihood of IBD increases as the child ages.² The evidence that environmental factors play a role has led to interest in treatment strategies designed to modify the environment, including FMT.

Current Practice

Ileocolonoscopy is the gold standard for the diagnosis of IBD. Magnetic resonance imaging (MRI) can be an attractive supplementary option to monitor treatment because it is relatively non-invasive, does not expose the patient to ionizing radiation, and requires minimal bowel preparation.^{3,24}

There is currently no cure for IBD. Current treatment practice focuses on the management of inflammation rather than management of an underlying cause.¹¹ Treatment goals include: control of symptoms with minimal use of corticosteroids; biological remission (normalization of inflammatory biomarkers); endoscopic remission (mucosal healing); and prevention of disease-related complications, disability, and death.²⁵ Treatment decisions are based on disease location and severity, complications, individual symptomatic response, tolerance to medical intervention, and patient access to diagnostic and treatment options.²

Drug treatment typically involves initial therapy followed by long-term maintenance. Conventional treatment algorithms feature sequential use of anti-inflammatory and immune-modulating drugs including aminosalicylates, corticosteroids, immune modifiers such as methotrexate, and tumour necrosis

factor alpha antagonists such as infliximab.^{22,26} However, these drugs have numerous side effects (notably an increased risk of infection), cannot be administered orally, and can be very costly.^{1,2}

The conventional management approach has been progressive intensification of therapy as the disease worsens, although more aggressive therapy at an earlier stage of disease may improve clinical outcomes.²⁵ Current drug treatment is imperfect, with some patients showing only modest gains and others showing minimal responses.^{27,28} Surgery to remove or temporarily bypass parts of the intestine, plus other procedures such as abscess drainage, is required for 55% to 75% of patients with Crohn's disease and up to 30% of those with ulcerative colitis.^{2,24}

Methods

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and The Cochrane Library. Grey literature was identified by searching relevant sections of the CADTH Grey Matters checklist (<http://www.cadth.ca/resources/grey-matters>). No methodological filters were applied. The search was limited to English language documents published between January 1, 2013 and June 8, 2015, and selections were further limited to

FMT in patients with IBD but without *C. difficile*. Regular alerts were established to update the search until August 31, 2015.

The Evidence

The evidence included two systematic reviews of FMT for IBD (Table 1)^{29,30} and six more recent studies (Table 2) of FMT treatment in patients with IBD not accompanied by *C. difficile*.^{28,31-35} The literature searches for the two systematic reviews ended in July 2013²⁹ and May 2014.³⁰ Despite the number of studies included in these reviews (n = 7 and n = 18), the total patient numbers were low. A little more than 100 patients were included in each review, with most patients affected by ulcerative colitis and few (5% to 35%) affected by Crohn's disease.

Systematic Reviews

The review of 18 studies³⁰ included nine prospective, uncontrolled, cohort studies, eight retrospective case studies or case reports, and one RCT. The studies included both adults and children (Table 1). Of the 122 patients included in the systematic review, 79 (65%) had ulcerative colitis, 39 (32%) had Crohn's disease, and four (3%) had unclassified IBD. Overall, clinical remission was achieved by 45% of patients. The authors conducted a meta-analysis of the nine cohort studies (70 patients). Follow-up was short, with only four of nine studies following patients for three months or longer.

Table 1: Included Systematic Reviews of Fecal Microbiota Transplantation for Inflammatory Bowel Disease

Authors (Year); Author Location(s); Literature Search End	Included Studies	Patients	Outcomes
Colman and Rubin (2014); ³⁰ US; literature search ended May 2014; no language restrictions	18 studies: 1 RCT, 9 cohort, 8 case studies	n = 122: 79 w/ UC, 39 w/ CD, and 4 w/ IBD unclassified	Overall, 45% of patients achieved CR; MA of cohort studies (i.e., case studies excluded) reported 36% CR (UC 22%, CD 61%)
Rossen et al. (2015); ²⁹ Netherlands, Canada, and Finland; literature search ended July 2013; restricted to English language studies	7 cohort studies ^a	n = 112: 106 w/ UC (4 had concomitant CDI) and 6 w/ CD	In UC, CR rates were 0% to 68%; in CD, no benefit was observed

CD = Crohn's disease; CDI = *Clostridium difficile* infection; CR = clinical remission; FMT = fecal microbiota transplantation; IBD = inflammatory bowel disease; MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review; UC = ulcerative colitis; w/ = with.

^a Overlap of five studies, i.e., five of the seven studies in Rossen et al. (2015) were among the 18 included in Colman and Rubin (2014).

The route of administration varied among studies as did the number of treatments. Meta-analysis results showed that the pooled proportion of patients who achieved clinical remission was 36% (95% confidence interval [CI], 17.4% to 60.4%). Subgroup analyses of the cohort studies by disease reported 22% clinical remission for patients with ulcerative colitis (95% CI, 10.4% to 40.8%) and 61% clinical remission for patients with Crohn's disease (95% CI, 28.4% to 85.6%), although the patient group with Crohn's disease across studies was small ($n = 39$). The authors noted that this technology is in its infancy, and more research is needed to determine the optimal treatment route, frequency and timing, as well as donor and microbiota characteristics.

The other systematic review was broader overall, examining FMT in gastrointestinal disease.²⁹ The subanalysis related to FMT in IBD included seven cohort studies (five of which were captured in the previously described review). The total number of patients was 112 with 95% having ulcerative colitis. Follow-up was generally at least three months (ranging from one to 198 months). All seven studies reported on clinical improvement (not clearly defined), with only four reporting on clinical remission. Clinical improvement ranged from 0% in a very small study of four patients with refractory Crohn's disease to 68% in a larger study of 62 patients with active ulcerative colitis. The four studies addressing clinical remission reported rates of 0% in two small studies of patients with refractory disease (one for Crohn's disease, one for ulcerative colitis) to 30% and 68% in two studies of patients with active ulcerative colitis. Endoscopic follow-up was employed in some of the studies, but these results were not reported. The authors concluded that patients with IBD should be treated with FMT only in the setting of clinical trials, due to the paucity of evidence in this patient group.

More Recent Studies

Six studies were published after the end of the literature searches for the two included systematic reviews: two double-blind RCTs,^{28,34,36,37} one comparative cohort study,³¹ and three case series studies (Table 2).^{32,33,35} Three studies were published only as conference abstracts.³¹⁻³³ The three comparative studies are discussed in more detail in the following paragraphs.^{28,37,38}

The two RCTs were limited to patients with ulcerative colitis. In both trials, patients in the intervention group received FMT, but administration routes varied (retention enema versus nasogastric tube), as did the frequency of administration (once weekly for six weeks versus at weeks 0 and 3) and the drug regimens of enrolled patients. In both cases, FMT was prepared from donated feces from healthy volunteers.

- One of the two RCTs was a Canadian trial conducted at three sites in Hamilton, Ontario.^{28,36} The primary outcome was clinical remission at week 7, defined as a favourable Mayo score (a composite of stool frequency, rectal bleeding, endoscopy findings, and physician global assessment) and complete healing of the mucosa. Of 75 adults enrolled, 70 completed the study with approximately equal withdrawals from each group (three in the FMT group and two in the control group). Patients received FMT ($n = 37$) or water only ($n = 38$) via retention enema once a week for six weeks. Patients, clinicians, and investigators were blinded to group assignment. There was no pre-intervention bowel lavage or antibiotic treatment. Results showed a statistically significant FMT benefit, with clinical remission at week 7 for nine of 38 (24%) patients in the FMT group versus two of 37 (5%) in the placebo group ($P = 0.03$). At longer follow-up (nine to 12 months), eight of the nine FMT group patients who were in clinical remission at week 7 remained in remission. Four patients were able to stop all medications and three patients continued with monthly FMT. Secondary outcomes between study groups were not statistically significant, including the proportions of patients with symptom improvement, quality of life scores, and serious adverse events (SAEs). Unfortunately, although enrolment was planned for 130 patients over 18 months, the study's Data Monitoring and Safety Committee terminated the trial at the halfway point because the trial did not meet its stated objectives, i.e., the difference between groups in the primary outcome (clinical remission) did not achieve statistical significance, nor did any of the secondary end points.

Table 2: Additional Individual Studies

Authors (Year), Location	Publication Type	Patients and Treatment	Outcomes
RCTs (double-blind)			
Moayyedi et al. (2015), ^{28,36} Canada (Hamilton, ON) ^a	Journal article (and conference abstract)	n = 75 pts w/ UC (FMT = 38, PL = 37); 50 mL infusion of donor FMT in water as a retention enema vs. water only for placebo group once weekly x 6	CR induced at 7 weeks: FMT 24% vs. PL 5%; 95% CI, 2% to 33% RCT was stopped by the DMSC before completion
Rossen et al. (2015), ^{34,37} Netherlands	Journal article (and conference abstract)	n = 48 pts w/ UC (FMT = 23, PL = 25); 50 mL infusion of 60 g donor FMT in water via NG tube vs. patient's own stool in water for placebo group, given at outset and 3 weeks later	No SS difference between groups after 12 weeks (ITT analysis: 30% vs. 20%; <i>P</i> = 0.51; PP analysis: 41% vs. 25%; <i>P</i> = 0.29) RCT was stopped by the DMSC before completion
Comparative cohort			
Scaldaferri et al. (2015), ³¹ Italy	Conference abstract	n = 15 pts w/ mild–moderate UC (FMT = 8, ST = 7)	CR induced at 12 weeks: FMT 38% vs. ST 29% (no statistics reported)
Case series			
Cui et al. (2015), ³⁵ China	Journal article	n = 30 pts w/ refractory CD	60% had CR at 6 months (peak CR was 70% at 3 months)
Ren et al. (2014), ³² China	Conference abstract	n = 4 pts w/ refractory IBD	100% had CR to different extents (no detail was provided)
Vaughn et al. (2014), ³³ US	Conference abstract	n = 8 pts w/ active CD	5 of 8 (62%) in CR at 4 weeks: 4 of 4 (100%) in CR at 8 weeks

CD = Crohn's disease; CI = confidence interval; CR = clinical remission; DMSC = Data Monitoring and Safety Committee; FMT = fecal microbiota transplantation; IBD = inflammatory bowel disease; ITT = intention-to-treat; NG = nasogastric; PL = placebo; PP = per-protocol; pts = patients; RCT = randomized controlled trial; SR = systematic review; SS = statistically significant; ST = standard therapy; UC = ulcerative colitis; vs. = versus; w/ = with.

^a An earlier report of this study with n = 53 (included in the Colman and Rubin SR) showed no statistically significant difference in outcomes between study groups.

- The other RCT was conducted at a single centre in the Netherlands.^{34,37} Adults with mild to moderate ulcerative colitis were randomized 1:1 to receive an infusion via nasogastric tube of donor FMT (n = 23) or their own fecal material (n = 25) after pre-FMT bowel lavage at the start of the study and three weeks later. Follow-up at 12 weeks included clinical and endoscopic assessment. Results showed no significant difference in rates of

clinical remission and endoscopic response between groups (intention-to-treat analysis 30% versus 20%, *P* = 0.51; per-protocol analysis 41% versus 25%, *P* = 0.29, for FMT versus controls, respectively). SAEs occurred in two patients in each group but were not considered to be related to the FMT. This trial was also stopped by the study's Data Monitoring and Safety Committee after the second interim analysis.

- A 12-week, open-label, comparative pilot study from Italy enrolled 15 patients with mild to moderate ulcerative colitis (FMT via colonoscopy = 8, standard therapy = 7).³¹ Feasibility and patient acceptance were of primary interest and, although two patients from each study group dropped out due to disease worsening, the authors concluded that the procedure was safe and well tolerated. For secondary outcomes, clinical remission occurred in 38% of patients in the FMT group versus 29% in those receiving standard therapy, and clinical response occurred in 50% versus 29% of patients (no statistics were reported).

ClinicalTrials.gov lists five studies (planned or underway) in adults with IBD, including four RCTs (Table 3). In addition, there is research published and underway in children with IBD.

Adverse Effects

FMT was generally well tolerated and authors described the treatment as safe, although not as safe as the experience showed for FMT in patients with *C. difficile* infection.^{20,22} Common adverse events (AEs) included fever, an increase in C-reactive protein (an indication of inflammation in response to infection), diarrhea, and vomiting.²² However, due to the sparse amount of evidence available to date, experts have questioned the long-term consequences of FMT with regards to infection, cancer, and autoimmune and metabolic diseases.²⁷ Both systematic reviews^{29,30} reported very few SAEs; however, some authors have commented that vigilance about potential SAEs is required in the absence of standard FMT protocols.^{29,39}

Table 3: Ongoing Trials of Fecal Microbiota Transplantation in Adults With Irritable Bowel Disease

Study Number; Type	Location	Status	Disease	n	Route of Administration	Follow-up
NCT02390726; RCT	US	Not yet recruiting	UC	20	NR	2 years
NCT02417974; RCT	US	Not yet recruiting	Prevention of CD recurrence after intestinal resection	44	Colonoscopy	6 months
NCT02335281; RCT	China	Recruiting	IBD (UC and CD)	40	NJ tube x 1 dose	1 year
NCT02199561; open-label cohort feasibility study	Canada	Recruiting	Active CD	20	Colonoscopy weeks 0, 4, and 8 + enema weeks 2 and 6	32 weeks
NCT01896635; RCT	Australia	Ongoing – not recruiting	UC	80	NR	8 weeks

CD = Crohn's disease; FMT = fecal microbiota transplantation; IBD = inflammatory bowel disease; NJ = nasojejunal; NR = not reported; RCT = randomized controlled trial; UC = ulcerative colitis.

In one RCT,²⁸ SAEs were reported in three (8%) patients in the FMT group and two (5%) patients in the control group. In the FMT group the three AEs included one patient with worsening abdominal discomfort who tested positive for *C. difficile* toxin after study exit and two patients who developed patchy inflammation of the colon and rectal abscess formation.

There is growing interest in patient-tailored approaches in the treatment of IBD, but currently it is not possible to determine which patients with IBD will benefit from FMT.

In the control group, the two affected included one patient who required a colectomy at three weeks for worsening colitis and one patient with patchy inflammation of the colon and rectal abscess formation.

In the other study,³⁷ two patients in each group suffered SAEs including cytomegalovirus infection (a patient in the control group), severe Crohn's disease, abdominal pain resulting in hospital admission, and cancer of the cervix (the study group was not reported for these three events).

Mild AEs during or shortly after treatment were reported in 78% of the intervention patients and 64% of the control patients ($P = 0.28$) in one study.³⁷ AEs reported by more than one patient included transient borborygmus (active bowel sounds), increase in stool frequency, vomiting after fecal infusion, transient fever, and nausea.

Administration and Cost

No standardized process for FMT is universally accepted or utilized.^{6,40} FMT material is medically classified as human tissue and is obtained from healthy anonymous donors or from patient-recruited family members or friends.⁷ There is no consensus as to the ideal donor, but currently donors undergo extensive screening via questionnaire (primarily aimed to identify high-risk behaviour), blood testing for diseases such

as hepatitis and HIV, and fecal testing to rule out pathological infections such as *C. difficile* and *Giardia*.^{6,7,27}

In a protocol used in some studies of FMT, stool is delivered for processing within several hours of collection and about 50 grams is mixed with 250 mL to 300 mL of water or saline, homogenized with a blender to achieve a liquid slurry, and filtered to remove particulate matter.^{7,13,28} The product is then delivered to the recipient's bowel via an upper gastrointestinal route (e.g., nasogastric tube) or a lower gastrointestinal route (enema or colonoscopy). The efficacy of FMT may be increased with the lower route over the upper route,^{7,27} although some sources maintain the efficacy is equal.⁹

Both fresh (within six to eight hours) and frozen products are used and oral capsules are becoming an option,^{7,27,41} as are synthetic forms of FMT.⁴² The advantages of a frozen product include the ability to shift from using individual donors selected for each patient to screened volunteer donors (as with blood donations), and to the banking of frozen processed material that is ready to use when needed.³⁹ Canadian researchers have formulated a stool substitute preparation, "RePOOPulate," a human probiotic from purified intestinal bacterial cultures of a healthy human donor, primarily for use for *C. difficile* infections.⁶

No economic analyses of FMT for IBD were identified. A 2013 report described the processing procedures and costs at one US academic centre.⁴⁰ The cost per screened donor was US\$441 including laboratory analysis of donor blood and stool, and the up-front cost of reusable processing materials (blender, filter, and scale) was about US\$600. Processing time per sample was 80 minutes to 110 minutes. Obtaining regulatory approval to acquire the processed fecal matter, through the clinical trials access route, takes additional time.

OpenBiome, a US non-profit organization, is devoted to making FMT easier, cheaper, safer, and more widely available by supplying hospitals with screened, filtered, and frozen material ready for clinical use.⁴³ The cost per unit is US\$635 (US\$385 for the unit and US\$250 for shipping and handling; the latter is waived for orders of 15 units or more). If stored correctly at -20°C , a specimen has a six-month shelf life. OpenBiome recruits healthy donors who must pass a 109-point clinical assessment; only 3% of prospective donors are accepted and OpenBiome pays US\$40 per donation.⁴⁴

Concurrent Developments

There is growing interest in patient-tailored approaches in the treatment of IBD, but currently it is not possible to determine which patients with IBD will benefit from FMT. Innovations in microbial-based therapies include basing treatment on an individual's particular intestinal microbiota profile to reduce pro-inflammatory species while also increasing the number or function of anti-inflammatory species, and the development of new biological drugs made in living cell lines.¹¹

Rate of Technology Diffusion

The success of FMT in treating *C. difficile* infection has raised the possibility of its use in IBD; however, regulation by Health Canada and the US FDA currently limits exploration of FMT for this indication to clinical trials. Despite this, a recent article noted that at least 80 clinics in the US are offering this treatment (medical conditions not specified).¹⁹

The possibility of a microbiological basis for conditions such as irritable bowel syndrome, obesity, metabolic disease, diabetes mellitus, and neurological diseases such as multiple sclerosis, Parkinson's disease, and chronic fatigue syndrome has been considered.^{7,13} There is also interest in FMT for autoimmune diseases such as rheumatoid arthritis, allergic disorders (atopy and asthma), idiopathic thrombocytopenic purpura, and various cancers.⁴⁵ Good evidence of the effectiveness of FMT for these conditions is still lacking.

Implementation Issues

Several researchers have surveyed patients with IBD to gauge their interest in this treatment, and responses have generally been positive.^{46,47} However, there is no consensus as to the ideal protocol for FMT – including patients most likely to respond, product preparation and storage, and the route and frequency of administration.^{7-9,12,22,28,48-51} For example, some IBD centres carry out bowel lavage before donor feces administration and also give antibiotics before FMT to facilitate the colonization of microbiota from the donor; however, it is not clear whether these steps are necessary.^{27,28,39}

There are advantages and disadvantages to each route of delivery.¹² FMT via nasogastric tube is minimally invasive and relatively low cost, but there is a risk of vomiting and aspiration. Gastroscopy may overcome some of these problems but it is invasive, requires sedation, and is a higher-cost procedure. Colonoscopy is more appealing to patients and enables evaluation of the lower digestive tract, but it requires sedation, has a risk of complications, and is also a higher-cost intervention.

There is also a concern that FMT's short-term benefits may not extend to the long term, as the adult microbiome is a highly stable structure resilient to short-term interventions and the patient may revert to the pre-treatment state once FMT treatment is completed.¹

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