REVIEW

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Therapeutic faecal microbiota transplantation: current status and future developments

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Purpose of review
Faecal microbiota transplantation (FMT) has undergone dramatic progression over the past year and continues to evolve as knowledge of the gastrointestinal microbiota (GiMb) develops. This review summarizes therapeutic advances in FMT, latest FMT therapies and presents the potential of FMT therapeutics in other gastrointestinal and extra-intestinal conditions.

Recent findings
The GiMb is now known to have a central role in the pathogenesis of many diseases. The success of FMT in curing *Clostridium difficile* infection (CDI) is well established and preliminary findings in other gastrointestinal conditions are promising. Published data from over 500 CDI cases suggest that FMT is generally well tolerated with minimal side effects. The commercial potential of FMT is being explored with several products under development, including frozen GiMb extract, which has been shown highly effective in treating relapsing CDI. Such products will likely become more available in coming years and revolutionize the availability and method of delivery of GiMb.

Summary
Recent literature unequivocally supports the use of FMT in treating relapsing CDI. Trials are underway to determine the therapeutic potential of FMT in other conditions, particularly inflammatory bowel disease. Therapeutic FMT is a dynamic field with new and emerging indications along with ongoing developments in optimal mode of administration.

Keywords
Clostridium difficile, colitis, Crohn's disease, faecal microbiota transplantation, inflammatory bowel disease, irritable bowel syndrome, sclerosing cholangitis

INTRODUCTION

In recent years, there has been considerable progress in our understanding of the gastrointestinal microbiota (GiMb) with consortiums such as the Human Microbiome Project [1] and the European-based Metagenomics of the Human Intestinal Tract (MetaHIT) established to investigate the resident microbiota of the human gastrointestinal tract. Studies resulting from these and other projects have helped elucidate the crucial role of microbiota in health homeostasis as well as disease pathogenesis and have altered the way we perceive the GiMb, no longer as just innocuous colonizers of our intestine but rather as active participants in determining human health and immune-mediated diseases. The GiMb has a much larger genome than its human host [2] and contributes to the development of various 'diseases' or 'microbiota pathology'. The GiMb is akin to a tissue, as it is a collection of various cell lines. The human GiMb, similar to any other tissue or organ in the body, exhibits not only such features as ontogeny, anatomy and physiology, which will not be described in this short review, but also the capacity to suffer from various pathological conditions and perturbations. An important therapy used to 'repair' the GiMb is faecal microbiota transplantation (FMT).

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KEY POINTS

- The gastrointestinal microbiota, its active role in health and disease and the therapeutic potential of FMT are areas of great global interest undergoing rapid developments and advances.
- The efficacy of FMT in multiple relapsing CDI and its superiority over antibiotic therapy is now unequivocal.
- FMT is an exciting potential therapy for IBD with encouraging case reports and series especially in ulcerative colitis, though at present controlled trial data are lacking.
- FMT may have therapeutic applications for a wide range of not only gastrointestinal but also systemic conditions (e.g. diabetes, obesity, autoimmune phenomena) found to have their pathogenesis related to gastrointestinal dysbiosis.
- There are several products under development, and in the future, FMT will likely shift from the use of crude, fresh whole stool to highly processed, filtered, frozen and potentially cultured formulations.

Manipulation of the GiMb through FMT is not a new concept. Records document its use by Ge Hong 2000 years ago in China to treat food poisoning and severe diarrhoea [3]. The first published use in western medicine was in 1958 by Eiseman *et al.* [4] for pseudomembranous enterocolitis. Since then, it has been offered in only a few centres globally, though this has changed in the last few years with growing mainstream acceptance.

FAECAL MICROBIOTA TRANSPLANTATION: RATIONALE FOR USE

In the setting of increasing research and understanding of the GiMb, along with growing global concern regarding antibiotic resistance, it is not surprising that there is mounting interest in FMT therapy for disease states related to dysbiosis. The main advantage of FMT over other forms of microbial manipulation, for example antibiotics, prebiotics and probiotics, is that FMT provides the full spectrum of microbial organisms from a healthy individual and therefore can treat as yet uncharacterized dysbiotic conditions, while bypassing the need to decipher the complex compositional and functional pathogenic intricacies of the dysbiosis.

The rationale for use of FMT is perhaps best understood from a murine CDI model in which antibiotic damage of the microbiota permits invasion by *Clostridium difficile*. Lawley *et al.* [5] treated mice with clindamycin and then infected them with *C. difficile* 027/BI isolated from patients with CDI. The mice developed chronic disease with persistent dysbiosis, ongoing CDI and reduced GiMb diversity. FMT using homogenized faeces from healthy mice suppressed CDI, allowing recovery of health. Although the mouse model does not fully reflect the human condition, it allows us to see that antibiotic damage to the GiMb permits invasion via lowered colonization resistance. This applies not only to CDI but also to other opportunistic pathogens, which can become established once the integrity of the GiMb is compromised. There are probably numerous mechanisms by which the bacteria in an FMT function, including bacteriocin production to inhibit pathogen growth [6]. The CDI model, however, does not apply uniformly to other dysbiosis conditions. For example, in idiopathic ulcerative colitis, FMT fails to cure with a single infusion as it generally does in CDI, likely reflecting a more established and chronic dysbiosis that requires longer FMT administration to allow healing and regrowth of the micro-ulcerated colonic epithelium [7].

FAECAL MICROBIOTA TRANSPLANTATION TREATMENT OF RELAPSING *CLOSTRIDIUM DIFFICILE* INFECTION

The success of FMT in CDI has been well established in many case series [8▪,9,10] and one randomized controlled trial [11▪▪], which have been discussed extensively elsewhere [12▪,13,14] and therefore will only be summarized in this review. Initial treatment of acute CDI entails the withdrawal of any precipitating antibiotics, if possible, and treatment with metronidazole, vancomycin or fidaxomycin; relapsing infection is treated either with further metronidazole or vancomycin, or prolonged vancomycin treatment in 'pulsed-tapered' protocols [15]. Patients with a first posttreatment recurrence have up to a 40% chance of a second recurrence and a 65% chance of recurrence after the next antibiotic retreatment [16]. It is this high relapse rate coupled with the epidemic proportions of CDI [17] that prompted the use of FMT, which had been accumulating a growing body of successful case reports and case series [18,19]. A systematic review of FMT in CDI from 27 countries involving over 300 cases [20] reported excellent cure rates for relapsing CDI of around 90% via colonoscopy and enema with 76.5% cure rates via nasogastric infusion. Consequently, FMT is now a recommended treatment for the third recurrence of CDI [15]. Acute CDI and first relapse are still treated with antibiotics, which seems counter-intuitive, as antibiotics are used to treat a disease that largely results from antibiotic-induced disturbance of the GiMb. Given its efficacy and the very low complication rate of FMT, we predict an exponential increase in patients who have their first relapse treated with FMT, particularly when a simplified

approved product such as encapsulated FMT oral therapy becomes available [13].

FAECAL MICROBIOTA TRANSPLANTATION TREATMENT OF INFLAMMATORY BOWEL DISAESE

Outside CDI, the greatest interest in FMT is as a potential therapeutic option in the inflammatory bowel diseases (IBDs).

Ulcerative colitis

Given the central role of GiMb dysbiosis in the pathogenesis of IBD [21], interest in FMT as a therapeutic option for ulcerative colitis is mounting. Case series suggest that it may be an effective therapy for some patients with ulcerative colitis [19,22,23,24▪,25,26], and formal randomized controlled trials are currently underway. Successful FMT for ulcerative colitis was first achieved in 1988 to reproduce in ulcerative colitis what Eiseman *et al.* [4] accomplished in pseudomembranous colitis. FMT treatment of this 1988 ulcerative colitis patient at the Centre for Digestive Diseases (CDD) resulted in durable clinical and histological cure to date of the patient's previously active disease. FMT was trialled as a treatment option for ulcerative colitis and other diseases at CDD, resulting in a case series that documented its use in 55 ulcerative colitis, Crohn's disease and irritable bowel syndrome (IBS) patients [22]. Historically, the first FMT for ulcerative colitis was reported in 1989 by Bennet and Brinkman [27] who 'proposed that bacterial metabolites of bile acids or cholesterol are involved in UC' and carried out an 'experiment implicating the colonic flora' by demonstrating reversal of Bennet's severe ulcerative colitis of 7 years duration using FMT enemas. Bennet became asymptomatic for the first time in 11 years, with no active inflammation 3 months after FMT. In 2003, a further case series of six patients with ulcerative colitis was reported, documenting the complete clinical, colonoscopic and histological reversal of ulcerative colitis in all patients who previously had severe, relapsing ulcerative colitis [23].

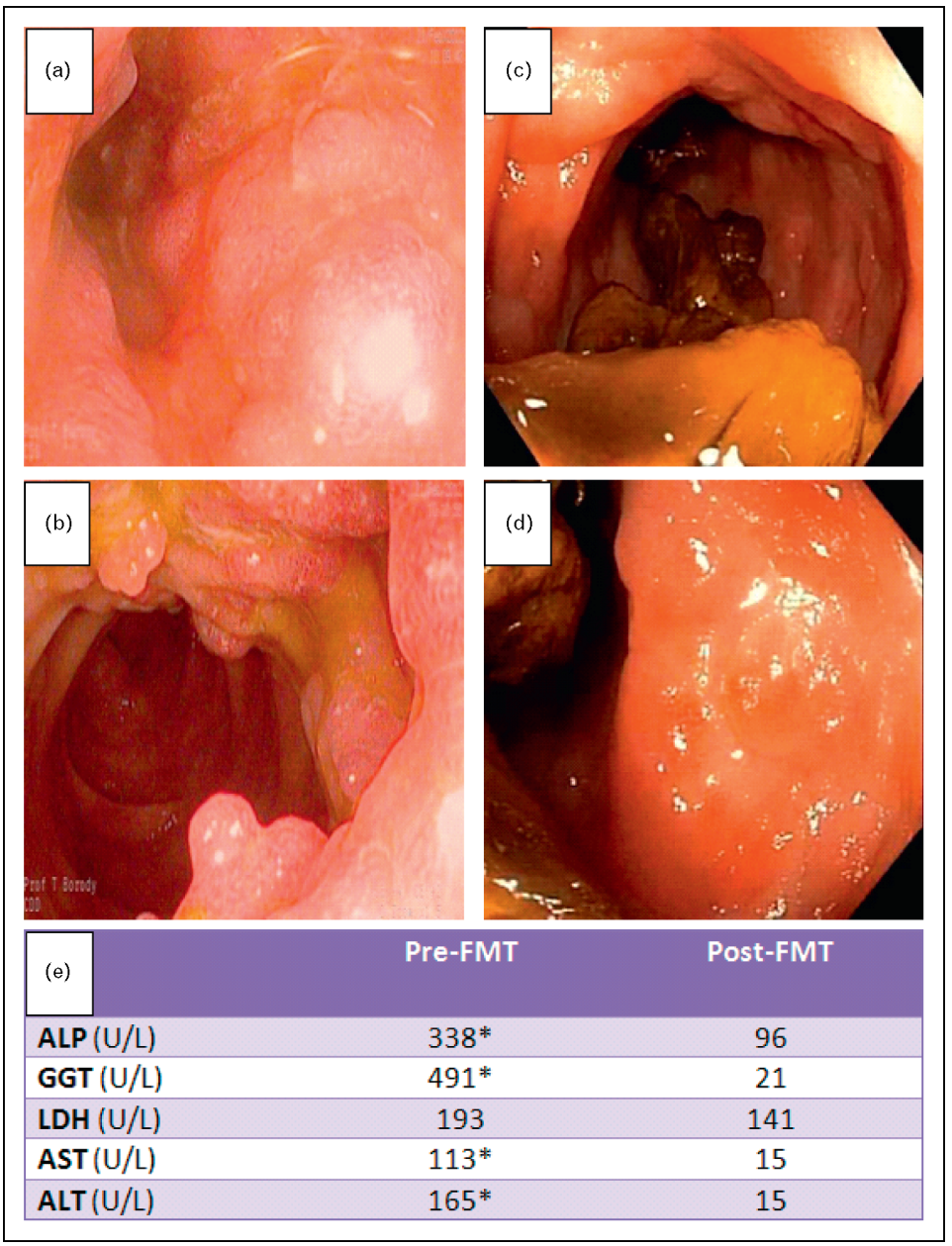
In 2012, a retrospective review was conducted of 62 ulcerative colitis patients who had undergone FMT over a 24-year period at CDD [24▪]. This study reported a 91.9% response rate to FMT with 67.7% achieving complete clinical remission after FMT, defined as a 0–1 score on a modified Powell–Tuck Index; 24.2% achieved partial remission (defined as a $\geq$2 point decrease) and only 8% were nonresponders. In 12 of the 21 (57%) patients who had a repeat colonoscopy performed (mean follow-up time 33 months; range 1–198 months), normal mucosa was documented with absence of histological inflammation. Noting that ulcerative colitis requires multiple FMT infusions, such patients are now treated in CDD with the first FMT transcolonoscopically followed by daily enemas for 14 days, then second daily, X3 per week, X2 per week and ultimately weekly at each step for a period determined by clinical response with a colonoscopic review at 12 weeks but without a bowel lavage to preserve the therapeutic microbial luminal contents.

In a small phase 1 paediatric trial of FMT in 10 children and young adults with mild–moderate ulcerative colitis using five consecutive daily infusions [28▪], 33% achieved clinical remission at the end of 1 week and 78% had a clinical response, with 67% maintaining a clinical response at 4 weeks. Although these results are promising, they confirm that FMT response in ulcerative colitis is not as robust as in CDI, and again suggest that recurrent FMT infusions are required. In our experience, this needs to be continued for a minimum 14 days, but in many patients for weeks, to obtain durable results in ulcerative colitis. Exceptionally, some patients with ulcerative colitis may achieve cure with one to two FMT enemas.

FMT in ulcerative colitis also potentially may have beneficial effects on the extraintestinal complications of the disease. Figure 1 relates to a patient with ulcerative colitis who not only showed improvement in colitis but also normalization of previously markedly elevated liver biochemical tests associated with sclerosing cholangitis, though no radiologic studies are available to confirm improvement.

Crohn's disease

Available data on FMT in Crohn's disease are limited to case reports and small case series [22,26,29]. Vermeire *et al.* [29] reported no significant clinical or endoscopic improvement at 8 weeks in four patients with refractory Crohn's disease administered FMT via nasojejunal tube three times over a 2-day period. Transient recipient GiMb changes were observed in all patients (weeks 2–4) returning to baseline microbial composition by week 8. These findings along with other studies suggest that Crohn's disease has an increased resistance to FMT relative to ulcerative colitis, although preliminary data suggest that intensive, prolonged FMT may result in a clinical response and sustained GiMb transformation in some Crohn's disease patients. An illustrative case of terminal ileal Crohn's disease that normalized histologically has been published [30]. We present here an example of a patient with CDI and Crohn's colitis treated with FMT 12 years ago in whom not only the CDI but also Crohn's colitis was cured (Fig. 2). The implication of the



	Pre-FMT	Post-FMT
ALP (U/L)	338*	96
GGT (U/L)	491*	21
LDH (U/L)	193	141
AST (U/L)	113*	15
ALT (U/L)	165*	15

FIGURE 1. Inflammatory bowel disease with concurrent sclerosing cholangitis pre and post-FMT. A 38-year-old man with a 6-year history of ulcerative colitis, concurrent multiple sclerosis, sacroileitis and sclerosing cholangitis was treated with an initial transcolonoscopic FMT infusion, followed by over 100 FMT enemas during the next 12 months. After 4 weeks of daily FMT enemas, the patient's IBD symptoms had dramatically improved, liver biochemical tests had normalized and sacroileitis pain was absent. (a, b) Transverse colon and hepatic flexure (respectively), pre-FMT. (c, d) Transverse colon and hepatic flexure (respectively), post-FMT without bowel prep. (e) Liver biochemical tests immediately prior to FMT, and 12 months post-FMT.

influence of *C. difficile* and other infections or alterations in the GiMb on induction and maintenance of Crohn's disease activity is a subject of immense current interest.

IRRITABLE BOWEL SYNDROME

FMT has also been explored as a potential therapy for refractory IBS.

Faecal microbiota transplantation in diarrhoea-predominant irritable bowel syndrome

Up to 30% of patients with IBS are thought to have acquired the condition after a bout of gastroenteritis, implicating a dysbiotic GiMb in at least this segment of IBS patients [31]. If the CDI pathogenicity model applies to IBS, then FMT also may be effective in this group of patients. Indeed, positive outcomes using

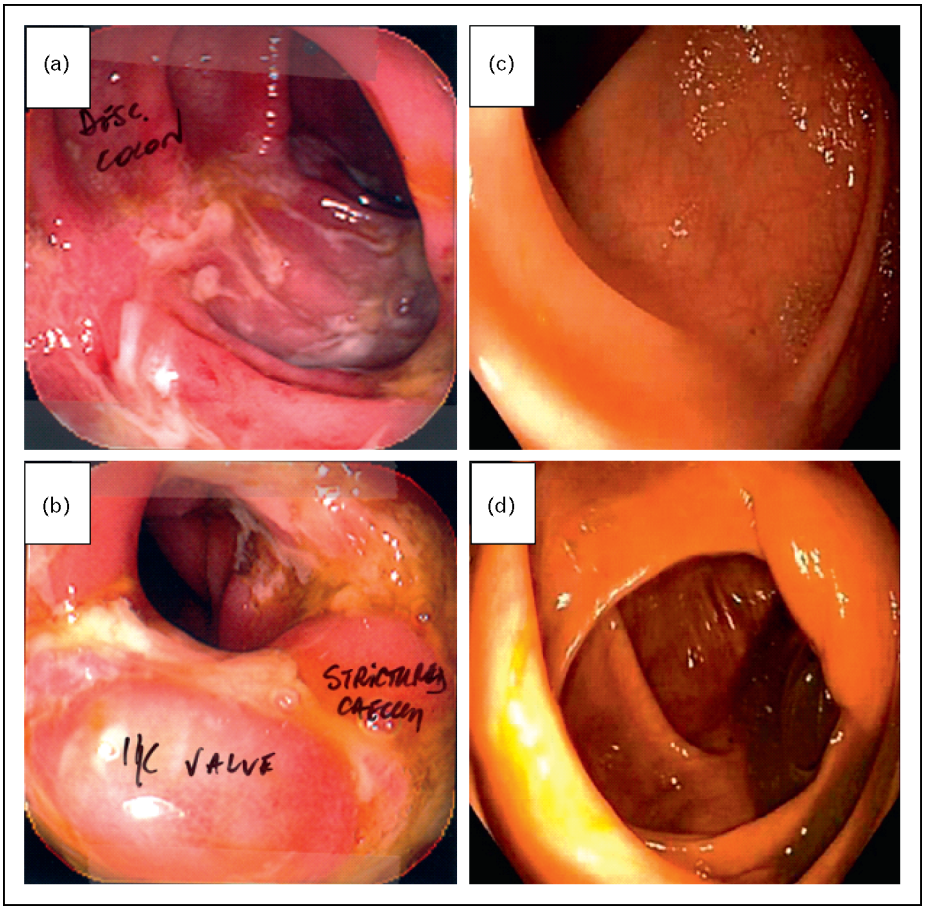


FIGURE 2. Crohn's colitis pre and postfaecal microbiota transplantation. A 46-year-old woman with a 2-year history of Crohn's colitis was treated with a single, large volume nasojejunal infusion of FMT over 6 h for concurrent CDI. (a, b) Descending colon and caecum (respectively), pre-FMT. (c, d) Descending colon and caecum (respectively), 12 years post-FMT. Stricture completely normalized.

FMT in IBS-D have been reported [22]. Pinn *et al.* [32] reported on 13 patients with refractory IBS (nine with IBS-D, three with IBS-C and one alternating IBS-D and IBS-C), 70% of whom had resolution or improvement in symptoms after FMT, including abdominal pain (72%), bowel habit (69%), dyspepsia (67%), bloating (50%), flatus (42%) and quality of life (46%) (Table 1).

Faecal microbiota transplantation in constipation-predominant irritable bowel syndrome

Patients with IBS-C have been shown to have increased levels of sulphate-reducing bacteria compared with healthy controls [33] and methane-producing bacteria are also closely associated with constipation [34]. If IBS-C is similar to the CDI model wherein a pathogen produces toxins that inhibit intestinal motility, use of FMT could be a viable treatment option. Borody *et al.* [22] first documented that FMT could cure constipation and this was followed by a more complete case description showing reversal of symptoms, melanosis and dysmotility [35]. A case series was later published of 45 patients with IBS-C who were treated with transcolonoscopic FMT followed by FMT enema infusions of 17 cultured GiMb components. Immediately following the procedure, 40 of 45 patients (89%) reported relief in defecation, bloating and abdominal pain. Normal defecation, without laxative use, persisted in 18 of 30 patients (60%) contacted 9–19 months later [36].

FAECAL MICROBIOTA TRANSPLANTATION IN AUTOIMMUNE CONDITIONS

Case reports suggesting possible therapeutic efficacy of FMT in autoimmune conditions exist, often noted as incidental phenomena detected during the use of FMT for CDI, ulcerative colitis and IBS.

Table 1. Faecal microbiota transplantation treatment in eight patients with diarrhoea-predominant irritable bowel syndrome

Patient	Pre-FMT condition	FMT regime	Post-FMT	
BW (78-year-old woman)	Symptom duration: >10 years		Antibiotic pretreatment schedule:	Three months post-FMT:
	• Chronic diarrhea (×years duration)	• Urgency	Oral vancomycin (500 mg b.i.d.), oral metronidazole (200–400 mg b.i.d.) for 9 months prior to FMT.	• Occasional diarrhoea
	• 4–6 stools/day	• Left iliac fossa (LIF) pain	FMT regimen: TC# infusion and 1 enema infusion	• ~2 stools/day
	• Nocturnal stools	• Long-term loperamide (10 mg daily)		• 5 kg weight gain
	• Incontinence			• Symptomatically much better
JG (40-year-old man)	Symptom duration: >3 years		FMT regimen: TC infusion and 9 enema infusions	Three months post-FMT:
	• Diarrhoea	• Nausea		• Marked improvement (75%) in bloating, tenesmus, feeling of incomplete evacuation, abdominal discomfort, nausea, joint pain and lethargy
	• Bloating	• Joint pain		• Complete resolution of diarrhoea
	• Tenesmus	• Lethargy		• No longer dairy intolerant
	• Feeling of incomplete evacuation	• Malaise		
	• Abdominal discomfort	• Lactose intolerance		
KP (49-year-old woman)	Symptom duration: > 4 years		Antibiotic pretreatment schedule:	Five months post-FMT:
	• Diarrhoea	• Flatulence	Oral vancomycin (250 mg mane, 500 mg nocte), oral rifaximin (200 mg b.i.d.) for 3 months prior to FMT.	• 1 stool/day
	• Occasionally explosive	• Decreased mental acuity	FMT regimen: TC infusion and 9 enema infusions	• 90% resolution of diarrhoea
	• Abdominal pain	• Daily nausea		• Improved food tolerances Markedly reduced bloating
	• Extensive food intolerances			
BL (78-year-old man)	Symptom duration: 5 years		Antibiotic pretreatment schedule:	Three months post-FMT:
	• Diarrhoea		Oral vancomycin (500 mg b.i.d.) for 12 months prior to FMT	• Resolution of diarrhoea
	• 2–3 watery motions/day		FMT regimen: TC infusion and 4 enema infusions	• 1–2 soft, formed motions/day

DH (51-year-old woman)	Symptom duration: 12 years		FMT regimen: TC infusion and 9 enema infusions	Six months post-FMT:
	• 1–12 watery motions/day	• Bloating		• Resolution of diarrhoea
	• Abdominal pain	• Fatigue		• 2–3 formed motions/day
	• Flatulence	• Decreased mental acuity		• Infrequent abdominal pain
				• Increased energy
BB (29-year-old man)	Symptom duration: 3 years		Antibiotic pretreatment schedule:	
	• Diarrhoea	• Severe urgency	Oral vancomycin (500 mg b.i.d.), oral metronidazole (200 mg b.i.d.) for 1 month prior to FMT.	• Resolution of diarrhoea, spare occasional episodic diarrhoea
	• 5 motions/day	• 10 kg weight loss	FMT regimen: TC infusion and 9 enema infusions	• Generally 1–2 motions/day
	• Abdominal cramping and pain	• Loperamide use to control symptoms		• Minimal pain
				• Resolution of bloating.
				• Cessation of UC medication
JM (58-year-old woman)	Symptom duration: > 28 years		Antibiotic pretreatment schedule:	Nine months post-FMT:
	• Explosive diarrhoea	• Up to 7 motions/day	Oral vancomycin (500 mg b.i.d.)	• 1–2 formed motions/day
			For 2 months prior to FMT	• Increased food tolerance
			FMT regimen: TC infusion and 4 enema infusions	• Cessation of Loperamide and cholestyramine medications previously used to control diarrhoea
RB (60-year-old man)	Symptom duration: >15 years		Antibiotic pretreatment schedule:	10 months post-FMT:
	• Long-standing diarrhoea	• Bloating	Oral vancomycin (250 mg b.i.d.), oral rifaximin (200 mg b.i.d.) for 2 months prior to FMT	• Intermittent symptoms: episodic diarrhoea with colicky pain, marked improvement
	• >10 watery motions/day	• Nausea	FMT regimen: TC + 4 enema infusions	
	• Severe abdominal pain	• Urgency		
	• Cramping			

b.i.d., twice daily; FMT, faecal microbiota transplantation; UC, ulcerative colitis.

Idiopathic thrombocytopaenic purpura

We have previously reported the unexpected reversal of idiopathic thrombocytopaenic purpura (ITP) in a patient with long-standing ulcerative colitis treated with FMT that resulted in prolonged normalization of platelet levels along with resolution of ulcerative colitis activity [37].

Multiple sclerosis

An infectious cause of multiple sclerosis (MS) has been speculated, though the potential for gastrointestinal pathogens to exert neurological effects remotely (as seen with many Clostridium species) has not been considered likely. In 2011, Borody *et al.* [38] reported three wheelchair-bound patients with MS treated with FMT for constipation. Bowel symptoms resolved following FMT; however, in all cases, there was also a progressive and dramatic improvement in neurological symptoms, with all three patients regaining the ability to walk unassisted. Two of the patients with prior indwelling urinary catheters experienced restoration of urinary function. In one patient of the three, follow-up MRI 15 years after FMT showed a halting of disease progression and 'no evidence of active disease'.

FAECAL MICROBIOTA TRANSPLANTATION IN METABOLIC DISEASES

A small, randomized, double-blind controlled trial demonstrated that FMT using stool from lean donors significantly improves insulin sensitivity in obese male individuals, with butyrate-producing intestinal bacteria increasing in intestinal samples [39▪]. These findings provide further evidence of a possible causal role for GiMb driving obesity, insulin resistance and perhaps hepatic steatosis [40–42].

FAECAL MICROBIOTA TRANSPLANTATION FOR OTHER CONDITIONS

There is also interest in FMT as a therapeutic option for conditions as diverse as halitosis, autism, chronic fatigue syndrome [43], nephrolithiasis, acne and for symptomatic relief in Parkinson's disease [44].

THE FUTURE OF FAECAL MICROBIOTA TRANSPLANTATION

The GiMb is in the midst of a revolution in terms of research interest, our understanding and therapeutic potentials. There are several products extracted from whole stool, which is traditionally utilized for FMT, under development that are either approaching or are under review by the U.S. Food and Drugs Administration (FDA). These include both high-level extracts that contain the entire spectrum of human gastrointestinal microbes and cultured products with much smaller numbers of microbiota specifically developed and targeted to fulfill a particular indication (e.g. curing relapsing CDI) along with 'cultured whole microbiota' that may have broader applications.

CONCLUSION

The last few years have seen this ancient therapy that is elegantly simple and cost-effective in its purest form finally embraced by mainstream medicine as a genuine therapeutic option. The efficacy of FMT in CDI is unequivocal. It is actively being studied as a treatment option in other conditions including IBD, IBS and metabolic syndrome/insulin resistance. In coming years, as outcomes of trials become available, it is expected that indications for FMT will broaden and it will become more available and easily accessible. Incidental evidence of FMT benefit in comorbidities may further expand indications to conditions previously not associated with gastrointestinal dysbiosis and for which therapeutic GiMb manipulation may play a role. At the same time, we need to remain actively vigilant of any long-term safety issues that may arise from modification of the GiMb, as we expand FMT indications and its use becomes more prevalent.

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Professor Thomas J. Borody has a pecuniary interest in the Centre for Digestive Diseases, where faecal microbiota transplantation is a treatment option for patients and he has filed patents in this field.

Conflicts of interest

Professor Lawrence J. Brandt has no financial interest or affiliation with any institution, organization or company relating to the manuscript.
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