REVIEW

Manipulation of the intestinal microbiome-a slow journey to primetime

Ofra Kriger-Sharabi, Stephen D H Malnick, David Fisher

Ofra Kriger-Sharabi, Institute of Gastroenterology, Assuta Medical Center, Ashdod 7747629, Israel

Stephen D H Malnick, Department of Internal Medicine, Kaplan Medical Center, Rehovot 76100, Israel

David Fisher, Department of Endocrinology, Soroka Medical Center, Beer Sheva POB 151, Israel

Corresponding author: Stephen D H Malnick, MD, Doctor, Department of Internal Medicine, Kaplan Medical Center, Derech Pasternak 1, Rehovot 76100, Israel. steve_m@clalit.org.il

Abstract

The gut microbiota has important functions in the regulation of normal body functions. Alterations of the microbiota are being increasingly linked to various disease states. The microbiome has been manipulated *via* the administration of stool from animals or humans, for more than 1000 years. Currently, fecal microbiota transplantation can be performed *via* endoscopic administration of fecal matter to the duodenum or colon or *via* capsules of lyophilized stools. More recently fecal microbial transplantation has been shown to be very effective for recurrent *Clostridoides difficile* infection (CDI). In addition there is some evidence of efficacy in the metabolic syndrome and its hepatic manifestation, metabolic associated fatty liver disease (MAFLD), irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). We review the current literature regarding the microbiome and the pathogenesis and treatment of CDI, MAFLD, IBS and IBD.

Core Tip: We review the current literature regarding the microbiome and the pathogenesis and treatment of *Clostridoides difficile* infection (CDI), metabolic associated fatty liver disease (MAFLD), irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Fecal microbial transplantation is an established treatment option in recurrent CDI. There is also promising evidence of efficacy in MAFLD, IBS and IBD which require further work to establish its role in managing these conditions.

INTRODUCTION

The human intestine comprises a mechanical, chemical, immune, and microbial barrier and plays a crucial role in maintaining a steady state between immune tolerance and immune responses in our gut. This barrier comprises a mucous layer and beneath it lies an epithelium. Underneath the epithelium lies the lamina propria which hosts innate and adaptive immune cells. The mucous layer (composed of mucins) serves as a physical barrier, enables the passage of nutrients, has anti-microbial activity, and is home to gut microbiota. The last decade has brought about a dramatic expansion in the understanding of the composition and function of the microbiota of the human gut. The human microbiota contains 10–100 trillion microorganisms, including bacteria, viruses, protozoa, and fungi[1]. Of these, bacteria are the most common with the majority being found in the phyla Firmicutes. Firmicutes and Bacteroides are dominant in the gut flora of the healthy host[2]. The gut microbiome is the largest known group of cells in the body and is now recognized as an organ in its own right. The microbiome has a key role in several aspects of host homeostasis including nutrition, immunity, metabolism, and defense mechanisms[3]. It should be noted that the microbiota also contains viruses and protozoa whose exact role has not yet been elucidated.

The gut microbiota is influenced by many factors, amongst them: Age, gender, hormonal state, nutrition, medications, antibiotic use, infections and smoking, therefore it is a dynamic environment[4]. Advances in genetic sequencing techniques and bioinformatics approaches for the analysis of large amounts of data have advanced our capacity to question the relationship of the microbiome to human health and disease.

HISTORY OF FECAL MICROBIOTA TRANSPLANTATION

Fecal microbiota transplantation (FMT) is a treatment that consists of the transfer of fecal material from a healthy individual to a patient with a disturbed microbiome. In so doing, FMT restores equilibrium to an imbalanced gut flora that has been implicated in numerous conditions, most notably in *Clostridoides difficile* infection (CDI).

Human feces is composed predominantly of water (typically around 75%)[5] and microbial material which is mainly bacterial[6]. The bacteria may be subdivided into viable (49%), injured (19%) and dead (32%) cells[7]. Other organisms that are present in stool include archaea, fungi and microbial eukaryotes[8].

Fecal matter was first known to have been used therapeutically in the 4th century in China. People with food poisoning and diarrhea were treated with 'yellow soup' which was described in contemporary medical works as consisting of a human fecal solution, which had a beneficial effect[9]. In modern medicine, in 1958, the realization that an abnormal gut microbial balance caused by antibiotic treatment could be ameliorated with fecal matter from healthy individuals resulted in the recovery of 4 critically ill patients with pseudomembranous colitis. Those individuals were treated with fecal enemas from healthy donors[10]. It was subsequently shown that pseudomembranous colitis was associated with CDI[11] and FMT is now an approved treatment option for resistant CDI in many countries.

Changes in the microbiota have also been suspected to contribute towards the development of inflammatory bowel disease (IBD). A recent systematic review and meta-analysis found a clinical and endoscopic benefit to using FMT as a treatment for ulcerative colitis (UC)[12].

A disrupted intestinal barrier has also been implicated in several other conditions and FMT has been proposed as a possible treatment option[13]. Conditions include the metabolic syndrome, kidney disease[14], multiple sclerosis[15] and osteoporosis[16].

The metabolic syndrome includes a constellation of findings including insulin resistance, dyslipidemia, hypertension and increased abdominal girth. One animal study induced metabolic syndrome in rats using a fructose-rich diet. When the rats started to produce biochemical markers of metabolic syndrome, they were also found to have increased colonization of different gut organisms compared to their gut flora before they had a received the fructose-rich diet. This reflected a reduction in microbial diversity[17]. In humans with metabolic syndrome, following duodenal FMT, peripheral insulin sensitivity was improved 6 wk post treatment which coincided with an increase in gut microbial diversity. It was concluded that FMT may be developed as a therapeutic agent to increase insulin sensitivity[18].

Metabolic associated fatty liver disease (MAFLD) is the liver manifestation of metabolic syndrome and is often associated with insulin resistance and obesity. It has been shown in mouse studies that inflammatory changes in the gut microbiota are associated with hepatic steatosis and inflammation which leads to MAFLD[19]. One animal study induced hyperglycemia and the production of pro-inflammatory cytokines in a mouse using a high fat diet to simulate metabolic syndrome. They then took intestinal microbiota from that mouse and used the material to colonize germ-free mice. Mice that received this microbiota developed hyperglycemia and insulinemia and hepatic steatosis thus showing the influence of microbiota on the development of MAFLD[20]. It has also been demonstrated that a more permeable intestinal barrier is involved in the development of MAFLD[21] and is associated with the degree of steatosis[22]. A trial of FMT to 21 patients with MAFLD did not improve insulin resistance although they did have a reduction of gut permeability[23]. However, a subsequent randomized controlled trial (RCT) which administered FMT *via* colonoscopy to patients with MAFLD, found a statistically significant reduction in liver fat attenuation which was calculated based upon liver elastography imaging[24].

The uses of FMT continue to be expanded and developed in a range of conditions. Similarly, the methods of administration have also developed. In Israel there are strict criteria that identify suitable donors (Table 1) and pre-donation screening tests (Table 2). Whilst initial methods of administration involved invasive colonoscopies, studies have shown that oral capsules are not inferior to colonoscopy-administered therapy when used to treat CDI[25,26] and colonic transendoscopic enteral tubing have proven a promising option for recurrent treatments[27]. Recently the use of washed microbiota transplantation has been reported from China[28]. This is similar to traditional FMT but the bacterial solution is prepared by an intelligent microorganism separation system. A recent report has shown an improvement in the metabolic syndrome using this method of fecal preparation. The protocol involves application of the washed fecal material *via* the upper gastrointestinal (GI) tract (nasojejunal tube) or the lower GI tract (endoscopic intestinal tube). There are three courses of treatment. Each course consist of 120 mL of washed bacterial solution, once a day for three days. This is done once a month for three months and then a further course three months after the last dose.

TREATMENT OF CDI

CDI causes pseudomembranous colitis. The first-line treatment of CDI is oral vancomycin which has been shown to be minimally systemically absorbed and has a high degree of activity against *Clostridium difficiles*[29]. Fidaxomicin is an alternative oral choice which was approved by the FDA in 2011 and has similarly highly activity against *Clostridium difficiles*. It has the advantage of being a narrow spectrum agent and it is rare for *Clostridium difficiles* to develop resistance to fidaxomicin[30]. The two agents are similarly effective although patients are less likely to develop a recurrent infection if they are treated with fidaxomicin rather than vancomycin following a first recurrence[31]. Guidelines therefore recommend initial treatment with either agent[32]. In non-severe infection, if vancomycin and fidaxomicin are unavailable, metronidazole (which is often cheaper) may be used instead although it has been shown that treatment failure and recurrence are more likely with this therapy[33].

It is thought that around 20% of patients with CDI will subsequently suffer from recurrent CDI (rCDI)[34]. Recurrence occurs due to a relapsed infection following unsuccessful bacterial eradication or due to reinfection by a different strain of the same bacteria from a difference source. Patients over the age of 65 years, or who are immunocompromised, or who have severe CDI when they present for treatment, are more likely to experience rCDI. These patients may benefit from treatment with a single intravenous dose of bezlotoxumab alongside antibiotic therapy if they re-present with a recurrence within 6 mo of their initial infection[32]. The human monoclonal antibody binds directly to the *Clostridium difficiles* toxin and thereby prevents further epithelial damage and colitis[35] and in patients at risk of rCDI, it reduces the chance of recurrence[36]. Caution should be used when considering the use of bezlotoxumab in patients with a history of congestive heart failure[32].

Guidelines suggest that if antibiotic treatment has been provided for 2 separate recurrences, on the third recurrence, FMT should be considered. In a randomized study of 46 patients who had previously had 3 or more recurrences of CDI despite a full course of vancomycin treatment, 90% were clinically cured following FMT treatment administered *via* colonoscopy, over an 8-wk follow-up[37]. In a study that investigated the long-term follow-up of patients (which ranged between 3 to 68 mo), 91% achieved a cure without recurrence with 90 d of colonoscopy administered FMT[38].

When compared with vancomycin, the differences in efficacy were stark in a study which compared the two treatments amongst patients with rCDI. Of 16 patients who were treated with a duodenal infusion of FMT, 13 (81%) had resolution of their symptoms after one infusion. These patients did not have a further recurrence in the 10 subsequent weeks of follow-up. A further 2 patients had resolution of their symptoms after a second infusion. This compared with 13 patients who received further vancomycin therapy, where a resolution of their symptoms was achieved in only 4 (31%) patients. Owing to the significant differences in efficacy between the two treatments the study was stopped early after an interim analysis[39].

It has also been suggested that FMT should be evaluated further for use in primary CDI. In a study to establish the proof-of-concept, 9 patients with primary CDI received FMT and 11 received metronidazole. 5 (56%) of the patients who received FMT were cured by the therapy and a further 3 patients received additional antibiotics and 2 of them were also subsequently cured. This compared with 5 (45%) patients in the metronidazole group who were cured by the treatment [40].

Table 1 Summary of pre-stool donation screening requirements and exclusion criteria based on Medical Circular of the Ministry of Health, Israel, date December 2022[107]

Pre stool donation screening	Exclusion criteria for stool donation
Current illness or exposure to endemic illness in the last 6 mo	Viral or bacterial illness in the week prior to donation, persistent fever, a visit in the last 6 mo to a country with an endemic infectious disease including parasitic diseases and traveler's diarrhea
Malignancy or gastrointestinal disease	Malignant disease (current or past), personal or family history of inflammatory bowel disease, personal history of IBS or symptoms of IBS, or celiac disease
Hepatitis risk and the risk of sexually transmitted infection	Tattoo or piercing or blood transfusion within 6 mo prior to donation, casual unprotected sexual intercourse within 3 mo prior to donation or previous sexual contact with an intravenous drug user or sex worker. Sexual contact with a person infected with HTLV or HIV or hepatitis in the previous 6 mo
Chronic disease	Chronic liver disease, neurological or autoimmune or rheumatological or hematological or metabolic or endocrine (aside from Hashimoto's disease) or heart or lung or atopic disease. Chronic pain or chronic fatigue syndromes. Previous malaria diagnosis or rare infectious disease
Surgical history	Previous gastrointestinal surgery, recipient of transplanted tissue
Medication history	Any long-term medication use or short-term use of immunosuppressive medication or probiotics, antibiotics use within the previous 6 mo, current or previous chemotherapy, previous recipient of growth hormone or recipient of a live attenuated virus injection in the last 3 mo
Illicit drug history	Previous illicit drug use (mariuana is an exclusion only if used within 3 mo of donation)

HTLV: Human T lymphocytic virus; HIV: Human immunodeficiency virus; IBS: Irritable bowel syndrome.

Table 2 Summary of testing prior stool donation based on Medical Circular of the Ministry of Health, Israel, date December 2022[107]

Test type	Test name
Blood tests	Complete blood count
	Urea and electrolytes including calcium
	Glucose
	Liver function testing
	Lipid studies
	Thyroid stimulating hormone
	Hepatitis A, B and C, HTLV, HIV and cytomegalovirus serology
	Syphilis testing
	Strongyloides stercoralis serology
	Immunoglobulin A level and anti- tissue transglutaminase serology
	Antinuclear antibodies
Stool testing	Stool culture including bacteria, viruses and parasites
	CDI culture including vancomycin resistant CDI
	Calprotectin ESBL and cryptosporidium calprotectin
	Helicobacter antigen
Nasal swab	Methicillin resistant staphylococcus aureus and carbapenem resistant enterobacteriaceae screening
	EHEC
	ESBL EHEC

HTLV: Human T lymphocytic virus; HIV: Human immunodeficiency virus; CDI: Clostridium difficiles; ESBL: Expended spectrum beta lactamase; EHEC: Enterohemorrhagic escherichia coli.

FECAL MICROBIAL TRANSPLANTATION FOR IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a functional disorder of the GI tract. There are several variants, according to the Rome

IV criteria[41]. These include IBS with constipation, IBS with diarrhea and mixed IBS.

IBS is very common with an estimated prevalence in the United States of 12%, 21% in South America and 7% in Southeast Asia[42]. The etiology of IBS is poorly understood.

There is evidence of a connection between the gut microbiota and dietary habits[43]. Dietary modulation effects the gut microbiota. One of the most effective treatments of IBS is a 6 wk low fermentable Oligo-, Di-, Monosaccharides and Polyols (FODMAP) diet[44-46]. A low FODMAP diet has been shown to alter gut microbiome composition[47,48], although there is no specific microbiota signature characteristic of the 60 to 70% of patients who respond to the low FODMAP diet[49,50].

In view of the effect of FMT on the treatment of rCDI, there have been attempts to manipulate the microbiome in IBS. Eight RCTs have been performed to investigate the role of FMT in IBS and a metanalysis included seven of these[51]. Five of the RCTs showed a decrease in symptoms and an improvement in the quality of life of the patients, whereas in the other three trials there was no positive benefit. The longest observation period of these studies was 3 years. Of the trials with positive results, one included 165 patients treated with placebo (own stools) or 30 g or 60 g of feces from a single donor, with a primary outcome at 3 mo[52]. Recently, a follow-up study to assess the beneficial effects after a 3-year follow-up period was published[53]. The follow-up study included 38 patients in the placebo group, 42 who received a 30 g of donor feces and 45 who received 60 g. The feces were administered *via* an endoscope to the distal duodenum. The fecal bacteria composition was examined by the GA-map dysbiosis test. The stool was examined at 2 years and 3 years post-transplant. The response was assessed by standardized quality of life questionnaires for IBS. The placebo response was 27% at 3 years compared to 64.9% in the 30 g group and 71.8% in the 60 g group. These results were similar to the results at 2 years. The dysbiosis index decreased only in the actively treated groups at 2 and 3 years.

Holster *et al*[54] randomized 17 patients to receive FMT *via* either allogenic feces from a healthy donor or autologous transplantation with their own stools. There was a significant decrease in symptom scores after transplantation at 8 wk, but there was no difference between autologous and allogenic transplanted patients. This suggests that the symptomatic improvement may have been an effect of the bowel cleansing performed prior to FMT. Another study of 49 IBS patients who were randomized to receive either autologous or allogenic fecal transplants[55], found only a transient reduction in the IBS symptom severity score at 12 wk after transplantation.

Johnsen *et al*[56] reported their 3 mo follow-up results on 90 patients with IBS undergoing FMT[56]. There were 90 patients of whom 60 received allogenic stool from healthy donors and a control group of 30 patients who received an autologous FMT. The stool was delivered by colonoscopy. On 3 mo follow-up there was an improvement. In the allogenic group 65% had an improvement in symptoms versus 43% in the control group (P = 0.049).

Another trial that included 62 patients with refractory IBS and predominantly symptoms of bloating, also reported a positive effect of FMT. Patients underwent FMT *via* nasojejunal administration of donor stools (43 subjects) or autologous stools (19 subjects). After 12 wk 56% of patients who had received donor stools reported an improvement in their IBS symptoms compared to 26% of patients in the control group. In 21% of patients the effect lasted for more than a year.

There are however, trials that did not find a positive effect of FMT. A study of 48 patients, 25 of whom received FMT from a healthy donor by oral administration of capsules were compared to 23 patients who received placebo capsules [57]. At 3 mo follow-up there was no difference in symptom relief. Another study included 52 patients with moderate to severe IBS who were randomized to receive FMT capsules or placebo for 6 d and followed up for 6 mo. After three months the quality of life was higher in the placebo group, despite there being a higher fecal diversity in the patients receiving FMT[58]. Two recent meta-analyses did not show an improvement in the symptoms of IBS.

Recently, the effect of the low-FODMAP diet has been examined on a gut organ culture system (developed by Bootz-Maoz *et al*[59]). Gut-organ cultures were colonized with longitudinal microbiota samples collected from newly diagnosed and therapy-naïve IBS patients receiving a standard 6 wk low FODMAP diet. The post-diet microbiota was shown to regulate the intestinal expression of inflammatory and neuro-muscular gene sets. *Bifidobacterium adolescentis* was identified as a diet-sensitive pathobiont that disrupts gut barrier functions and alters tight junction integrity[59].

In summary, the gut microbiome plays a critical role in the pathogenesis of IBS and the response to a low FODMAP diet. FMT may be a therapeutic modality of resistant cases but further investigation is required. It will be of interest to determine what role recurrent FMT by use of capsules containing donor stool has on the response.

GUT MICROBIOTA DYSBIOSIS AND IBD

There is a close relationship between gut barrier mucins and the gut microbiota. Chronic inflammatory conditions are associated with reduced mucin expression and reduced anti-microbial activity, thus allowing a more hostile microbiota population and a thinner barrier between the epithelium and gut pathogens[60]. This results in a "leaky gut" (a less effective mucosal barrier) which is the signature of several 'GI barrier-related diseases'[61]. The composition of the gut microbiota is important in maintaining hemostasis. Microbiome diversity is therefore considered to be a marker for human health[1]. A fall in the microbiota diversity results in an imbalance between helpful and harmful bacteria taxa and results in a more vulnerable microenvironment. This has been implicated as a contributing factor in the development of IBD[62,63]. New molecular techniques have facilitated a deeper understanding of the alterations that occur in the microbiome and lead to pathological states. The gut microbiota in IBD patients is typically less diverse and contains fewer beneficial fecal bacteria such as Firmicutes and Bacteroidetes, and an increased concentration of harmful Proteobacteria [64]. Patients with IBD have fewer microorganisms such as *Faecalibacterium* and *Roseburia* spp and an increase in pathogenic microorganisms such as *Escherichia*, *Fusobacterium*, and *Mycobacterium* spp.[65]. A unique microbiota signature could be a biomarker of disease and may also be useful to identify patients who achieve remission after the onset of

therapy. For example, in addition to baseline microbiota variability in responders *vs* non-responders with higher Faecalibacterium being of particular importance, patients who responded to ustekinumab had an increase in the diversity of their microbiota community[66]. Another recent study also suggests that a lower abundance of diverse microbial families in patients could predict stricturing and penetrating disease phenotypes[67].

There is also increasing evidence that the genetic effect on gut microbiota is similarly related to the pathogenesis of IBD. Genome-wide association studies have identified > 200 IBD-associated-susceptible genes, some of which are known to be involved or implicated in mediating host responses to gut microbiota[68]. The mechanisms through which the affected genes contribute to the disease include microbe recognition, lymphocyte regulation, cytokine release, and intestinal barrier defense[69]. Two prominent IBD-related genes (Caspase recruitment domain family member 9 and Nucleotide-binding oligomerization domain containing 2) were found to be significantly associated with a low abundance of protective taxa[70,71]. The altered gut microbiota lead to a state of 'chronic dysbiosis' which enables the development of GI and non-GI disorders, including IBD[72,73]. Other observations supporting a role for the gut microbiota in IBD pathogenesis include the predisposition to inflammation for anatomical regions with relative fecal stasis (terminal ileum and rectum), the effectiveness of fecal diversion as a treatment for Crohn's disease[74,75], and the rapidly increasing incidence of IBD globally associated with industrialization and accompanying alterations in diet and environmental exposures.

Another area of interest which highlights this connection between the gut microbiota and GI-related-diseases is the association between primary sclerosing cholangitis (PSC) and IBD. PSC is a prototype model disease for exploring the gut-liver-axis due to the close bidirectional relationship between the gut and the liver. An integral part of this gut-liver axis is comprised of the ileocolonic microbiota, thus suggesting a pathogenic role for the gut microbiome in the development of PSC, which can also be referred to as a "gut-associated sclerosing cholangitis"[76].

As mentioned above, non-GI disorders have also been linked to the intestinal microbiome. Insulin resistance and type 2 diabetes have long been associated with intestinal bacterial metabolites which can influence glucose homeostasis and lead to the presence of a systemic low-grade inflammation which, in turn, contributes to insulin resistance and diabetes development[77].

Microbiome dysbiosis is clearly a fundamental contributor in the development of functional and inflammatory intestinal and non-intestinal disorders. Consequently, the development of strategies aimed at repairing the microbiome has become a priority in many medical fields. There is however an ongoing debate about whether chronic dysbiosis and reduced diversity are a cause or a consequence of GI disorders[78].

FECAL MICROBIOTA TRANSPLANTATION AND IBD

The possibility that inflammation in IBD might be driven by the gut microbiota has led to the development of several clinical approaches aimed at correcting dysbiosis by dietary or microbial interventions. Examples include the use of probiotics, antibiotics, defined enteral nutritional therapy, and FMT. FMT is considered an unrefined form of bacterio-therapy that utilizes a healthy donor's diverse microbial gut community. The hope is that FMT will modify the microbial composition and create a taxonomic equilibrium between gut viruses, bacteria, and fungi in the dysbiotic gut of the recipients. Thus, FMT is considered a promising treatment for microbiome-related disorders. As previously mentioned, FMT cures approximately 90% of rCDI and has changed the morbidity and mortality of this severe clinical entity[79]. FMT's success in treating refractory Clostridium difficile infection has generated strong interest in using this approach in IBD. However, the data on FMT success rates in IBD are limited, as RCTs are scarce and are often underpowered[80].

CLINICAL TRIALS APPLYING FMT IN UC

The first implementation of FMT in UC was reported in 1989[81], where one of the authors of the paper received FMT (*via* an enema) for his continuously active UC, resulting in drug-free remission. Since then, many reports and RCTs have been published on this subject.

In 2015, Moayyedi *et al*[82] published an RCT study of 75 mild to moderate UC patients receiving FMT *via* retention enema (single donor) *vs* placebo. The patients were evaluated 7 wk later for a clinical and endoscopic response and the results were statistically significant for a positive response in the FMT group as opposed to the placebo group[82]. Contrary to these encouraging results, Rossen *et al*[83] published that same year an RCT comparing mild to moderate UC patients who underwent FMT with feces from healthy donors *vs* patients who were given autologous fecal microbiota (control)[83]. The results indicated that there was no statistically significant difference in clinical and endoscopic remission between patients with UC who received fecal transplants from healthy donors and those who received their own fecal microbiota. In 2017, Paramsothy *et al*[84] demonstrated that intensive-dosing, multi-donor FMT induces clinical remission and endoscopic improvement in active UC and is associated with distinct microbial changes that relate to outcome[84]. Březina *et al*[85] also supported the effectiveness of multi-donor FMT *via* retention enemas *vs* 5 ASA enemas in mild to moderately active UC patients[85]. They too proposed that targeted microbiome modification may improve FMT efficacy, and that further investigation is warranted to guide donor and patient selection. In a recently published meta-analysis, a total of 9 RCTs comprising 425 UC patients (213 FMT and 212 control) were included. Clinical remission was observed in 86 of the 213 patients in the FMT groups and 47 of the 212 patients in the control groups[86].

Nonetheless, contrary to these seemingly favorable results, some recent analyses have reported conflicting outcomes. Pai *et al*[87] reported similar rates of clinical remission in FMT and placebo-treated pediatric patients[87] and Sarbagili Shabat *et al*[88] found a UC exclusion diet to be more beneficial than FMT in achieving remission[88]. Thus, despite the publications of several reports on the positive value of FMT in IBD, the exact efficacy of FMT in UC treatment remains to be determined.

CLINICAL TRIALS IMPLEMENTING FMT IN CD

Only a few studies have explored FMT for the treatment of Crohn's disease, most of which have demonstrated variable results[89,90]. In a multivariate analysis, long disease duration (> 5 years) and moderate or severe disease (HBI ≥ 8) were associated with poor response to FMT[91]. This indicates that Crohn's disease patients in the early stage of the disease or with mild disease might show better response rates to FMT.

All the studies mentioned above highlight that further deciphering the ideal routes of delivery, the optimal methods of preparation of the transplanted microbiota, and the ideal donor and recipient characteristics will no doubt have a great influence on FMT results in IBD patients. Moreover, a recently published RCT demonstrated that multi-donor FMT combined with an anti-inflammatory diet effectively induced deep remission in mild-moderate UC which was sustained with an anti-inflammatory diet over 1 year[92]. This data reinforces the notion that additive beneficial interventions can further boost the therapeutic success of FMT in IBD patients.

POSSIBLE EXPLANATIONS FOR INCONSISTENT SUCCESS RATES OF FMT IN IBD PATIENTS

A state of 'chronic dysbiosis'

One likely explanation for this partially reduced efficacy (compared to the high success rate of FMT in rCDI) lies in the chronic state of dysbiosis which characterizes these diseases[93]. The main cause of FMT's high success rate in rCDI is that it is a model of *acute, simple dysbiosis*. In rCDI we witness a huge drop in microbial alpha and beta diversity[93]. These changes are acute and relatively easy to restore to the normal state. However, *chronic dysbiosis* is a much more challenging condition that involves a stable rearrangement of microbial disequilibrium in a pathogenic way. It includes the perseverance of aggressive, proinflammatory bacteria and a decrease of beneficial taxa[94,95]. Consequently, this chronic, pathogenic equilibrium, which is well-established and much more difficult to restore, may perhaps explain (at least partly) the reduced efficacy of FMT in chronic intestinal disorders.

UNSUCCESSFUL DONOR MICROBIOME ENGRAFTMENT RATES

FMT success is primarily defined by a positive clinical response in the recipient, with the main objective being a long-term therapeutic effect. FMT is thought to manipulate the host intestinal microbiota, leading to an increase in host diversity and ultimately shifting the composition of the host microbiota towards that of the donor profile[96]. Thus, FMT success is defined by a change in the host gut microbiome profile of an individual toward that of the donor. *Engraftment* is defined as the colonization of the donor strains in the recipient's gut after FMT[97,98] and serves as a useful marker per se to assess the success of the procedure. An overall positive association was shown between donor engraftment rate and clinical response to FMT. A longer duration of engraftment leads to a longer and more sustained clinical response[97]. As mentioned above, due to the chronic nature of their dysbiosis, patients with chronic inflammatory Gi disorders are less likely to be engrafted (and potentially cured) by donor microbiome than those with acute infectious diseases[99].

FACTORS INFLUENCING DONOR MICROBIOME ENGRAFTMENT

The mechanisms and dynamics dictating which donor microbes will ultimately engraft in the recipient are poorly understood. The recent availability of larger FMT trials and the advances in strain-resolved metagenomics enabled deeper analyses that started unraveling the engraftment capacity of FMT across diseases and led to the development of statistical models to predict the post-FMT microbiome composition[98]. There is also a pivotal role for host immunity, which is determined by the host genetics. Genetics similarly influence the microbiome composition by regulating the expression of immune and regulatory proteins. There are many proteins that are upregulated in inflammatory states, and these, in turn, can sequester host-derived nutrients and enable the growth of pathogenic organisms. Inflammation gives a fitness advantage to facultative anaerobes, and therefore they are more prevalent in inflamed tissue than in the normal state. All these alterations in the inflamed tissue set in motion a more "hostile" microbiota environment with reduced host immunity, most likely negatively affecting engraftment rates. Interestingly, this trait can paradoxically be used to our advantage, as it has been shown that reduced host immunity can also serve as a potential target for therapy and it has been demonstrated that IBD patients treated with immunosuppression (*e.g.*, steroids) prior to FMT showed higher rates of engraftmens[100]. Thus, various diets, fermented foods, prebiotics, probiotics, steroids and phage therapy-all serve as potential methods to manipulate the host gut microbiome, further enhancing the likelihood of a successful FMT

engraftment in IBD patients.

FMT-A COMPLEX PROCEDURE WITH MANY CHANGING VARIABLES INFLUENCING SUCCESS RATES

There is marked variability in the study designs of various FMT clinical trials, ranging from differences in approach to donation (single donor *vs* FMT pooled from more than one donor), route of administration of FMT (upper GI *vs* lower GI), the total number of FMT treatments administered (one to 40 infusions), FMT preparation (anaerobic *vs* aerobic), placebo comparator and differences in the definition of primary outcomes[101]. This variability undoubtedly has a significant impact on the inconsistent success rates of FMT clinical trials.

It is unfortunate that information on a recipient's genetic background or dietary intake is not yet routinely assessed, particularly given that many cases of IBD have an underlying genetic component. Due to the lack of genetic information, investigators have instead focused on the donor-dependent effect and proposed the existence of so-called "super-donors" to explain the variation in recipient responses[102].

THE "SUPER-DONORS PHENOMENA"

The composition of the donor microbiome plays a vital role in the treatment success rates of FMT. "Super donors" have been identified whose recipients were much more likely to achieve engraftment as opposed to recipients of other donors [102]. These 'super donors' were found to have a microbiome enriched with Lachnospirochea and Ruminococcus species. Recently, a striking finding demonstrated that the stability in richness of donor species over time (assessed for up to 70 wk), rather than richness itself, was associated with therapeutic efficacy[103].

It has also been suggested that remission rates might be improved by pooling donor's stool together which would reduce the probability that a patient would receive only ineffective stool[97]. Therefore, the donor's microbiome appears to be vital in engraftment success. However, more studies are clearly required to compare single-donor *vs* multi-donor applications. Future advancement is also needed in terms of deciphering unknown species of the human gut microbiome by high-resolution metagenomics and other advanced techniques.

INFUSION PROTOCOLS

Infusion protocol is also central to the engraftment success rate. Multiple infusions and repeat FMT appear to be key to successful engraftment[84]. A multivariate metanalysis has sought to define the characteristics of the microbial engraftment post-FMT in cohorts of patients with various diseases (amongst them Crohn's disease and UC) and to determine the association of this microbial engraftment with treatment success[104]. Results showed that 58% of the post-FMT samples taken from the recipients had shared strains with their donors (as opposed to 4% shared strains in the pre-FMT samples taken from the recipients). All these variables will, hopefully, pave the way for improving FMT protocols and enabling FMT to be a successful therapy for many GI diseases in the future, in addition to rCDI.

A schematic representation of the various factors influencing engraftment rates can be found in Table 3.

INTEGRATING FMT IN ROUTINE IBD TREATMENT PROTOCOLS - WISHFUL THINKING OR CLINICALLY APPLICABLE?

Outcomes from clinical trials evaluating FMT in IBD patients were non-inferior to other clinical trials testing new biologic molecules in IBD. And yet, those molecules were approved for treatment in the years to come, but FMT is still not considered a valid therapeutic option.

Why is this?

As specified above, there are many factors thought to be associated with FMT success rates (in the general population and more specifically in IBD), amongst them: Clinical characteristics of the basic disease, various FMT working protocols (route of delivery, amount of feces infused), and donor microbial characteristics. Additional recipient factors that are associated with success rates of FMT, are: Genetics, immunity, microbiota, metabolomes, and lifestyle[100]. It has also been revealed that the diversity of the host microbiome at baseline and the composition of the donor's microbiome are essential to the success of the procedure. Assumingly, due to the complexity of the process, the multifactorial elements that need to be addressed in order to achieve clinical success and the high costs of this procedure-it is not yet to be implemented as every day clinical practice. In addition, there are reports of side-effects related to FMT.

Another plausible explanation for the underuse of FMT in IBD is the notion that FMT is a 'one-time treatment', designed to be an effective management strategy in the acute setting only, thus rendering it less suitable for the treatment of chronic disorders. However, FMT can be considered a chronic treatment (especially if given by multiple infusions) and should potentially be considered amongst other approved treatment options in chronic conditions.

Table 3 Factors influencing donor microbiome engraftment

Host-related factors	Donor-related factors	Procedure-related factors
Chronic dysbiosis state[94,95]	Donor genetics	Preconditioning of the gut: Various diets, fermented foods, prebiotics, probiotics, steroids and phage therapy[100]
Host immunity state, determined by the host genetics[98], creates a hostile "hostile" microbiota environment	'Super-donors'[102]	Treatment-related protocols: Single donor *vs* multi-donors, route of administration of FMT (upper GI *vs* lower GI), the total number of FMT treatments administered (one to repeated), FMT preparation (anaerobic *vs* aerobic)[101]
	Donor species richness of microbiome[99]	Industry microbiota suspensions[106]
	Donor microbiota stability and species evenness[103]	

FMT: Fecal microbiota transplantation; GI: Gastrointestinal.

The Lyophilised oral faecal microbiota transplantation for ulcerative colitis (LOTUS) trial recently published used an innovative design, which included: Lyophilized capsules, host antibiotics preconditioning, and daily treatment of FMT in tapered-down dosages for a year in UC patients[105]. This is the first published trial that introduces the concept of *chronic modulation* of the microbiota in IBD. The results (albeit a small sample size) showed treatment success in the group receiving the chronic treatment as opposed to placebo[105]. Furthermore, the LOTUS trial reinforced the concept that donor composition is crucial for treatment success, showing a higher microbiome diversity and higher stability in the donor's feces which resulted in higher engraftment rates. However, it is precisely this concept that may lead to further difficulty given that donor microbial signatures are hardly reproducible and can be referred to as a "moving target" so the need for multiple infusions may be challenging[97]. As mentioned above, a potential solution is to focus on the recipient as a target to improve the chances of engraftment. This may be done by various interventions, amongst them: Targeting the recipient's immune system through immunosuppressant therapy, dietary interventions to control the recipient's environment, preparing the host's bowel by bowel cleansing/antibiotics, and more[92]. Hopefully, in the future, more advanced donor conditioning may be possible using genetic and microbiota manipulation to improve the matching and engraftment rates. Recently, progress has been demonstrated in the form of industry microbiota suspensions (termed RBX2660) which have been approved by the FDA for the treatment of rCDI[106]. Another suspension (SER-109) has shown success rates in phase 3 trials.

CONCLUSION

In conclusion, as of today, there is still a significant gap between the basic science of FMT and the routine use of this therapy in chronic 'dysbiosis-associated diseases' such as IBD. It has even been proposed to minimize this gap with the generation of a new medical field called 'microbiomedicine', training advanced '*microbiome clinicians*' who will run a multidisciplinary *microbiome clinic*. Clearly, this is still an unmet need.

FOOTNOTES

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