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Review Article

Internal Medicine Section

Faecal Microbiota Transplant: A New Biologic Frontier in Medicine

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ABSTRACT

Faecal Microbiota Transplantation (FMT) refers to the process of introducing the gut microbiome into a compromised patient's Gastrointestinal (GI) tract after obtaining it from a healthy donor. It is one of the chief treatment options for people afflicted with a chronic *Clostridium difficile* infection. Recently, other possible applications of FMT have been gaining worldwide consideration as an emerging approach to treat a multitude of disorders, such as metabolic syndrome, neurological diseases like autism, Inflammatory Bowel Disease (IBD), and so on. FMT is not currently being used in clinical practice due to practical objections though research on how to overcome the same is ongoing. This article seeks to explore FMT as a procedure, its current indication and the results from various studies, applications of FMT as a course of treatment in other diseases, and the limitations that the procedure poses for the same, upon which further studies can commence and advancements can be made in the field of medicine.

Keywords: Autism, Metabolic syndrome, Microbiome, Pseudomembranous colitis

INTRODUCTION

The Faecal Microbiota Transplantation (FMT) refers to a procedure that involves obtaining a filtrate of liquid feces from a carefully screened donor and introducing it into the recipient's GI tract to cure certain diseases. The suspension is via a naso-duodenal/gastric tube, enema, capsule, or colonoscope. The main implicated application for the procedure is the treatment of Recurrent *Clostridium Difficile* Infection (RCDI), which has a high success rate. Additionally, FMT is being considered as a possible course of treatment for several other disorders like IBD, obesity and metabolic, neuropsychiatric disorders such as autism, cancer, and so on [1]. The procedure is well suited for children and adults [2].

The idea of faecal transplantations was born back in China in the 4th century, where cases of severe diarrhea and food poisoning were treated with the 'yellow soup'. By the 16th century, several products of faecal origin were available in China to relieve Gastrointestinal (GI) and even systemic symptoms such as pain and fever [3]. It wasn't until the 1950s that FMT as a procedure was applied for the treatment of RCDI [4]. First published research on FMT demonstrated the use of faecal enemas in antibiotic-induced pseudomembranous colitis as an adjunct. It is now an accepted therapy for RCDI treatment [5].

The Gut Microbiota

The microbiome is a collective term used to refer to the diverse microbial lifeforms that inhabit the gut and the web of effects they produce in the body [6]. Thus, the gut microbiota is diverse in composition, comprising microorganisms in the GI tract ranging in trillions. After the introduction and multiplication of these organisms in the gut at birth, nutritional, genetic, and environmental factors modify it throughout life [7].

The microbiota plays a major role in developing the enteral layout and mucosal immune system and overseeing their regulation. It also plays a significant role in processes such as digestion, assimilation, metabolism, and production of vitamins in the body. Recent studies have also discovered the significant bidirectional influence of the gut and nervous system on each other, termed the microbiota-gut-brain axis [8-10].

A disbalance in the composition of the gut microbiome is brought on by factors such as stress, diet, genetics, and antibiotic therapy [11]. It can lead to a pro-inflammatory state that can, in turn, lead to many diseases.

Principle of FMT

The normal composition and functioning of the gut microbial flora are essential for the host's health. Any disruption in the same can lead to dysbiosis characterised by an increase in the number and decrease in the diversity of the flora. With the most common causal agent being antibiotics, a *Clostridium difficile* infestation thrives in the dysbiotic environment and causes an infection [12]. FMT opts to reintroduce the normal flora of the gut, collected from a healthy donor and restores the balance of the recipient's gut flora.

PROCEDURE

Selecting the Donor

Factually, anyone over the age of 18 years can be a donor and can be the recipient's friend, family, spouse, or even a stranger. But typically, family members, especially first-degree relatives of the maternal line are preferred to share most of the recipient's microbiome. Significantly, others are also preferred since they share common environmental risk factors [1]. Clinical approach for FMT is depected in [Table/Fig-1].

Donor Selection criteria
History of donor
No history of antibiotics over the last three months
No history of incarceration, tattoos, or piercings over the last three months
No history of constipation, CRC or polyp, IBD, chronic fatigue syndrome, MS, diarrhea, atopy, or IBS
No history of allergies
Serological testing of donor
Syphilis
Hep B surface antigen
Abs to Hep B surface antigen
Hep A IgM
Hep C antibody
HIV type 1 and 2 Abs
Stool testing for donor
Clostridium difficile
Stool parasites and ova
Giardia antigen

Isospora
Cryptosporidium antigen
Rotavirus
H. pylori antigen

[Table/Fig-1]: Depicting clinical approach for FMT [1].

Stool Collection and FMT Preparation

- The passed stool should ideally be used as soon as it is expelled, preferably in the first six hours. In cases of delay, it should be chilled, rather than frozen. General precautions such as handling the transfusion material with gloves, masks with an eye shield, and a fluid-resistant gown.
- The stool sample is diluted with 4% milk or normal saline for intravenous injection. A conventional household blender can be used for the same. Following this, the stool should be homogenous with a slurry, liquid consistency [13].
- The slurry should be filtered to get rid of all particulate matter and the finished product should be used instantly.
- Large inter-institutional variations have been observed in the preparation of FMT such as some institutes giving high-dose doxycycline to patients with FMT to decrease the dysbiotic flora. Others give patients a polyethylene glycol preparation to patients before FMT to increase the chances of proper colonisation of the transplanted flora into the recipient's gut [14].

Administration of Sample

Three delivery pathways are used to deliver FMT:

- The upper gut delivery: intake of oral capsules
- The mid-gut delivery: use of nasogastric and nasoduodenal tubes and endoscopic channels
- The lower gut delivery: via coloscopies, enemas, infusions, and transendoscopic enteral tubing (under trial) [15].

Although statistically, there has been no difference in the outcome of the procedure due to the route of administration, it is wise to consider the associated potential risks with each of the methods [16].

Evaluation of Success

Primary outcome is evaluated by the resolution of symptoms due to gut dysbiosis and secondary outcome by absence of relapse eight weeks after the procedure [17].

Safety and Side-effects

FMT has a few immediate side-effects such as abdominal discomfort, low-grade fever, flatulence, vomiting, diarrhea, constipation and complications of sedation and endoscopy (rare) [18].These symptoms run a course of 2 days and are self-limited. However, the long-term effects of FMT are still a mystery, and information on the same is needed. There are concerns revolving around the 'do-it-yourself' approach of FMT, with done without medical assistance may potentially have adverse consequences [1]. Another study reported two cases in which, following the transplant, bacteremia was induced by a transmitted organism. These patients had existing co-morbidities which increased their subsequent risk for bacteremia [19].

Due to the high chances of disease transmission, researchers are keen to find an alternative to FMT despite its effectiveness.

Indications of FMT

Current indication is recurrent pseudomembranous colitis. Other potential indications include Irritable Bowel Syndrome (IBS), IBD, metabolic syndrome, autism, cancer, multidrug-resistant organism infection, Multiple Sclerosis (MS), and other autoimmune disorders [20].

1) Pseudomembranous colitis

Caused by the notorious bacterium, *Clostridium difficile*, Pseudomembranous colitis is one of the most commonly acquired HAIs and poses a major healthcare problem. According to a research done in Mumbai, India has a prevalence rate that ranges from 7.1-26.6% with a much lower incidence of fulminant infections in comparison to the western countries [21].

C.difficile infection in itself isn't an indication of FMT. It is performed only in cases of:

- Multiple recurrent infections
- Moderate infection with no response to therapy for atleast a week
- Severe infection with no response to therapy for 48 hours

Patients with RCDI have been found to have a dysbiosis of their gut flora, with a decrease in bacterial diversity, which accounts for such high recurrence rates despite initial treatment with antibiotics. Hence, infusion with the donor feces restores the normal flora of the gut and strengthens the host defence against recurrent CDI. It also increases the Bacteroidetes species and clostridial [22].

The first FMT clinical trial included 43 patients that were given 14 days of FMT via naso-intestinal tubes along with oral vancomycin, followed by oral vancomycin alone and another 14 days with vancomycin coupled with gastric lavage. Symptoms resolved in 81% of patients receiving FMT, 31% of whom were on vancomycin only and another 23% received vancomycin plus gastric lavage [1]. This could be because antibiotic therapy doesn't restore the imbalanced gut microbiota whereas reintroduction of normal flora via FMT does.

FMT has now been adopted as an accepted regimen for treating recurrent CDI since Eisenman's experiment. A recent study conducted in Taiwan had an overall success rate of 91.7% for recurrent clostridial infections [23]. It generally has a lasting effect with almost no side-effects even among vulnerable patients [24].

2) Irritable Bowel Syndrome (IBS)

The IBS is a recurrent GI disorder with a chronic course affecting about 9-23% of people worldwide, typically manifesting as pain or discomfort in the abdomen with changes in stool consistency, that are eased by defecation [25].

A possible trigger for the condition can be dysbiosis of the gut since a study found a decrease in *Lactobacillus* and *Veillonella* in diarrhea and constipation predominating IBS, respectively [26]. These are also implicated in bringing about changes in the permeability and mobility of the intestine, triggering inflammation and altering the Quality of Life [27].

Studies conducted in the past do not draw a definitive relation between the application of FMT and IBS. But recently, a randomised trial conducted in Belgium noted a decrease in the symptoms of IBS in 56% of the subjects, though the therapeutic effect subsided after a month. But it was also reported that there was restoration of response in these subjects, after a second dose of FMT [28].

3) Inflammatory Bowel Disease (IBD)

The IBD is an immune-mediated disease of chronic course that includes Crohn's disease and ulcerative colitis [15].

Factors likely to influence its course include genetics, environmental factors, and dysbiosis of the gut, in which the normal flora is greatly diminished and have lower proportions of normally dominant flora, bacteriodetes, and firmicutes. Corticosteroids, being among the chief lines of treatment for IBD, are not usually recommended for their maintenance therapy and have limited effectiveness on relapse [29].

The FMT seeks to restore the normal flora of the gut and could be possibly therapeutic in IBD but its application remains highly controversial, its efficacy unestablished. A recent holistic therapy 'step up FMT strategy' has been seen to be beneficial to steroid-

dependent IBD patients. For these patients, while the first transfusion showed little to no effect, a clinical improvement has been seen after a repeated FMT-corticosteroid therapy following a singular one. Thus, a combination of FMT and steroid therapy constitutes the step-up FMT strategy' and has shown to induce improvement in 57.1% of patients with the disease who were treated using this strategy [15]. Another systematic review for FMT in IBD noted a cure rate of only 45%. These variations in the findings put a question mark on the effect of FMT in IBD [30].

4) Metabolic syndrome

Metabolic syndrome refers to a group of conditions that include dyslipidemia, high BP, increase in abdominal girth, and insulin resistance, and may lead to type 2 DM. It has become one of the leading global health problems with its prevalence reaching epidemic proportions [31].

The pathogenesis implicates an impaired function of the gut barrier causing leakage of the bacterias into the system that leads to low-grade exo-toxemia and stimulates the inflammatory cascade, leading to macrophage influx, causing low-grade inflammation of the body and insulin resistance. Specific changes in the microbiota have also been noted in metabolic syndrome with an increase in harmful bacteria such as *Prevotella copri* and *Bacteroides vulgatus* with a simultaneous decrease in beneficial bacteria such as *Akkermansia municiphila*, and *Faecalibacterium prausnitzii*, that increase the insulin sensitivity [16].

An attempt to increase these beneficial bacterias in the gut is done by using an anaerobic preparation to increase the viability and chances of acceptance of these strict anaerobes by the recipient. Due to limited research in the field, the efficacy of the anaerobic preparation, varying effect of routes of administration, and the dose and duration of FMT have not yet been elucidated [17].

5) Autism

Autism is a primary Autism Spectrum Disorder (ASD) which, in itself, comprises a multitude of developmental neuro-behavioural disorders that are marked by restrictions and repetitions in behaviour, impairment in social interaction and communication; The involvement of gut microbiota in its pathogenesis has been widely studied in animal models by drawing comparisons between the microbiota of an affected and a healthy individual and observing changes in behaviour after the procedure [32]. Autistic children show an imbalance in their gut flora with an increase in the number of gut commensals such as *Bifidobacterium*, *Prevotella, Lactobacillus*, *Bacteroidetes, Ruminococcus genera*, Sutterella, and *Alcaligenaceae* family [8].

Standard treatment for ASD comprises social and speech therapy, behavioural therapy, and dietary interventions but there is still no approved medical therapy for the same. Taking into account the microbiota-gut-brain axis, reintroducing normal flora into the recipient may be a possible therapeutic option. A case study with 18 participants with ASD was done and notable improvements were seen in the behavioural and GI symptoms, compared to the beginning of the trial [33].

6) Multiple Sclerosis (MS)

The MS is an autoimmune disorder characterised by the demyelination of the CNS, affecting about 2.5 million people worldwide, with a female predominance [34]. It has multifactorial pathogenesis characterised by disruption of the GBA leading to altered microbiota composition, permeability, and motility of the gut and functions of both enteric and endocrine NS functions.

The FMT has been considered a possible course of therapy for the disease, restoring the normal flora of the gut. In a study conducted with a patient receiving FMTs from five donors daily, an increase in the *F.prusnitzii* in the gut was seen, along with increased butyrate, propionate, and a decrease in cytokine-mediated inflammation, following the transplant. A change for the better was also seen in his walking and balance. Another study with three MS patients receiving FMT every day for 2 weeks showed a resolution in symptoms for 2-15 years [35].

7) Cancer

Various studies have found associations between dysbiosis of the gut and various cancers [36-38]. A striking difference is seen in the microbiota of a cancer patient and a healthy one which can be used to deduce the potential as prognostic and diagnostic markers of certain microbial pathogens in cancer progression. Dysbiosis has been known to activate certain tumorigenic pathways that lead to inflammation and damage to the host DNA. It has also been linked with the progression of cancer in various tissues such as hepatocellular, gastric, pancreatic, colorectal, melanoma, and breast [11].

Important clinical responses such as anti-PD-1 monoclonal Abs survival time have a positive correlation with the quantity of Akkermansia in the gut. Clinical trials have been conducted with cancer patients responding to immunotherapy, where patients were given oral supplements of *Akkermansia* and an improvement in the effectiveness of the immunotherapy was seen. By integrating the two, a beneficial treatment of cancer may emerge and FMT may prove to deliver promising therapeutic and diagnostic strategies [11].

- **Multidrug-Resistant Organism Infection**

The gut is host to many multidrug-resistant organisms, especially after an aggressive course of antibiotics or a prolonged stay in the hospital. While in most people, this doesn't lead to a symptomatic presentation, infections were precipitated in the vulnerable population compromising immunocompromised patients, children and elderly, travellers, and patients in the Intensive Care Unit (ICU) [39].

Most non medicated approaches to combat these infections are focused on replacing the pathogenic bacteria with beneficial gut flora and restructuring the gut with a healthy microbiome.

A case study with 20 people conducted in France showed that, 14 days after receiving FMT, 80% of people had overcome *Acinetobacter* colonisation. Another study with 8 people showed an 87% decolonisation of VRE in a span of three months [39]. Given the results, FMT needs to be explored as an option to combat hospital-centered outbreaks. However, case studies with a larger sample population are needed before conclusive claims can be made.

Summary

Having been successfully applied in the treatment of RCDI, more research is needed to clearly define the role and extent of dysbiosis in these conditions to gain a better insight into the complex changes that follow FMT, within the gut flora and clinical trials of high-quality with large sample groups focusing on the mechanisms via which the gut bacteria influence the host's defence system are required for the same [39].

CONCLUSION(S)

The article emphasises the importance of a normal functioning gut microbiome in maintaining the health of an individual and the extensive influence it has on the rest of the body. This article underlines the emergence of FMT as an alternative therapeutic approach in numerous conditions that were previously tackled mostly with pharmacotherapy. The last decade has seen a remarkable change concerning FMT, which has gone from being considered an evidence-free, alternative form of medicine to a considerable therapeutic option with wide application. With growing recognition of the effect of the gut, not only on the nervous system but also on the overall health of the organism, it becomes essential to explore the therapeutic benefits this procedure has to offer. The current data on the same isn't sufficient for FMT to be considered an FDA-approved procedure and naturally, a lot of research is needed before it can be put to use to its full potential. Being a possible gold procedure for treatment, studies on the same would go a long way in making advancements in the field of medicine. Furthermore,

research on the dose and route of delivery of the FMT, along with their advantages and setbacks is also essential before considering it as a promising therapeutic strategy for the future.

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