AN OVERVIEW OF FAECAL MICROBIOTA TRANSPLANTATION

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Abstract. Faecal Microbiota Transplant (FMT) is a medical intervention in which stool from a healthy person is transplanted into another individual's large intestine. This method is meant to help restore the normal microbiota of the recipient's gut, including cases with dysbiosis due to recurrent Clostridium difficile infection and other gastrointestinal diseases. Though the procedural detail of FMT is complex, it has some fundamental biological concepts such as replantation of reduced microbial balance, pathogenic microorganism inhibition, regulation of immunity, and metabolite production. Moreover, the current regulation and future studies by professional bodies regarding synthetic microbiota and individualised FMT have exciting potential for improved therapeutic use; there is a need for more standardisation and safety measures on the practice. To maximize its clinical potential, we also focused on data for developing uniform guidelines, enhancing donor screening procedures, and ensuring safety and efficacy through rigorous study. As FMT applications expand beyond recurrent Clostridium difficile infection to include inflammatory bowel disease, irritable bowel syndrome, and other microbiome-related conditions, advancements in personalized and synthetic microbiota therapies are expected to pave the way for their safer and more versatile use. Therefore, continuous exploration and strong regulatory frameworks are essential in unlocking the therapeutic potential of FMT while safeguarding patient outcomes.
Keywords: *faecal material, faecal microbiota transplant, clostridium difficile, gastrointestinal diseases, pathogen suppression*

Introduction

Faecal Microbiota Transplantation (FMT) has emerged as a promising therapeutic option for the management of recurrent Clostridium difficile infections (CDI) (Terrier et al., 2014). CDI is a major public health concern and is responsible for significant morbidity and mortality, particularly among older adults and patients with underlying medical conditions (Rao et al., 2016). Despite the availability of several antibiotics for the treatment of CDI, there is a high rate of recurrence following initial therapy, which poses a significant challenge to healthcare providers and patients alike (Baunwall et al., 2021). This has led to an urgent need for alternative treatment options that can address the underlying cause of the infection and prevent its recurrence. FMT involves the transfer of faecal material from a healthy donor into the gastrointestinal tract of a recipient (Sunkara et al., 2018). The primary goal of this therapy is to restore the balance of the gut microbiota, which is often disrupted by antibiotics and other factors that contribute to the development of CDI. The procedure is typically performed via

colonoscopy, nasogastric/nasoenteric tubes, or enema and is shown to be highly effective in treating recurrent CDI (Gupta et al., 2016). The use of FMT for the treatment of CDI has gained significant attention over the past decade, and numerous observational studies have demonstrated its safety and efficacy (Rao and Safdar, 2016). The success rates of FMT in treating recurrent CDI have been reported to be as high as 90%, surpassing those of traditional antibiotic therapy (Patel et al., 2013). Despite the promising results of FMT, there has been a lack of regulatory oversight and standardization in the field, limiting its adoption as a standard care approach in healthcare. This is expected to change with the recent approval of a first-in-class microbiota-based live biotherapeutic, originally termed RBX2660, by the U.S. Food and Drug Administration (FDA) on November 30, 2022 (Afzal et al., 2023). RBX2660 is specifically indicated for the prevention of recurrent CDI in adults aged 18 or above and is expected to significantly impact the healthcare delivery system.

The approval of RBX2660 represents a major milestone in the field of FMT, particularly for patients experiencing recurrent CDI with no alternative treatments. It underscores the growing recognition of the potential benefits of microbiota-based therapies. RBX2660 has the potential to transform the management of CDI and could lead to improved outcomes with reduced healthcare costs. Moreover, RBX2660 is expected to pave the way for the development of additional microbiota-based therapies for other conditions, further expanding the potential applications of FMT and related approaches. This systematic review aims to pool current clinical trial evidence of FMT success rates when used for recurrent CDI. During the COVID-19 pandemic, when screening patients before FMT, it was found that SARS-CoV-2 RNA may be present in stool, which raised the risk of screening for an emerging pathogen during FMT. This led to further concern with regard to the sufficiency of the existing protocol being observed. From the Lancet Infectious Diseases, it is clear that "the emerging pathogens like SARS-CoV-2 reveal the gaps on how best to screen donors before FMT and the need to have laid down standard procedures for screening donors.

Overview of gut microbes

The amount and type of microorganisms in the human gut are substantial, and together these are referred to as gut microbiota, which comprises bacteria, archaea, viruses, fungi, and protozoa. Microbes are located on all body surfaces, but a large number of microbes are found in the gastrointestinal tract/gut. The human gut hosts more than one thousand (1000) microbial species within its population that come together to form a community known as gut microbiota. These gut microbiotas are crucial in human health since they help in the digestion process, nutrient assimilation, and immune support, as they form part of the gut barrier, particularly the colon. Most of the microorganisms that are part of the human gut are mutualistic; they assist in performing functions that require participation in a host of biochemical pathways of human metabolism that are critical for sustaining human life. Most of these are bacterial phyla: The two most dominant are Firmicutes and Bacteroidetes, and the rest include Actinobacteria and Proteobacteria. Recently, various aspects that influence the formation of gut microbiota have been identified, including “diet, the method of delivery, antibiotic therapy, and some environmental factors”. However, diet is today among the main factors (modifiers) of shifting the gut microbiota (Simões et al., 2022). Human microbiota has good potential in obesity, functions to satiety, appetite regulation, enhanced nutrient extraction, and energy extraction from foods. Microbes

are also involved in the metabolism of xenobiotics. In xenobiotic metabolism, various gut microbes also change the structure of various dietary components, medications, toxins, and numerous pesticides (Nakov and Velikova, 2020). Other functions of gut microbes include breaking down non-digestible substrates like dietary fibres to produce small-chain fatty acids (SCFAs) needed for energy by colon cells and metabolic control. They also produce necessary vitamins (B-group of vitamins and vitamin K) and play a role in the maintenance of the integrity of the intestinal barrier as an immunological barrier against pathogens. Additionally, the GMP plays roles in shaping immune regulation with more specific immunological function and establishing how to differentiate the good microbes from the bad ones.

Mechanism of FMT

The premise of Faecal Microbiota Transplantation (FMT) involves the introduction of a diverse assemblage of live or viable derived faecal microorganisms that displace pathogenic microbes, stimulate the immune system, and affect its general function of colonisation resistance. These gut microbiotas are crucial in human health since they help in the digestion process, nutrient assimilation, and immune support, since they form part of the hostile barrier, particularly the colon. Most of the microorganisms that are part of the human gut are mutualistic; they assist in performing functions that require participation in a host of biochemical pathways of human metabolism that are critical for sustaining human life. FMT is a treatment strategy that has the goal of improving overall internal microbial composition with the hope of achieving a physiological state in the context of disease (Quigley and Gajula, 2020).

Restoration of microbial diversity

FMT is known to have a therapeutic capacity through restoring the quality and number of microorganisms present in the gut. Serosity health donor faeces contains a variety of microorganisms in healthy faeces, these include friendly bacteria that could suppress dangerous microbes (Martin-Gallausiaux et al., 2021). Reintroduction of different microbial species aids in the correction of the dysfunctional gut, which is important when it comes to infection. Numerous studies have demonstrated that the best solution achieves pronounced shifts in the microbial pattern of the recipient, which is quite similar to the donors within the first 72 hours after FMT (Chen and Vitetta, 2021).

Competitive ecological and pathogen suppression

FMT fosters direct ecological competition within the intended habitats, the gut microbiome. The newly introduced beneficial bacteria, as described above, struggle and occupy spaces on the gut lining that would otherwise accommodate nutrient and growth-fostering pathogens like C. difficile (Wortelboer et al., 2019). The injected healthy microbiota by FMT creates a barrier against invading pathogens through providing colonization resistance by outcompeting them for the available nutrients, occupying the space on sources, and secreting substances that inhibit the growth of pathogens. This has a role in reducing the incidence of pathogenic bacteria and also helps in good gut flora.

Modulation of immune response

Another critical aspect of FMT's mechanism involves modulation of the host's immune responses. The gut microbiota plays a vital role in educating and regulating the immune system (Smits et al., 2013). Beneficial microbes can enhance mucosal immunity and promote the production of anti-inflammatory cytokines while suppressing pro-inflammatory responses. This immune modulation helps maintain intestinal barrier integrity and reduces inflammation, which is particularly beneficial in conditions like inflammatory bowel disease (IBD). It also strengthens the gut's mucosal immune barrier, improving the body's defence against invasive pathogens. By restoring beneficial microbial populations, FMT enhances the production of immunoglobulins and antimicrobial peptides, which protect the gut lining from infections (McDonald et al., 2018).

Production of metabolites

The SCFA and other metabolites originating from the gut microbiota are essential metabolites that influence health. Butyrate, SCFAs, resulting from the bacterial fermentation of dietary fibres, include essential nutrients for colonocytes, increase gut barrier integrity, and possess anti-inflammatory properties. By replacing the lost microbial cultures in the gut, FMT improves the production of SCFA derived from the dietary fibres, with added benefits to gut and metabolic functions.Lactulose and polyethylene glycol also bring back the ratio of total bile acids in feces in human individuals with microbial imbalances. People with a balanced bile acid synthesis capability can control the growth of infections caused by C. difficile and other pathogenic microorganisms because some of the secondary bile acids synthesized by the gut microbiota can hinder the germination as well as the growth of such pathogens.

Clostridioides Difficile Infection (CDI)

C. difficile is a Gram-positive, anaerobic, spore-forming, toxin-producing bacillus.The illness caused by CDI includes symptoms from mild watery diarrhoea to a potentially deadly condition, pseudomembranous colitis (Bauer et al., 2011). The infection is spread primarily through the faecal-oral route, where spores can remain viable in the environment for many months. Difficile toxins A and B mediate the pathogenesis of CDI Toxin A acts as an enterotoxin, which impairs gut epithelial integrity, inducing inflammation of the bowel. In general, CDI continues to be a common cause of illness both in and out of the healthcare setting, especially in older adults with cofounding comorbid conditions.Advanced age, prolonged hospitalization, prior antibiotic therapy, and immunocompromised states are some of the risk factors.Because CDI is a bacterial infection, antibiotic therapy is a standard of care in the treatment of CDI.That antibiotic therapy is a cornerstone in the treatment of CDI was emphasized by the failure of tolevamer, a nonantibiotic, toxin-binding polymer, as stand-alone therapy (Johnson et al., 2014). All CDI treatment regimens have thus continued to incorporate an antibiotic backbone.One limitation of antibiotics is the inability to kill spores.The spores of Clostridium difficile are widespread in the environment, and their ingestion followed by germination into vegetative, toxin-producing cells leads to infection in susceptible hosts (Paredes-Sabja et al., 2014).This proliferation of difficile spores following antibiotic treatment contributes to recurrence, which occurs in approximately 15–25% of patients and thus is a major burden in care (Louie et al., 2011).

Recurrent CDI (rCDI)

Recurrent CDI is defined as a return of symptoms within 12 weeks following successful treatment of an initial episode. Recurrence after a first episode has been estimated at 20% to 35% of patients, whereas recurrence rates after subsequent infections have been reported to reach 40% to 65% (Chen et al., 2019). Most of these recurrences are due to relapses of the original strain rather than re-infection with a new strain, emphasizing the persistent nature of C. difficile spores within the gut environment.

Challenges in rCDI

The most problematic aspect of rCDI pertains to the disruption of gut microbiota. This usually emanates from antibiotic intake. Antibiotics that kill good gut bacteria create favourable environments for C. difficile to grow and produce toxins that can damage the lining of the intestines. Initial treatment reduces the bacterial load but fails to reconstitute protective microbial diversity in the gut and thus predisposes one easily to recurrence. Another challenge is the spore formation of C. difficile. C. difficile is a spore-forming bacterium, and the spores have a very high level of resistance to environmental stresses, including those of antibiotics. These can remain dormant in the gut or environment and re-germinate after treatment, leading to recurrent infections. It is also a complication to avoid because spores are persistent even after effective treatment. Other challenges are: Antibiotic Resistance: The repeated use of antibiotics in treating CDI promotes resistance and, over time, reduces the effectiveness of standard treatments. These increasing rates of recurrence and severity have been further enhanced with the emergence of hypervirulent strains such as NAP1/BI/027, which characteristically produce higher levels of toxins.

Impaired immune response

The host's immune system shows impaired responses to the toxins produced by C. difficile. In such scenarios, the geriatric population and immunocompromised patients are well-known victims of the mentioned bacteria. A weak immune response does not put up an appropriate response to the bacteria and hence leads to reinfection.

Treatment options for CDI

Antibiotic therapy

Initial recurrence of CDI is managed with repeated administration of either oral metronidazole or vancomycin for 10-14 days. This yields a sustained cure in only 50% of patients. The first recurrence of CDI marks a point beyond which the use of metronidazole is not advised owing to a risk of azole metabolite neurotoxicity (Baunwall et al., 2021). Second recurrences may be treated by fidaxomicin or by a tapered, pulsed vancomycin regimen. Fidaxomicin is a poorly absorbed, orally administered macrolide antibiotic that is bactericidal towards C. difficile compared to metronidazole and vancomycin, which are bacteriostatic. Fidaxomicin has a narrower spectrum of antimicrobial activity than first-line antibiotic therapy, resulting in less disruption of normal gut flora.In an RCT, it had a similar cure rate but a significantly lower rate of recurrence than treatment with vancomycin (13% vs 24%), although this

was in non-NAP Type 1 strains (Louie et al., 2011). Fidaxomicin is considerably more expensive than vancomycin and appears less effective against NAP1 CDI. Rifaximin, another rifamycin, has also been studied in small case series.

Clinical efficacy of FMT in CDI

Faecal microbiota transplantation (FMT) has emerged as a highly effective treatment for recurrent Clostridioides difficile infection (CDI), particularly in cases where standard antibiotic therapies fail (Aroniadis and Brandt, 2013). The mechanism of action and clinical efficacy of FMT in treating CDI involve several key processes that restore the balance of gut microbiota and enhance patient outcomes.

Use of RBX2660 in Faecal Microbiota Transplantation

RBX2660, marked as REBYOTA, is an investigational microbiota-based live biotherapeutic designed to prevent recurrent Clostridioides difficile infections (rCDI). Developed by Rebiotix, a Ferring Pharmaceuticals company, RBX2660 represents a standardized and scalable approach to faecal microbiota transplantation (FMT), addressing some challenges of traditional FMT. RBX2660 is derived from rigorously screened human faecal matter, processed to eliminate pathogens, and prepared as a single-dose enema. Each dose contains a diverse consortium of live microorganisms, designed to restore the gut microbiome disrupted by antibiotic treatment and recurrent CDI (Kwak et al., 2020). The product is administered rectally and is notable for being the first FDA-approved microbiota-based live therapeutic product for this indication. In the clinical efficacy of RBX2660, the pivotal phase III trial, known as PUNCH CD3, demonstrated that RBX2660 significantly reduces the recurrence of CDI compared to placebo. In this study, 70.6% of patients treated with RBX2660 remained free from CDI recurrence after 8 weeks, compared to 57.5% in the placebo group (Khanna et al., 2022). Furthermore, over 90% of those who achieved initial treatment success maintained this response for up to 6 months.

Mechanism of action

The efficacy of RBX2660 is believed to stem from its ability to restore microbial diversity in the gut. After administration, patients exhibited increased diversity in their gut microbiomes, which became more similar to that of healthy donors. This restoration includes an increase in beneficial taxa such as Bacteroides and Clostridia, while reducing potentially harmful bacteria (Blount et al., 2019). Additionally, RBX2660 has been shown to alter bile acid composition favourably, which may further inhibit CDI recurrence.

Safety profile

The RBX2660 has a favourable safety profile, with most adverse events reported as mild or moderate. The incidence of treatment-emergent adverse events was higher in patients receiving RBX2660 compared to placebo; however, these were primarily gastrointestinal and manageable (Dubberke et al., 2018). Comprehensive safety monitoring during clinical trials indicated that serious adverse events were infrequent andtypically related to underlying conditions rather than the treatment itself (Orenstein et al., 2022).

Case studies and clinical trials

Fecal Microbiota Transplantation (FMT) has emerged as a groundbreaking therapy for recurrent Clostridioides difficile infection (CDI), especially in patients who fail to respond to conventional antibiotic treatments. The therapeutic principle of FMT is to restore the diversity and balance of gut microbiota by introducing a healthy stool sample from a donor into the patient's gastrointestinal tract. Van Nood et al. (2013) conducted a landmark randomized controlled trial (RCT) that set the foundation for FMT's clinical applications. In their study, the FMT group showed a significantly higher cure rate (81%) compared to conventional treatments like vancomycin (23%) and vancomycin plus bowel lavage (31%). This finding highlighted FMT's superior efficacy in managing recurrent CDI, which traditionally presents high recurrence rates despite antibiotic therapy. The success of this study was pivotal, influencing subsequent trials and establishing FMT as a potential first-line treatment for CDI. However, its widespread clinical adoption requires further investigation into standardizing procedures, including identifying optimal routes for administration, donor screening protocols, and long-term outcomes. FMT's transformative potential lies not only in its efficacy but also in its ability to address the root cause of CDI recurrence: the disruption of gut microbiota diversity. This marks a paradigm shift in treating infections, emphasizing the importance of the microbiome in health and disease.

FMT has evolved significantly, with advancements in administration techniques driving its clinical utility. The traditional methods of FMT delivery, such as nasoduodenal infusion and colonoscopy, are effective but invasive, limiting patient acceptance and access to therapy. Youngster et al. (2016) innovated by exploring the use of oral FMT capsules, a less invasive and more patient-friendly method. The trial demonstrated that one dose of oral capsules achieved a cure rate of 82%, with a second dose increasing the cure rate to 91%. This breakthrough in FMT administration is crucial for its integration into routine clinical practice, particularly for patients who are hesitant or unable to undergo more invasive procedures. The oral route of administration not only improves patient comfort but also broadens the accessibility of FMT, making it a viable option for outpatient care. Furthermore, the flexibility of oral capsules could also promote the use of FMT in home settings, reducing healthcare costs and improving patient convenience. However, while oral FMT capsules show great promise, further studies are needed to evaluate their long-term effectiveness and potential side effects in larger, diverse populations. As we move forward, optimizing FMT delivery methods will be crucial to increasing its adoption and ensuring its success in treating recurrent CDI.

A major concern with the widespread use of FMT is its feasibility in settings outside specialized academic hospitals, where resources and expertise may be limited. Kassam et al. (2013) addressed this by demonstrating the successful use of FMT in a community hospital for treating recurrent CDI. In their case series, patients who received FMT by colonoscopy after failure of standard treatments showed a cure rate of 91%, with minimal side effects. This finding is particularly important because it suggests that FMT can be effectively performed in non-academic, community-based settings, thus expanding its accessibility to a broader population. The implications of this study are far-reaching, as they demonstrate that the logistics of FMT, including donor stool procurement, screening, and preparation, can be streamlined and implemented in various healthcare facilities. It also underscores the potential for FMT to be integrated

into routine clinical practice, especially in under-resourced settings, which could significantly improve patient outcomes across diverse healthcare systems. However, the implementation of FMT in community hospitals still requires further protocol development and training to ensure safety and efficacy, as well as regulatory frameworks to guide its use in less specialized environments.

While traditional FMT has shown considerable efficacy in treating recurrent CDI, safety concerns regarding the transmission of unidentified pathogens from donor stool have prompted the exploration of more controlled alternatives. Petrof et al. (2013) investigated the microbial ecosystem therapeutic (MET-1), a defined microbial population consisting of 33 bacterial species, as an alternative to traditional FMT. The results indicated that MET-1 was effective in treating recurrent CDI, with additional animal model studies suggesting that MET-1 could reduce local and systemic inflammation independently of the C. difficile burden. This finding highlights the potential of using well-defined, standardized microbial preparations as a safer alternative to the variability associated with donor stool. MET-1 offers several advantages, including a reduced risk of transmitting harmful pathogens and the ability to precisely target the microbiota imbalances associated with CDI. The future of FMT may lie in these controlled therapeutic formulations, which could address some of the limitations and safety concerns of traditional FMT. However, further clinical trials and regulatory approvals are needed to validate the long-term effectiveness and safety of MET-1 before it can be widely adopted.

The long-term effectiveness of FMT is another critical area of research, especially given that recurrent CDI can significantly impact patients' quality of life and health outcomes. Costello et al. (2020) conducted a prospective clinical trial assessing the long-term safety and efficacy of FMT in 100 patients with recurrent CDI. At the one-year follow-up, 90% of patients remained free from CDI, demonstrating that FMT provides durable and lasting relief from recurrent infections. This finding positions FMT as not only an effective treatment for acute CDI but also a viable long-term solution, making it an attractive option for managing chronic or recurrent gastrointestinal disorders. Long-term follow-up studies such as these are essential for understanding the sustained impact of FMT on gut microbiota and overall health. As FMT continues to evolve, the focus must shift to understanding its role in maintaining long-term gut health and preventing the recurrence of infections. Future research should also explore how FMT can be integrated into broader therapeutic strategies for other gastrointestinal conditions, such as inflammatory bowel disease and obesity, where microbiota imbalances also play a significant role. FMT represents a paradigm shift in how we approach gut health and disease, and its future success hinges on further research to optimize its delivery, safety, and long-term effectiveness.

The safety considerations of FMT

The overall safety of FMT is considered to be generally safe, and the short-term risks reported for this treatment are also more due to the mode of delivery/endoscopic procedure rather than the actual procedure of FMT. Common adverse effects are usually transient, nonserious, and self-limited and include loose stools, abdominal pain/cramps, bloating, flatulence, and constipation (Baxter and Colville, 2016).

Short-term side effects

FMT is generally a very safe procedure. All the adverse effects are most often mild and self-limiting. Most of the common, short-term side effects, such as abdominal cramping, bloating, diarrhoea, nausea, fatigue, and headache, normally resolve within hours to days after the procedure. Some patients can have more protracted symptoms or complications, like blood in the stool or even infection of the urinary and respiratory systems. These are usually unrelated to FMT.

Long-term risks

The long-term effectincludes, but is not limited to, re-colonization of pathogenic bacteria into the gut, antibiotic resistance gene transfer, and other bacterial types that could perturb the recipient's microbiota, and need consideration. A mechanism to establish these concerns includes large studies and registries that are currently available, which would allow follow-up for an extended period for adverse events and long-term outcomes associated with FMT.

Donor screening

FMT involves donor screening, which usually means the testing of donors for infectious diseases and a medical history examination. This sometimes leads to the rejection of a large percentage of potential donors as a way of reducing risks. Despite the strict selection and screening processes, reports have implicated the pathogens in donor stool as sources of infection in patients. Hence, donor selection must always be one of great vigilance.

Risk associated with FMT

Infection transmission

The transmission of infections from the donor to the recipient, especially in the case of immunocompromised patients or patients with other health issues, may occur. For example, one case of ESBL-producing E. coli resulted in bloodstream infection among recipients post-FMT. This is the reason why regulatory bodies, including the FDA, now require additional screening among donors.

High-risk populations

The safety of FMT among high-risk populations remains under investigation, including in patients with immunocompromised states or those with IBD. While several reports suggest that FMT is safe even in these selected groups of patients, serious adverse events are reported, including infection, flare-ups of IBD, and co-infection by opportunistic pathogens derived from the donor. Clinicians should exercise caution while considering the risk-to-benefit ratio when advising this procedure in such patients.

Regulatory oversight

FMT, owing to associated safety concerns, has been labelled by regulatory agencies such as the FDA as a biologic product. It therefore needs to be pursued with strict protocols of an IND. Further research needs to be done in standardizing practices and guidelines while performing FMT in order to enhance its safety profile.Although FMT has been practiced in general as a relatively safe and highly effective treatment for rCDI, its applications in other conditions warrant cautious optimism. This, however,

involves stringent donor screening, standardization of protocols, and prospective long-term follow-up with the view of minimizing risks. Further studies are needed to establish long-term safety and efficacy in specific patient populations and disease states.

Current challenges in FMT

Lack of standardized protocols

There is no universally accepted approach for FMT regarding donor selection, stool preparation, and administration methods. This inconsistency can result in varying clinical outcomes across institutions. For instance, donor screening criteria range from highly stringent to minimal checks, and stool processing techniques, including dilution ratios and storage conditions, also vary, potentially affecting the viability of microbiota and treatment efficacy (e.g., donor screening stringency and stool preparation variability).

Donor variability

Differences in the gut microbiota composition of healthy donors significantly impact FMT outcomes. Research shows that individual donors with specific microbiota profiles may achieve better clinical results for certain conditions. This variability highlights the need for rational donor selection and ongoing identification of microbiome characteristics associated with positive outcomes.

Processing and administration variability

Methods of stool processing and administration, such as colonoscopy, enema, or oral capsules, influence engraftment rates and symptom resolution. Factors like homogenization techniques and preservative use further affect microbial viability and diversity. Standardizing these procedures is crucial to maintaining consistency in quality and efficacy across clinical settings.

Regulatory and ethical issues

Regulatory frameworks for FMT are still evolving, classifying it as an investigational therapy in many regions. This restricts accessibility for patients. Ethical concerns include donor screening processes and the risk of transmitting infectious agents through fecal material. Balancing comprehensive screening to ensure safety without limiting donor availability remains a critical ethical challenge.

Guidelines in FMT

These guidelines, developed by various organizations and regulatory bodies, cover aspects of patient selection, donor screening, stool processing, methods of administration, and even ethical considerations.

Patient selection

The primary indications of FMT in practice are for recurrent or refractory infection due to Clostridioides difficile, although there is active research into other indications. Guidelines advocate for FMT in the following: Recurrent CDI: Patients with multiple relapses of CDI despite treatment with standard antibiotic courses with either

vancomycin or fidaxomicin. Severe CDI: When treatments for severe CDI fail to alleviate the patient's condition, FMT may then be considered. Other Conditions (Experimental): For conditions like IBD, IBS, and neurological disorders such as autism and Parkinson's disease, FMT is still under study, and application should generally be confined to clinical trials.

Donor screening guidelines

One of the most critical points of FMT is stringent donor screening to avoid the transmission of infectious agents and ensure the safety of the transplant. General recommendations include Medical History: Potential donors should fill out an elaborate health questionnaire assessing for risk factors for infectious diseases, gastrointestinal disorders, antibiotic use, and chronic diseases. Lifestyle Assessment: Screening for donors with a history of unsafe behaviours that may put them at an increased risk for the transmission of infections, such as intravenous drug use or high-risk sexual behaviour. Laboratory Testing: Donor stool is tested for the following pathogens: Bacterial Infections: Salmonella, Shigella, Campylobacter, etc. Viral Infections: Hepatitis A, B, C, and HIV. Parasites: Giardia, Cryptosporidium. Clostridioides difficile: Ensuring the donors are free from C. difficile. Multidrug-Resistant Organisms: Testing for MDROs, including ESBL-producing Enterobacteriaceae, carbapenem-resistant organisms, and other species.

Stool collection and processing guidelines

Donor stool preparation processing is a highly regulated process to maintain microbial viability and patient safety. Stool Collection: Fresh stool is collected from screened donors into sterile containers. Stool Preparation: Generally, the stool is homogenized, filtered, and diluted with saline or other solutions. It is processed to remove large particulate matter while preserving beneficial microbial content. Stool Storage: According to the protocol, stool can be used fresh or frozen at -80°C for later use. Frozen stool has been shown in many studies to be comparable to fresh stool when testing the effectiveness of stool for the treatment of CDI.Some centres also explored the freeze-drying or lyophilizing of stool to make oral capsules as a more available and perhaps less invasive mode of administration.

Routes of administration

FMT can be carried out via various routes, and suggestions for an apt selection often take into consideration factors based on the patients. Colonoscopy: This is the most traditional form of FMT, where the donor stool is directly instilled into the colon. Indeed, this form of action has high success rates associated with the mode. It allows for proper bowel cleansing and is also suitable for recurrent cases of CDI. Enema: Less invasive than colonoscopy, FMT via enema may not be delivered as far into the gastrointestinal tract. It is oftentimes utilized for home-based administration but yields a slightly lower success rate. Nasogastric/Nasoduodenal Tube: A delivery of stool into the upper gastrointestinal tract is provided. It is also less invasive than a colonoscopy, with certain patients experiencing nausea or aspiration risks. Oral Capsules: Frozen or lyophilized faecal microbiota capsules have been developed for oral administration. These are considered safe, convenient, and show high efficacy rates, particularly for CDI.

Clinical monitoring and follow up

Post-FMT, patients should be followed up in the clinic for any possible side effects and treatment response. Short-term Monitoring: Monitor for immediate adverse events related to FMT, which may include gastrointestinal discomfort, bloating, or diarrhea. Serious adverse events, which could be fever, infection, or perforation, are unlikely yet possible. Long-term Monitoring: Follow-up is indicated to determine recurrence of CDI and to monitor for long-term risks such as transmission of undiagnosed pathogens, particularly in the immunocompromised patient. These clinical trials may further monitor the outcomes of the patients in detail, which may involve a change in gut microbial diversity and modulation of the immune responses.

Indications and contraindications for FMT

Clostridium difficile infection

FMT is most widely used, and now recommended, in the indication of Clostridium difficile infection (CDI) (Surawicz et al., 2013). This is caused by gut dysbiosis and the overgrowth of C. difficile. Traditionally, CDI has been treated with antibiotics such as metronidazole, vancomycin, and, more recently, fidaxomicin or rifaximin. But these therapies often result in further microbiota damageand a high recurrence rate of at least 20%, which rises with each subsequent CDI episode (Cohen et al., 2010). On the other hand, FMT restores a balanced microbiota by introducing healthy bacteria from the donor, addressing the root cause of CDI.

Severe or refractory CDI

FMT can be considered for patients with severe or refractory CDI who do not respond to conventional antibiotic treatment. This includes cases where CDI leads to significant complications such as colitis or toxic megacolon.

Inflammatory Bowel Disease (IBD)

FMT is being explored in the treatment of ulcerative colitis (UC) and Crohn's disease (CD). he original report of this approach included 6 patients, 4 with UC and 2 with Crohn's disease (CD). All were treated successfully with improvement in colitis symptoms. Other cases of successful treatment have recently been reviewed by Anderson et al. (2012), who identified eight case series/reports with a total of 15 patients treated with FMT for CDI coinfecting IBD (9 UC, 6 CD). All had resolution of CDI, with 86 % demonstrating improved response to IBD medications.

Irritable Bowel Syndrome (IBS)

FMT is under investigation for IBS due to its ability to modulate he gut microbiome, although results are variable, and more research is needed to establish efficacy. Published use of FMT in irritable bowel syndrome (IBS) is limited to some 50 case reports in diarrhoea-predominant IBS (D-IBS). Since that publication, the lead author has treated with FMT, over 5–14 days, more than 300 D-IBS patients whose severe symptoms had failed to respond to conservative measures. Clinical response has been most marked in those with more severe diarrhoea and pain, but results in this group are not as dramatic or consistent as in CDI. A few reports on the use of FMT in

constipation-predominant IBS are available (Borody et al., 2004). While anecdotal reports are encouraging, no controlled trials to date have been performed, and these are required to validate efficacy and determine whether the GI microbiota may possess the key for unlocking the etiology and effective treatment of IBS, as in CDI.

Contraindications for FMT

Immunocompromised Patients: Because of the risks regarding the transmission of infection from donor stool, generally, FMT is absolutely or relatively contraindicated in immunocompromised patients. Such patients include those with active malignancies, organ transplants on immunosuppressive therapy, and severe primary immunodeficiencies. Severe Comorbidities: Patients with severe comorbidities or unstable medical conditions are not candidates for the procedure because of the risks involved. Active Infections: Patients with active infections, which may be exacerbated by the addition of new microbiota through FMT, should avoid the procedure until their infection has been treated to an acceptable degree. Known Pathogen Carriers: To this end, donors should be qualitatively investigated to rule out carriers of infectious agents, including multidrug-resistant organisms. In case a donor is identified to carry such pathogens, his stool shall not be used in FMT. Lack of Informed Consent: Patients must provide informed consent before undergoing FMT; this also means being aware of the potential risks and benefits of the procedure. In those situations where informed consent is not possible due to cognitive impairments or other reasons, a course of FMT should not be undertaken.

Conclusion

Fecal microbiota transplantation (FMT) holds immense promise as an innovative therapeutic approach, particularly for addressing recurrent Clostridioides difficile infection (rCDI). By restoring microbial diversity and balance in the gut, FMT effectively targets the root cause of dysbiosis, offering superior outcomes compared to conventional antibiotic treatments. However, challenges such as the lack of standardized protocols, variability in donor selection, stool processing, and administration methods, as well as ethical and regulatory complexities, pose significant barriers to its broader implementation.

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Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

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