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Review Article

Faecal microbiota transplantation for recurrent *Clostridiodes difficile* infection & its global regulatory landscape

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For recurrent *Clostridioides difficile* infection (rCDI), faecal microbiota transplantation (FMT) is a known and useful treatment that involves introducing faeces from a healthy individual into the digestive tract of a diseased person. *Clostridioides difficile* is a substantial global health burden due to its high death rate in elderly populations and its ability to produce colitis and diarrhoea. Despite being used since millennia, FMT has recently become more well-known and two FMT products, namely Vowst and Rebyota also received FDA approval. Different nations address regulation in different ways. For instance, FMT is regulated as a drug in the US but is classified as a medicinal product in the UK. The regulatory frameworks among various European countries also vary; a working group, citing FMT as a transplant product, has requested for complete regulation. There are other classifications as well; in Australia, FMT is categorised as a biologic by the Therapeutic Goods Administration. Research indicates that FMT is beneficial in various illnesses, apart from CDI, due to its impact on the gut flora. Challenges include insufficient FMT product characterisation, ethical concerns, and limited hospital accessibility. There are still issues with data accessibility, security, and privacy, especially considering FMT's commercialisation. The official FMT recommendation for recurrent CDI is emphasised from the perspective of public health, with the argument that early implementation could limit antibiotic overuse and prevent antibiotic resistance. Initiatives like the Universal Stool Bank concept aim to streamline donor selection and distribution procedures to minimise operational restrictions.

Key words *Clostridioides difficile* infection (CDI) - colitis -faecal microbiota transplantation (FMT) - gut flora -public health -recurrent CDI (RCDI) - stool - stool bank

Faecal microbiota transplantation (FMT) involves infusing a healthy person's faeces into another person's (generally a patient) gastrointestinal tract to treat a specific ailment. It is most commonly used as a treatment for recurrent *Clostridioides desdifficile* infection (rCDI)[1].

The bacterium *Clostridioides difficile*, sometimes known as *C. difficile*, is reported to cause diarrhoea and colitis (inflammation of the colon). *Clostridioides difficile* can affect anyone. Most infections occur during or soon after the end of an antibiotic medication course[2]. Symptoms likely manifest a few days after beginning antibiotics. The illness presents as a fever, diarrhoea, sore or painful stomach, nausea, and appetite loss[2]. One in six people who have a *Clostridioides difficile*

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infection (CDI) usually get it again in the following two to eight weeks due to the high intermittence of CDI. This is known as rCDI. FMT is among the best treatments available for CDI[2].

In the initial episode of CDI, the clinical response to antibiotic treatment is reportedly 80 per cent; however, in recurrent disease, this quickly drops to approximately 30-40 per cent[3].

Recently, medical professionals, scientists, and physicians have paid close attention to FMT and FMT-based drugs. Nonetheless, FMT is an old notion with historical citations from several locations and eras. In the fourth century of Chinese history, Ge Hong wrote the first account of orally suspending human faeces to patients experiencing extreme diarrhoea or food poisoning[4]. In the 16th century, Li Shizhen wrote about the use of different stool products to treat a variety of ailments, including vomiting, fever, diarrhoea, and constipation[4]. The term 'transfaunation' was coined in the 17th century when FMT was first used in veterinary medicine[5].

In 1958, Eiseman *et al*[1] documented the initial application of faecal enemas in treating pseudomembranous colitis in humans[1]. Given the significant burden of CDI, prioritising the deployment of FMT is essential for its success. It is estimated that each year in the US, CDIs cause roughly 5,00,000 illnesses. One in eleven persons over 65 who are diagnosed with a CDI related to healthcare die within a month of the diagnosis[6].

An estimated 1,89,526 healthcare-associated CDI infections occurred annually in the European Union/ European Economic Area (EU/EEA) in 2016–2017. According to this, there were 7864 fatal HA CDI healthcare-associated CDI (HA CDI) cases in the EU/ EEA each year, with CDI playing a role in the outcome that was fatal[7].

Another comprehensive review and meta-analysis included 229 studies with data from 41 different countries. The 95 per cent confidence interval for Community-Associated- CDI (CA-CDI) was 0.55 to 0.37 per 1000 patients per year, indicating lower incidence. In general, CDI rates were higher in North America, particularly among the elderly, even though equivalent rates were seen in other regions and age groups[8].

This review aimed to analyse available literature on the efficacy and safety of faecal microbiota transplantation (FMT) as a treatment for recurrent CDI. The objective was to explore the current global regulatory landscape governing FMT, examining variations in guidelines, approval processes, and clinical practices across different regions. The goal was to provide a comprehensive overview of the therapeutic potential and regulatory challenges associated with FMT for CDI.

FMT today

Regulation of FMT: In the United States (US), FMT is controlled as a drug. An IND (Investigational New Drug) application is typically submitted to test FMT on a novel indication. For the initial and every subsequent IND application, three copies of Form 1571 must be submitted after which the clinical trials start[9].

The US Food and Drug Administration (FDA) has acknowledged the burden associated with CDI. This is clear from the numerous guidelines the FDA has released regarding FMT and its safe application. Rebyota and Vowst, two FMT-based medications, were also authorised by the FDA on November 30, 2022, and April 26, 2023, respectively[10]. These two therapies received a special approval. Rebyota received orphan, breakthrough therapy, and fast-track approval status. Similarly, Vowst's application was granted orphan, breakthrough therapy, and priority review status. For a fast-track approval, the innovator company typically requests fast-track approval, which allows for regular communication with the FDA throughout the whole drug development and review process, ultimately resulting in early approval and medicine availability for treatment. The FDA answers fast-track requests in a maximum of sixty days. The category of breakthrough therapy includes all expedited approval requirements. If any of the attributes of the designation are to be gained, the request must be submitted by the drug company and received by the FDA no later than the end-of-phase-2 meetings, as the major objective of the designation is to construct affirmations essential to aid approval skilfully. The FDA does not anticipate that requests will be made as an addendum or after the first Biologics Licence Application (BLA) or New Drug Application (NDA) is submitted[10].

FMT is regarded as a drug in the United Kingdom (UK). Originally overseen by the Human Tissue Authority in the UK, FMT has been categorised as a medicinal product since 2015 and is now under the jurisdiction of the Medicines and Health Care Products

Regulatory Agency[11]. The U.K.'s change in perspective is a sign of the ongoing uncertainty surrounding the regulatory environment for FMT since the intrinsic mechanism and active ingredient of FMT are yet unknown[11].

Even though several European countries have not yet made an official pronouncement about FMT legislation, the European Commission has given the individual member States the flexibility to decide what framework works best at the national level. In certain European member States, such as the Netherlands, Belgium, and Italy, faecal microbiota is currently controlled under tissues and cells; nevertheless, in other countries, like France and Germany, it is classified as a drug[12]. However, a working group backed by United European Gastroenterology considers the stool to be a transplant product and asks the appropriate authorities to establish a comprehensive legal framework that ensures the security and broad application of FMT[12].

Products based on FMT are categorised by the Therapeutic Goods Administration (TGA) as biologics. An FMT product is categorised as a class 1 biological if it was obtained under the supervision, advice, or compliance with regulations of a medical practitioner licensed as a medical practitioner in a State or internal territory. An FMT product is most likely a class 2 biological if it is made in a hospital and used in multiple hospitals or clinics or if it is produced in a non-hospital facility with minimal alteration[13].

Health Canada is responsible for overseeing FMT as a new biologic medicine. A clinical trial application for a novel biologic drug must include a risk-benefit analysis. Because the therapy is considered experimental, it can only be used in conjunction with a clinical trial that has been approved[14].

Although FMT is approved for clinical use in Canada, patients with rCDIs frequently need to meet specific clinical conditions before receiving treatment[15]. In India, so far there are no guidelines or regulations offered by the Central Drug Standard Control Organization (CDSCO) on FMTS. The first successful trials on FMT in India were conducted in 2014. According to a meta-analysis[16] involving four randomised control trials, FMT may be superior to placebo in causing clinical remission and improving clinical response in individuals with ulcerative colitis.

All in all, FMT is classified as a biological drug in the United States and Canada, while other regulatory frameworks are in place in Europe due to the lack of an official position from the European Medicines Agency[3].

Current scenario: Several studies show that FMT is a novel treatment strategy for a variety of diseases with unique pathophysiologies and clinical characteristics[17]. Research on the role of the gut microbiota under FMT therapy is being conducted in neurological, pulmonary, gastrointestinal, cardiometabolic, and cancer diseases. There are several ongoing and concluded studies on FMT listed in the EU Clinical Trials Register[18]. These studies target a large number of indications, such as ulcerative colitis, steroid-refractory gastrointestinal acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation, antibiotic resistance, malignant melanoma, liver cirrhosis, hepatocellular carcinoma, colitis, Crohn's disease, *etc*[18]. The results of these studies are quite promising and positive. The common adverse effects reported in these studies are diarrhoea, constipation, abdominal distension, infections, musculoskeletal disorders, *etc*. There are no long-term adverse effects or events reported for FMT. Application-wise, FMT facilitates the introduction of bacteria that produce acetate and propionate, which lowers intestinal permeability under dysbiosis conditions. Elevations in these compounds have been associated with enhanced integrity of the epithelial barrier and reduced severity of disease, especially in the brain-gut, lung-gut, heart-gut, and gastrointestinal axis. Moreover, FMT was found to enhance the preservation of alveolar structures and regulate inflammation by reducing levels of interferon gamma (IFN-γ) and interleukin – 6 (IL-6), with a particular focus on the lungs-gut axis[18].

For FMT, retrospective, randomised clinical trials (RCT) and non-RCT have been conducted. Almeida *et al*[18] in their study reported that frozen stool was utilised most frequently and that healthy donors were the most frequent donors. Endoscopy was the most common method of delivery, followed by enema and oral capsules. The most common reason FMT was used, was to treat recurrent CDIs. The incidence of minor and serious adverse effects was 11.63 per cent and 1.59 per cent, respectively, whereas the overall efficacy of FMT was 76.88 per cent. It is expected that in the future, we will be able to obtain many FMT protocols for the broadest range of illnesses to further individualise the approaches[18].

There are still many difficulties with FMT procedures and related drugs, even after years of

progress. The first and most debatable is the FMT-based product characterisation[19]. Health authorities classify FMT and its products differently around the world[19].

Establishing a stool bank and FMT centre requires a designated space with a biological risk level of two, specific tools and an ultra freezer for storage. A biobank specialist supported by an interdisciplinary team, ensures consistent sample handling and preservation. Quality management systems and laboratory information systems (LIS) are essential for transplant traceability, safety, and quality standards[20,21].

When establishing an FMT centre and stool bank, it is crucial to implement thorough cleaning protocols, recruit and assess donors, manufacture FMT formulas and monitor donor health. Additionally, manage FMT material distribution ensure patient safety and address any new safety or quality concerns[22,23]. These factors not only fulfil the infrastructural requirements but are also essential for the clinical success of the FMT technology.

Ethical implications of FMT: Even though FMT is a salvage therapy, the fact that its administration is still experimental and not formally approved raises several significant ethical, legal, and societal concerns. For example, getting informed consent for FMT may be extremely challenging due to the patient's vulnerability and desperation, the treatments' untested nature, and the lack of knowledge surrounding its potential negative effects. Furthermore, the donor profile has several unknowns, in addition to strict screening requirements and donor commitment limitations. Other than this, the number of hospitals that provide FMT-based treatments is extremely low.

Concerns about risk, safety, and privacy are related to admistering FMT. It is difficult to balance the possible benefits and risks of FMT because the clinical and microbiological elements of the procedure are still largely unknown[24]. The notion of commercialising FMT hence raises concerns about biological material rights, data accessibility, and the impact of direct-to-consumer products. When developing commercial FMT, significant ethical considerations must be considered[24]. By refusing routine medical care and the counsel of authorised healthcare practitioners, patients put their safety in danger. In the meantime, if the results of their self-administered transplantation are not favourable, then disappointed parties may stop trusting FMT.

FMT is now only formally advised in cases of recurrent CDI in which antibiotic treatment has failed due to safety concerns about public health. This implies that antibiotic use might be avoided if FMT was used sooner rather than as a last option. By addressing the growing prevalence of antibiotic resistance, reducing the usage of antibiotics should aid in the achievement of public health goals[24].

Long-term effects of FMT: A study from El-Sahly *et al*[25] found that most patients with Inflammatory Bowel Syndrome who responded to FMT maintained their response one year after treatment, with improvements in symptoms and increasing quality of life[25]. Additionally, FMT has been shown to be a durable, safe, and acceptable treatment option for patients with recurrent CDI, with no significant differences in the incidence of severe diseases or weight gain compared to antibiotic treatment[26].

Long-term follow up studies have reported no significant differences in adverse events among treatment groups, with all symptoms cured by symptomatic treatment and no serious adverse events reported during treatment or follow up[27].

Regulatory challenges: FMT in clinical studies and for patient use raises a number of regulatory concerns[28-31], such as: (*i*) FDA classification: FMT is categorised as a biological product as well as a drug; (*ii*) Applications for investigational new drugs (INDs): In order to execute FMT for any condition other than recurrent or refractory CDI, doctors or businesses must submit an IND application; (*iii*) Product characterisation and safety: The FDA makes sure that FMT products are made correctly and that clinical trials are planned to ascertain their efficacy and safety. Potency tests, stool tests, donor screening and testing, and stability studies are all included in this; (*iv*) Donors are required to give their informed permission; (*v*) Disease transmission: There are concerns that FMT may spread illness[28-31]; (*vi*) Mental health: It is feared that FMT may lead to the spread of mood disorders and mental illnesses; False claims: FMT may give rise to false claims on improvements in lifespan and health. DIY techniques: Since FMT may be done outside of a hospital, patients may try variations at home without a doctor's supervision[28-31]. There are, however, not many attempts as of now to address such related issues.

The Universal Stool Bank model (USB) is one such method[32]. The operational burden related to donor selection, material processing and delivery is relieved for the physician and patient by the USB paradigm. The process starts with tight donor selection. Those who want to be considered as active donors must complete a rigorous three-step process. To screen for infectious diseases and potential risk factors for microbiome-mediated disorders, donors first go through an on-site clinical evaluation. If the prospective donor meets the inclusion criteria, second, laboratory testing is done to look for the presence of infectious microorganisms. This testing includes stool-based, nasal swabs, and serological assays[32].

To lessen the costs associated with donor membership and stool preparation, stool banks have been established in several countries, including the United States (Open Biome and Advancing Bio), the United Kingdom (Taymount Clinic), the Netherlands (Donor Faeces Bank (NDFB), and the Chinese FMT bank[24].

Studies have shown that FMT can induce significant and persistent changes in the gut microbiota, shifting it towards a composition similar to that of the donor[33]. These changes can be observed even after several months and up to a year after treatment. For example, a study[33] on patients with rCDI found that FMT resulted in rapid normalisation of bacterial faecal sample composition from a dysbiosis state to one representative of normal faecal microbiota. While the microbiome appeared mostly similar to the donor implant material initially, it diverged variably at later time points, remaining within the larger cloud of faecal microbiota that are characterised as healthy[33].

Lifestyle changes can significantly impact the longevity of FMT benefits. A healthy diet rich in fibre, fruits, and vegetables can help maintain a resilient gut microbiota, which is essential for the long-term benefits of FMT[24]. Regular monitoring and follow up after FMT are crucial to ensure the long-term effectiveness of the treatment and to address any potential adverse effects[34].

Recommendations for advancing FMT

Establish a global FMT registry: Create an international database to collect and analyse data from FMT procedures worldwide. Collaborate with healthcare institutions and regulatory bodies to systematically record patient outcomes, adverse events, and the long-term efficacy of FMT. This registry would facilitate large-scale studies, enhance understanding of FMT's effectiveness across diverse populations, and identify best practices.

Develop personalised microbiota therapies: Innovate FMT protocols tailored to individual patients' microbiomes. Use advanced genomic and metagenomic sequencing to profile patients' gut microbiota and customise donor stool samples to optimise therapeutic outcomes. Personalised FMT could significantly improve treatment efficacy for various diseases by addressing individual microbiome imbalances more precisely.

Integration of artificial intelligence (AI) in FMT: Leverage AI and machine learning to predict FMT outcomes and optimise donor-recipient matching. Develop AI algorithms that analyse patient data, including microbiome composition, medical history, and genetic markers, to recommend the most compatible donor and predict treatment success.AI can enhance the precision and success rate of FMT by providing data-driven insights and personalised treatment plans.

Expansion of FMT indications: Broaden the clinical indications for FMT beyond rCDI. Conduct comprehensive research and clinical trials to explore the efficacy of FMT in treating a wider range of conditions, such as autoimmune diseases, metabolic disorders, and mental health conditions. Expanding the therapeutic use of FMT could provide new treatment options for diseases with limited or no effective therapies currently available.

FMT donor biobank and certification programme: Create a centralised, certified biobank for FMT donors to ensure high-quality and safe stool donations. Establish a standardised certification programme for donors, including rigorous health screenings and regular monitoring, and maintain a biobank that supplies certified stool samples to medical facilities. A certified donor biobank would streamline the donor selection process, ensure the availability of high-quality stool samples, and reduce variability in FMT outcomes.

Overall, FMT represents a promising and evolving therapeutic approach for a variety of conditions, particularly CDI. Despite regulatory challenges and ethical considerations, the progress in FMT research and its application has been significant. The recent FDA approval of FMT-based medications, along with

advancements in understanding the gut microbiota's role in health and disease, highlight the potential of FMT. Moving forward, establishing a global FMT registry, developing personalised microbiota therapies, integrating AI, expanding clinical indications, and creating a certified donor biobank are crucial steps to enhance the safety, efficacy, and accessibility of FMT. As we continue to explore and refine this innovative therapy, FMT holds the promise of transforming treatment paradigms and improving patient outcomes across a range of diseases.

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