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Review Article

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Faecal Microbiota Transplantation: From Historical Curiosity to Standard Therapy for Recurrent Clostridioides difficile Infection

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ABSTRACT

Faecal microbiota transplantation (FMT) has evolved from a marginal concept to a prevalent therapeutic intervention, particularly for individuals with recurrent *Clostridioides difficile* infection (CDI). FMT addresses the root cause of dysbiosis, a critical aspect of CDI pathogenesis, by re-establishing a healthy intestinal microbiota via the transplantation of donor stool. The objective of this mini review is to provide an overview of the history of faecal microbiota transplantation (FMT), encompassing its clinical validation, regulatory progression, evolving safety profile, and emerging position in next-generation microbial therapies. A comprehensive literature review was conducted using databases such as PubMed, Scopus, and Web of Science to identify peer-reviewed studies, clinical trials, and regulatory documents on faecal microbiota transplantation (FMT). Selection focused on sources addressing clinical efficacy, safety, regulatory status, and emerging microbial therapies for recurrent *Clostridioides difficile* infection. Faecal microbiota transplantation (FMT) has a cure rate over 90% in certain studies, and can be administered by several methods. The FDA has granted conditional regulatory approval within its enforcement discretion. Although FMT shows high success rates, there are increasing concerns about the risk of transmitting harmful bacteria—such as STEC and EPEC—and the uncertain long-term effects these microbes may have on the recipient's gut health and immune system. Researchers are currently concentrating on standardized microbial consortia that may more precisely and securely reproduce the advantages of faecal microbiota transplantation (FMT). FMT represents a significant shift in the treatment of CDI and has paved the way for microbiome-based medicine. Long-term safety surveillance, explicit protocols, and the development of precisely specified microbial therapies will be crucial for future success.

Keywords: faecal microbiota transplantation, gut dysbiosis, recurrent Clostridioides difficile infection, microbial therapies, microbiome engineering, regulatory microbiology, microbiota-host relationship

INTRODUCTION

The gut microbiome, comprising trillions of microorganisms, is crucial for digestion, immunity, and maintaining metabolic equilibrium. Dysbiosis refers to an imbalance within this ecosystem that may occur due to excessive usage of broad-spectrum antibiotics. This increases the likelihood of individuals contracting infections, including Clostridioides difficile. Conventional antibiotic therapies are notoriously challenging for managing recurrent CDI, with failure rates escalating with each subsequent occurrence. [1]

FMT alters the management of CDI by directly rectifying microbial imbalances. The concept is straightforward: introduce healthy donor microbiota into the patient's gastrointestinal tract to restore microbial diversity and inhibit excessive growth of C. difficile. This analysis examines the evolution of FMT from traditional treatments to clinical protocols and its shifting significance in contemporary medicine.[2]

This review was conducted to synthesize current knowledge on faecal microbiota transplantation (FMT), with a focus on its clinical efficacy, regulatory evolution, safety considerations, and future directions in microbiome-based therapies. A comprehensive literature search was performed using databases such as PubMed, Scopus, and Web of Science, covering publications from inception to 2025. Search terms included "faecal microbiota transplantation," "Clostridioides difficile," "microbiome therapy," "FMT safety," and "FMT regulation."

Inclusion criteria encompassed peer-reviewed clinical trials, systematic reviews, regulatory documents, and expert

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consensus statements related to FMT in the context of recurrent *Clostridioides difficile* infection (CDI). Articles were selected based on relevance, methodological rigor, and contribution to the evolving understanding of FMT. Regulatory guidance from the U.S. Food and Drug Administration (FDA) and other international health agencies was also reviewed to contextualize the current approval landscape and enforcement discretion policies.

The findings were thematically organized to highlight the historical development of FMT, its clinical validation, delivery methods, donor screening protocols, safety concerns, and the emergence of standardized microbial consortia as next-generation therapeutic strategies.

History

The concept of transferring faecal matter for health advantages is not novel; it has existed for centuries. Fourth-century literature in traditional Chinese medicine references the use of "yellow soup," a faecal concoction, for the treatment of individuals suffering from acute diarrhoea or food poisoning. Individuals in ancient Greece and during World War II in North Africa engaged in similar activities. For instance, Bedouins utilized camel excrement to remedy diarrhoea.[1]

The initial documented application of modern Western medicine occurred in 1958, when Eiseman et al. effectively employed faecal enemas to treat four patients suffering from pseudomembranous colitis. [1] Previously, the aetiology of the sickness was ambiguous; however, it is now widely accepted that it was attributable to C. difficile. Despite its initial effectiveness, FMT remained obscure for an extended period due to cultural taboos, insufficient scientific understanding, and the predominant focus on antibiotic therapies.

FMT has lately regained recognition as a scientifically acceptable and therapeutically essential treatment due to the resurgence of recurrent CDI and the limitations of antibiotics.

Clinical Efficacy and Regulatory Evolution Following van Nood et al.'s seminal 2013 randomized controlled trial, which demonstrated a 94% cure rate for recurrent CDI in contrast to a mere 31% with vancomycin, FMT emerged as a prevalent subject in scholarly discourse. The trial was prematurely terminated for ethical considerations, as it was evident that FMT was superior, and continuing would have deprived the control group of an effective treatment. [2] This significant trial generated several research studies that validated its findings. In 2013, the FDA released a regulatory notice indicating its intention to exercise discretion in enforcing FMT for the treatment of recurrent CDI. The results of this study indicated that FMT might be utilized in a therapeutic environment without an Investigational New Drug (IND) application, provided that informed consent and fundamental donor screening were conducted. [3]

Current national and international guidelines state that faecal microbiota transplantation (FMT) is the best treatment for patients with repeated Clostridioides difficile infection (CDI) who haven't improved after at least two rounds of standard antibiotics.

Current Clinical Practice

There are various methods for administering FMT, each with its advantages and disadvantages. Table 1 gives Comparison of common delivery methods for faecal microbiota transplantation (FMT). Each method varies in terms of invasiveness, efficacy, patient convenience, and associated risks.

Delivery Method	Description	Advantages	Limitations
Colonoscopy	Direct visualization and delivery to the colon	Precise placement	Invasive, costly
Enema	Rectal administration of FMT	Less intrusive	May not reach proximal colon; limited retention
Nasogastric/ Nasojejunal Tube	Delivers FMT to the upper GI tract	Useful when lower GI access is limited	Risk of aspiration; requires patient cooperation
Oral Capsules	Ingestible, often frozen capsules containing FMT	Convenient, non-invasive	Newer method; requires freezing and proper storage

Table 1 -Summary of common methods for FMT administration including key characteristics, advantages, and limitations to guide clinical decision-making.

Regardless of the method of acquisition, donor stool must be meticulously screened for pathogens that may be transmissible. HIV, HBV, HCV, *Salmonella, Shigella, E. coli* O157:H7, MRSA, and VRE are among the most prevalent species subjected to testing. Screening additionally examines lifestyle and behavioural concerns.

Stool banks such as Open Biome have standardized the donor process, facilitating swift access for all individuals. The FDA's recent decision to restrict enforcement discretion to stool processed in licensed healthcare facilities has complicated access to third-party stool products. [3]

Clinical Case Studies and Efficacy Data Numerous trials and observational studies demonstrate the efficacy of FMT.

- The first four cases from 1958 show how well faecal microbiota transplantation worked for serious, hard-to-treat conditions, even though back then, modern microbiology did not fully understand how it worked. [1]

- Research at Massachusetts General Hospital has shown that frozen, encapsulated faecal microbiota transplantation (FMT) was effective in 70% of patients after a single treatment and 90% after a subsequent dosage. This demonstrates its simplicity and efficacy. [4]
- A comparative trial using colonoscopy and capsule-based FMT in 116 patients revealed cure rates of 96.2% and 96.8%, respectively. This indicates that less intrusive alternatives do not diminish efficacy. [5]
- A Norwegian study examined the application of FMT as the initial treatment for CDI. The first results indicated that it was equally effective as metronidazole in initial infections, suggesting its potential for earlier application in the treatment regimen. [6]

  Considerations for Safety FMT is effective; yet, it entails certain hazards. The primary concern is the potential transmission of diseases. Following faecal microbiota transplantation (FMT) in 2019, two immunocompromised patients developed bacteraemia caused by extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli. One individual has died. This tragedy resulted in the FDA implementing more stringent regulations for donor screening and emphasized the necessity of adhering to safety protocols meticulously. [7]

  The emergence of new illnesses, like the mpox outbreak in 2022, illustrates the inadequacy of present screening methods, as even the most comprehensive systems can overlook asymptomatic carriers. Long-term safety concerns extend beyond infection to encompass the potential transmission of microbiota-related illness predispositions, including obesity, mental disorders, and autoimmune diseases. Although these relationships remain speculative, the potential for unforeseen consequences necessitates ongoing monitoring.

  A nationwide registry is now monitoring over 4,000 FMT users for a decade to assess their long-term outcomes and any adverse events that may occur. [8]

  Future Directions: Commercial FMT Therapeutics Individuals have endeavoured to develop defined microbial consortia—next-generation therapeutics that harness the advantages of faecal microbiota transplantation (FMT) in a standardized, laboratory-cultivated format—due to the inherent complexity and variability of FMT. These artificial ecosystems consist of specific bacterial strains recognized for their safety and use.

In November 2022, the FDA approved RBX2660 (Rebyota), the first commercial faecal microbiota transplantation (FMT) product, for preventing recurrent *Clostridioides difficile* infection (CDI) in adults. Administered rectally, RBX2660 is derived from donor stool and contains a complex, undefined mix of microbes. However, it ensures a minimum concentration of beneficial bacteria such as *Bacteroides*, which are part of the normal gut microbiota and help resist *C. difficile* colonization. In clinical trials, RBX2660 demonstrated a 71% sustained clinical response, compared to 58% with placebo.[9]

A major advancement followed in April 2023, when the FDA approved SER-109 (Vowst)—the first oral FMT product for recurrent CDI. Unlike RBX2660, SER-109 contains only purified spores from *Firmicutes* bacteria, a dominant group in the healthy gut microbiome. These bacteria are often depleted by antibiotics, creating conditions that favour CDI recurrence. By restoring *Firmicutes*, SER-109 aims to re-establish colonization resistance.[10]

The ECOSPOR III phase 3 trial enrolled 182 patients with three or more CDI episodes in a year. After completing standard antibiotic therapy, participants received either SER-109 or placebo. Results showed that only 12% of patients in the SER-109 group experienced recurrence within 8 weeks, compared to 40% in the placebo group. These findings were supported by the ECOSPOR IV trial, which showed sustained efficacy and a recurrence rate of just 8.7% at 8 weeks .[11]

Several businesses are developing these treatments, with several having commenced preliminary clinical trials for CDI and inflammatory bowel disease (IBD). These commercial products may provide:

- Enhanced safety via regulated composition.
  - Explicit regulations facilitated by definitive production standards.
- Increased capacity for expansion and stability on the shelf. [9]

CONCLUSION

Faecal microbiota transplantation has revolutionized the treatment of recurrent Clostridioides difficile infections. This is one of the rare instances where microbiome-based therapy has successfully transitioned into clinical practice and demonstrated superior efficacy compared to conventional pharmacotherapy. This breakthrough has also demonstrated the challenges and hazards associated with working with living microbial communities.

Future microbiome therapeutics must prioritize safety, standardization, and a mechanistic understanding of their functionality. FMT has initiated a new era of microbial precision medicine, as increasing numbers of individuals express interest in microbiome engineering. The potential advancement of this new medical field will rely on further study, enhanced safety monitoring, and innovative methods for developing microbial formulations.

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