

REVIEW



Expanding horizons of fecal microbiota transplantation: Beyond *C. Difficile* to treating other infections

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ABSTRACT

Fecal Microbiota Transplantation (FMT) has surfaced as a revolutionary therapeutic method, mainly acknowledged for its success in treating recurrent *Clostridioides difficile* infections (CDI). By reinstating the gut's microbial diversity, FMT has shown recovery rates over 90% in individuals with recurrent CDI, providing a secure and economical alternative to conventional antibiotic treatments. In addition to CDI, the possible uses of FMT are broadening into different infectious diseases. Studies reveal hopeful results in tackling multidrug-resistant bacterial infections, where standard therapies frequently fall short. Moreover, FMT is under investigation for its potential to modify the gut microbiota to boost immune responses against viral pathogens, indicating a wider range of therapeutic opportunities. However, despite its promise, the extensive implementation of FMT encounters numerous obstacles. Guaranteeing standardized procedures for donor evaluation and stool preparation is vital to reduce risks associated with pathogen transmission. Regulatory structures must develop to keep pace with this emerging therapy, tackling ethical issues and ensuring patient security. Additionally, comprehending the long-term consequences of microbiota alteration remains a significant focus for future investigations. FMT is at the leading edge of groundbreaking treatments for infectious diseases, with its achievements in CDI paving the path for broader uses. Continuous research and thorough clinical trials are necessary to fully utilize its capabilities, resolve current challenges, and incorporate FMT into standard medical practice for various infections.

KEYWORDS

Clostridioides difficile; Gut microbiota; Clinical trials; Microbiome therapy

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Introduction

Fecal Microbiota Transplantation (FMT) is a medical procedure that involves transferring fecal material from a healthy donor into the gastrointestinal tract of a recipient. This procedure seeks to restore the recipient's gut microbiota, fostering a balanced microbial environment and enhancing health outcomes. The idea of using fecal matter for medicinal purposes can be traced back to 4th century China, where a fecal suspension known as yellow soup was used to treat severe diarrhea and food poisoning [1].

In the 16th century, Chinese medicine further detailed the use of fecal preparations for gut-related issues. In Western medicine, the first documented instance of FMT occurred in 1958 when Dr. Ben Eiseman and colleagues successfully treated patients suffering from pseudomembranous colitis through fecal enemas. The human gut microbiota consists of trillions of microorganisms, including bacteria, viruses, fungi, and archaea, predominantly found in the intestines. These microorganisms are essential for various physiological functions, including digestion, metabolism, immune system regulation, and defense against pathogenic organisms [2]. A well-balanced gut microbiota is critical for maintaining health, while dysbiosis an imbalance within the microbial community has been linked to numerous diseases, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), obesity, diabetes, cardiovascular diseases, and specific cancers. FMT

has garnered significant interest due to its effectiveness in treating recurrent *Clostridioides difficile* infection (CDI), which is characterized by severe diarrhea and colitis. CDI typically arises after antibiotic treatments, which disrupt the normal gut microbiota, allowing *C. difficile* to flourish. Traditional treatments rely on antibiotics, but recurrence rates remain high. FMT provides an alternative solution by reinstating the gut's microbial diversity, resulting in resolution rates exceeding 90% among patients with recurrent CDI [3].

Beyond CDI, there is increasing curiosity about FMT's potential to address other conditions related to gut microbiota imbalances. Research has examined FMT's role in gastrointestinal disorders such as IBD and IBS, with some studies reporting favorable results. Additionally, FMT is being investigated for metabolic syndrome, a collection of conditions that elevate the risk of heart disease, stroke, and type 2 diabetes. Emerging findings indicate that FMT may impact metabolic parameters by modifying the composition of gut microbiota. Furthermore, the gut-brain axis, which pertains to the two-way communication between the gut and the brain, has become a central topic in FMT studies. There are indications of FMT's potential in addressing neurological disorders like bipolar disorder, emphasizing the necessity for additional clinical trials to validate these findings [4,5].

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In conclusion, FMT signifies a significant transformation in the treatment of diseases connected to gut microbiota imbalances. Its historical background highlights its long-standing therapeutic potential, and its effectiveness in managing recurrent CDI has opened avenues for broader uses. Ongoing research is focused on clarifying FMT's efficacy for various conditions, potentially broadening its application in modern medicine [6].

Mechanisms of Action of FMT

Fecal Microbiota Transplantation (FMT) has surfaced as a key therapeutic approach, mainly acknowledged for its effectiveness in addressing recurrent *Clostridioides difficile* infections (CDI). In addition to CDI, FMT's possible uses are broadening, due to its diverse mechanisms of action. Grasping these mechanisms is essential for enhancing FMT's therapeutic effectiveness and extending its clinical uses [7].

Microbiome restoration and competitive exclusion of pathogens

The human gut contains a diverse microbial ecosystem that is vital for sustaining health. Alterations to this ecosystem, known as dysbiosis, may result in an overgrowth of pathogens and illness. FMT seeks to revitalize microbial diversity by delivering a healthy donor's fecal microbiota into the recipient's gastrointestinal system, reinstating a balanced microbial community. This revitalization enables competitive exclusion, wherein beneficial microbes effectively outcompete pathogens for nutrients and adhesion sites, thereby preventing pathogen colonization. In the case of CDI, for example, FMT reintroduces beneficial bacteria that inhibit *C. difficile* growth through competition and the release of antimicrobial compounds [8].

Modulation of host immunity and inflammation

The gut microbiota has a crucial role in regulating the host's immune system. FMT can affect both innate and adaptive immune reactions, aiding in immune balance. Research has shown that FMT can boost the production of anti-inflammatory cytokines, including interleukin-10 (IL-10), while lowering pro-inflammatory cytokines like tumor necrosis factor- α (TNF- α). This modulation of cytokines assists in managing intestinal inflammation. Moreover, FMT has been proven to change immune cell distributions, increasing regulatory T cells that support immune tolerance and reducing pro-inflammatory monocytes. These immunomodulatory effects are advantageous in ailments marked by chronic inflammation, such as inflammatory bowel disease (IBD) [5,9].

Metabolic contributions of gut microbiota

The gut microbiota plays a vital role in influencing host metabolism by producing metabolites such as short-chain fatty acids (SCFAs), which include acetate, propionate, and butyrate. These SCFAs act as energy sources for colonocytes, help regulate glucose and lipid metabolism, and show anti-inflammatory effects. FMT has the ability to restore the production of these advantageous metabolites, thus enhancing metabolic functions. In models of metabolic disorders like type 2 diabetes, FMT has shown improvements in insulin sensitivity and the modulation of metabolic pathways. This reprogramming of metabolism highlights FMT's potential in

the treatment of metabolic diseases associated with gut microbiota dysbiosis [10,11].

Impact on gut barrier function

A vital role of the gut microbiota is to preserve the integrity of the intestinal barrier, which stops pathogens and toxins from entering the bloodstream. Dysbiosis can weaken this barrier, resulting in heightened intestinal permeability, often termed as leaky gut. FMT has demonstrated the ability to boost the expression of tight junction proteins, such as zonula occludens-1 (ZO-1) and occludin, which are crucial for sustaining barrier integrity. By strengthening these tight junctions, FMT diminishes intestinal permeability, thus averting systemic inflammation and infection. This recovery of barrier function is especially advantageous in conditions such as IBD and metabolic syndrome, where barrier dysfunction is a major pathological aspect [12].

In conclusion, FMT exerts its therapeutic effects through various interconnected mechanisms: restoring microbial diversity to competitively eliminate pathogens, modulating immune responses to lessen inflammation, affecting metabolic pathways through microbial metabolites, and enhancing gut barrier integrity. A thorough understanding of these mechanisms is vital for optimizing FMT protocols and broadening its application to numerous diseases linked with gut microbiota dysbiosis [13].

FMT for Bacterial Infections Beyond *C. difficile*

Fecal Microbiota Transplantation (FMT) has been thoroughly confirmed as an effective treatment for recurrent *Clostridioides difficile* infections (CDI), but its therapeutic capabilities reach further than CDI to different bacterial infections. This investigation includes cases like *Helicobacter pylori* eradication, multidrug-resistant (MDR) bacterial infections, and urinary tract infections (UTIs), emphasizing case studies and clinical trials that demonstrate FMT's effectiveness in these scenarios [14].

Helicobacter pylori eradication

Helicobacter pylori is a bacterium associated with chronic gastritis, peptic ulcers, and gastric cancers. Typical eradication protocols frequently include a mix of antibiotics and proton pump inhibitors; nonetheless, rising antibiotic resistance has resulted in unsuccessful treatments. Recent research has examined fecal microbiota transplantation (FMT) as a supplementary treatment for *H. pylori* eradication. A pilot study investigated the practicality and effectiveness of washed microbiota transplantation (WMT) for *H. pylori* eradication, indicating possible advantages. Furthermore, a randomized controlled trial evaluated the lasting effects of FMT on gut microbiota after *H. pylori* eradication using bismuth quadruple therapy, offering insights into the role of FMT in preserving microbial balance after eradication. These results suggest that FMT might improve eradication rates and restore gut microbiota diversity affected by antibiotic treatments [10,15].

Multidrug-resistant (MDR) bacterial infections

The emergence of MDR bacterial infections presents considerable challenges to public health, as traditional antibiotics are becoming increasingly ineffective. FMT has

surfaced as a plausible approach to address these infections by reinstating healthy gut microbiota, which can inhibit MDR pathogens through competitive exclusion and immune modulation. An important case documented the successful eradication of colonization with various MDR organisms following FMT administered for relapsing CDI, indicating FMT's potential in eliminating MDR bacteria. Nonetheless, caution is necessary, as there have been instances of transmission of drug-resistant bacteria through FMT, highlighting the necessity for thorough donor screening and standardized protocols. Current studies seek to clarify the effectiveness and safety of FMT in managing MDR infections, with clinical trials investigating its function in decolonizing pathogens such as *Klebsiella pneumoniae* and *Enterobacter* species [16].

Urinary tract infections (UTI's) and gut microbiota interplay

Recurrent UTIs are a prevalent clinical issue, frequently linked to dysbiosis of the gut microbiota. The gastrointestinal system acts as a reservoir for uropathogens, and an imbalance in gut microbiota may promote the movement of these pathogens into the urinary tract. FMT has been evaluated as a treatment option for recurrent UTIs by reestablishing a healthy gut microbiome, which in turn reduces the reservoir of uropathogens. A case report highlighted the impact of FMT on recurring UTI in a patient with a long-term suprapubic urinary catheter, observing a decline in UTI episodes following FMT. Additionally, a study noted a reduction in UTI frequency after FMT for recurrent CDI, suggesting a possible additional benefit of FMT in lowering UTI occurrence. These findings imply that modifying the gut microbiota through FMT might contribute to the prevention of recurrent UTIs, although larger controlled trials are required to confirm efficacy and safety.

Case studies and clinical trials supporting bacterial infection treatment

Several case studies and clinical trials have examined FMT's use beyond CDI:

- **Recurrent UTIs:** A study indicated a notable reduction in UTI occurrence after FMT for recurrent CDI, emphasizing FMT's potential in lowering UTI rates [18].
- **MDR organism decolonization:** A case study recorded the effective removal of MDR organism colonization following FMT for relapsing CDI, implying FMT's function in decolonizing MDR bacteria [18].
- **H. pylori eradication:** A pilot study assessed the effectiveness of washed microbiota transplantation (WMT) in eliminating *H. pylori*, suggesting possible advantages [17,18].

These studies highlight FMT's promise as a treatment option for various bacterial infections beyond CDI. Nevertheless, additional research is crucial to establish uniform protocols, evaluate long-term results, and ensure patient safety [19].

In conclusion, FMT offers a hopeful therapeutic strategy for bacterial infections beyond *Clostridioides difficile*, encompassing *Helicobacter pylori* elimination, multidrug-resistant bacterial infections, and recurrent urinary tract infections. Although initial studies and case reports are optimistic, thorough clinical trials are required to confirm these results, refine treatment

protocols, and completely clarify FMT's role in addressing these difficult infections [12,19].

Safety, Regulatory, and Ethical Considerations

Fecal Microbiota Transplantation (FMT) has emerged as an important therapeutic option, especially for recurrent *Clostridioides difficile* infections. Nevertheless, its wider usage requires a comprehensive evaluation of safety, regulatory, and ethical factors to guarantee patient welfare and public health.

Risks of pathogen transmission

Although FMT is typically regarded as safe, there are associated risks, particularly the possibility of pathogen transmission. Adverse occurrences, such as the spread of antibiotic-resistant bacteria, have been reported. For example, the FDA released safety warnings indicating serious infections connected to FMT, highlighting the need for thorough donor screening and testing procedures [20].

Standardization of donor screening and stool banking

To reduce risks, it is vital to have standardized donor screening and stool banking methods. Detailed screening protocols consist of extensive medical histories, laboratory tests for infectious agents, and lifestyle evaluations to verify donor eligibility. Centralized stool banks have been established to deliver consistent and secure FMT materials, ensuring stringent and uniform safety standards. These banks promote equitable access to FMT and maintain traceable processes that uphold the quality and safety of procedures [21].

Ethical concerns in microbiome manipulation

The alteration of the human microbiome through FMT presents several ethical dilemmas:

- **Informed consent:** Patients should be fully informed about the potential risks, benefits, and uncertainties related to FMT to make informed decisions [20].
- **Donor privacy:** Safeguarding donor anonymity and managing sensitive health information with confidentiality is essential [21].
- **Long-Term effects:** The long-term impacts of changing the gut microbiota are not completely understood, thus requiring ongoing research and ethical consideration [22].

Addressing these ethical challenges calls for transparent communication, solid consent processes, and continual ethical oversight in clinical practices.

Regulatory frameworks across different countries

Regulatory strategies for FMT differ worldwide, reflecting varied views on its classification and regulation:

- **United States:** The FDA categorizes FMT as a biological product and drug, necessitating Investigational New Drug (IND) applications for its administration. However, enforcement discretion has been utilized for cases of recurrent *C. difficile* infections that do not respond to standard treatments, provided informed consent and suitable screening are performed [22].
- **European Union:** Regulatory frameworks vary among member countries, with some treating FMT as a medicinal

product and others as a transplantation procedure. This diversity results in differing regulatory obligations and practices throughout Europe [23].

- **Australia:** The Therapeutic Goods Administration (TGA) has sanctioned specific FMT products, such as Biomictra, for therapeutic purposes, indicating a structured regulatory path for microbiota-based treatments [24].

Aligning these regulatory approaches is vital to ensure uniform safety standards and promote international cooperation in FMT research and implementation. Through FMT presents considerable therapeutic potential, tackling safety risks, standardizing donor screening and stool banking, addressing ethical issues, and aligning regulatory frameworks are essential for its responsible incorporation into clinical practice [22,24].

Future Directions

Fecal microbiota transplantation (FMT) has shown considerable potential beyond its well-known application in treating recurrent *Clostridioides difficile* infections. Nevertheless, its complete therapeutic capability is still being explored, necessitating comprehensive research, regulatory enhancement, and the creation of alternative microbiome-based therapies. Future developments in this domain should concentrate on improving clinical trials, customizing microbiome interventions, and investigating synthetic microbiota options to tackle current obstacles and expand the applications of FMT [20,21].

Need for well-designed clinical trials

In spite of promising initial findings, the efficacy of FMT in addressing conditions aside from *C. difficile* infections requires confirmation through meticulously organized clinical trials. Randomized controlled trials (RCTs) that involve larger patient groups are vital for determining the safety, effectiveness, and reproducibility of FMT across various infectious and non-infectious conditions. A significant challenge is the inconsistency in donor microbiota, which can result in variable treatment outcomes. To tackle this, forthcoming studies need to standardize donor screening, stool processing, and administration methods. Furthermore, long-term monitoring is essential to assess the longevity of FMT's benefits and to detect any possible adverse effects [16,18].

Enhancing the mode of FMT delivery constitutes another vital research area. While colonoscopic infusion continues to be a commonly utilized technique, oral encapsulated formulations are becoming increasingly popular due to their non-invasive characteristics and improved patient adherence. Comparative research is necessary to identify the most effective and practical method for various patient demographics. Additionally, the mechanisms through which FMT delivers its therapeutic benefits are not fully understood, highlighting the need for mechanistic investigations that examine the interactions between the microbiome, the immune system, and host metabolism [24].

Personalized FMT and microbiome-based therapies

With the progress in precision medicine, a tailored approach to

FMT is emerging as a topic of considerable interest. Individual gut microbiomes exhibit significant variation, impacting responses to microbial therapies. High-throughput sequencing and microbiome profiling technologies can assist in customizing FMT interventions to meet each patient's specific requirements, enhancing efficacy and minimizing the likelihood of adverse reactions. AI-driven predictive modeling is also emerging as a method for evaluating patient eligibility for FMT and predicting treatment results based on microbiome composition [20].

An alternative approach includes autologous FMT, which involves preserving a patient's own microbiota for later reintroduction following a disruption, like antibiotic usage or chemotherapy. This technique mitigates the risks linked to variability in donor microbiota and the potential spread of pathogens. Nevertheless, the practicality of long-term stool banking and its clinical applicability warrant further exploration [22].

Synthetic microbiota as alternatives to FMT

One of the main issues associated with FMT is the unpredictability of microbiota derived from donors, which may pose unforeseen risks. To address this concern, researchers are creating synthetic microbiota therapies that aim to replicate the positive effects of FMT while allowing for greater control over microbial composition. These methods involve defined bacterial consortia, which incorporate the cultivation and administration of a carefully chosen group of beneficial bacterial strains to restore the gut microbial balance. Such therapies can be standardized, removing the dangers related to variability from donors [21].

In addition to bacterial consortia, therapies based on postbiotics and bacteriophages are being investigated as substitutes for traditional FMT. Postbiotics, which are made up of bacterial metabolites and bioactive compounds, have the capacity to modify the gut microbiome without introducing live microorganisms. Bacteriophage therapy, which employs viruses that specifically target harmful bacteria, offers a highly targeted method of microbiome manipulation. These synthetic strategies show considerable promise in addressing infections and other diseases related to the microbiome while circumventing the regulatory and safety issues tied to conventional FMT [20,21].

Expanding FMT Beyond CDI

The effectiveness of FMT in treating recurrent *C. difficile* infections has generated interest in its use for a wider variety of conditions. Emerging studies indicate that FMT may aid in managing inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, by restoring microbial diversity and modulating immune responses. Although initial research has shown encouraging results, additional clinical trials are essential to establish the long-term safety and efficacy of FMT in these patient groups [22].

Beyond gastrointestinal disorders, the gut microbiome has been associated with metabolic diseases such as obesity and type 2 diabetes. Dysbiosis within the gut microbiota is believed to contribute to insulin resistance and systemic inflammation, leading to investigations into whether FMT could act as a

therapeutic strategy. Similarly, increasing evidence connects gut microbial composition to neuropsychiatric disorders, including depression, anxiety, and autism spectrum disorder. The gut-brain axis is crucial for neurological function, and preliminary research indicates that microbiome modulation through FMT or other probiotic-based strategies might provide innovative treatment options [25].

Conclusions

FMT constitutes a rapidly advancing therapeutic method with potential uses extending beyond its established role in the treatment of *C. difficile* infections. Nonetheless, several obstacles need to be tackled before it can be widely utilized for other conditions. Standardization of donor screening and stool processing is vital to reduce risks and ensure consistent treatment results. Regulatory frameworks must be updated to suit the expanding use of microbiome-based therapies while prioritizing patient safety. Moreover, additional research is necessary to clarify the mechanisms driving FMT's effects and to pinpoint patient populations that would gain the most from this intervention.

The creation of personalized microbiome therapies and synthetic alternatives to FMT offers significant potential for the future of microbiome-based medicine. By harnessing advancements in microbiome sequencing, AI-driven predictive modeling, and engineered microbial consortia, researchers are progressing toward creating targeted and safe interventions for a broad spectrum of diseases. As the field continues to grow, FMT and associated microbiome-based therapies may evolve into essential elements of personalized medicine, providing renewed hope for patients facing conditions influenced by gut microbiota dysbiosis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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