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Fecal Microbiota Transplantation: An introduction to FMT, its history, and therapeutic potential

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Abstract

Fecal Microbiota Transplantation (FMT) has a long history dating back to 300 AD China, but it has only recently been adopted by Western medical practice. In this paper, we review the basic definition of FMT, its development into the standard for care for recurrent *C. difficile* infection, and how it may advance medical care for other illnesses.

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What is FMT?

Fecal Microbiota Transplantation (FMT) is a medical procedure where the microbial community from stool of a healthy donor is transplanted into the intestinal tract of the recipient to confer a health benefit.^{1,2}

The stool, and its associated microorganisms, typically undergoes minimal processing that involves filtering out undigested material, such as fiber, and suspension in buffer that facilitates long term storage of the live microorganisms at -20 or -80 degrees Celsius. This minimal processing preserves the full consortium of microorganisms found in the donor's digestive tract, which differentiates FMT preparations from other microbiome-based therapeutics comprising a defined community of rationally selected microbes.

FMT material may be delivered to patients through three modalities: upper delivery (through nasoenteric/gastric tube or EGD), lower delivery (through colonoscopy, sigmoidoscopy, or enema), and a capsule form, which is taken orally. Depending on the medical history and contraindications of the patient, a particular modality may be more suited for them. FMT is typically an outpatient procedure, and patients are usually able to return home a few hours after the procedure.

How Does FMT work?

Fecal Microbiota Transplantation (FMT) has primarily been used to treat recurrent *C. difficile* infection, although it is also being investigated as a potential treatment for a wide range of indications including other infectious diseases, gastrointestinal disorders, autoimmune disorders, and neuropsychiatric disorders.

Fecal transplants work by repairing the gut microbiome, which is involved in many bodily processes including digestion, training the immune system, synthesizing vitamins, and producing neurotransmitters.^{3,4} A functional gut microbiome may be damaged through dietary factors, exposure to environmental toxins and pathogens, or, in the case of *C. difficile*, exposure to antibiotics. After these traumas, a microbiome may be missing key species required for a specific function or have high amounts of pathogenic bacteria that are normally kept in check by other species. These disturbances may be reversed through a fecal transplant that restores a diverse community of bacteria. In this way, a FMT is similar to an organ transplant, where a nonfunctional collection of cells is replaced by a working equivalent.

Over the past decade, researchers have begun developing a detailed understanding of the cellular and molecular mechanisms underlying FMT's therapeutic action in patients with recurrent *C. difficile*. These mechanisms involve competition between

donor bacteria and *C. difficile* as well as metabolites secreted from donor bacteria such as secondary bile acids, which inhibit *C. difficile* growth, and short chain fatty acids, which may reduce inflammation and improve gut barrier function.

More comprehensive explanations on the mechanisms of FMT can be found in reviews by [Baktash et al.](#) and [Sadowsky and Khoruts](#). Continuing research on the therapeutic mechanisms of FMT will inform optimization of current FMT treatment protocols, design of next-generation microbiome-based therapeutics, and application of FMT to other indications beyond *C. difficile*.

The History of FMT

Fecal transplantation dates back to 4th century China, and has been implemented in several different contexts. However, the use of FMT for recurrent *C. difficile* infections (CDI) only began in the 1980s.⁵ This use increased after a pivotal clinical trial in 2013 and the expansion of access to FMT through stool banking. FMT is now the standard of care for recurrent CDI recommended by several medical societies in the United States and elsewhere in the world.

A summary of the key points in FMT history is listed below:

- 300: First records of FMT demonstrate that Chinese physicians used human fecal matter to treat severe diarrhea. Later records, from the 16th century, describe the use of fresh or fermented fecal preparations to treat diarrhea, constipation and abdominal pain.⁶
- 1500s: Italian anatomist and surgeon Girolamo Fabrizi d'Acquapendente develops the term “transfaunation” to describe the transfer of stool preparations from a healthy animal to a sick one. This concept was primarily used in veterinary medicine.⁷
- Unknown time period: Bedouins, a nomadic Arab tribe primarily located in Northern Africa, consume fresh camel feces as a treatment for dysentery. German soldiers stationed in Northern Africa adopted this practice during World War 2.⁵
- 1958: Ben Eiseman and a team of physicians in Colorado use fecal enemas to treat four patients with pseudomembranous colitis. Their subsequent report in the journal *Surgery* is the first published use of FMT in Western Medicine. Although *C. difficile* had not yet been discovered, it was most likely the cause of the patients' colitis.⁸
- 1983-1984: First report of FMT used to treat *Clostridioides difficile* infection is published by a group of Swedish physicians.
- 2013: Researchers in the Netherland perform the first randomized controlled clinical trial comparing FMT delivered via nasoduodenal tube to antibiotics for

the treatment of recurrent *C. difficile*. Resolution of diarrhea occurred in 81% of patients who had received FMT and 31% of patients who had received antibiotics. The trial was stopped early because researchers felt it would be unethical to withhold FMT from the control group receiving antibiotics. This study, along with subsequent randomized controlled trials, provided foundational evidence for expanding access to FMT for the treatment of *C. difficile*.⁹

- 2013: The United States Food and Drug Administration enables access to FMT through enforcement discretion—a policy that defines FMT as an investigational new drug (IND) but allows physicians to treat patients with recurrent *C. difficile* without filling out an IND application. Patients with illnesses other than recurrent *C. difficile* must access FMT through a clinical trial or a single patient IND application.¹⁰
- 2013-2021: OpenBiome, a nonprofit stool bank, increases access to FMT by helping to overcome logistical limitations of FMT.¹¹ To relieve the burden on patients and physicians to find and screen their own donor, OpenBiome operates from a centralized facility that screens donors, processes stool, stores FMT preparations, ships preparations to hospitals, and monitors patient outcomes. Centralized stool banking operations enables more rigorous and consistent donor screening, and makes treatments more cost efficient as qualified donors can provide FMT material to treat many patients. As of 2018, 98% of people in the United States lived within a two-hour drive of a hospital served by OpenBiome.

The Future of FMT and Microbiome-based Therapies

The development of FMT from the medical fringe to an established treatment has demonstrated that targeting the microbiome can help treat patients with limited medical options. Further development of FMT depends on two complementary aims: realizing the therapeutic potential of FMT by expanding its use to other indications and better understanding the therapeutic actions of FMT to engineer more defined therapies.^{12,13}

FMT is currently being evaluated as a treatment option for a wide range of indications that are potentially mediated by the gut microbiome including metabolic disorders (e.g., obesity, malnutrition, diabetes), gastrointestinal disorders (e.g., inflammatory bowel disease (IBD), irritable bowel syndrome), immune dysfunction (e.g., food allergies, response to cancer immunotherapies, multiple sclerosis), and neuropsychiatric/neurodevelopmental disorders (e.g., depression, autism spectrum disorder).¹³⁻¹⁶

A review of online, international clinical trial registries quantified the increase in both the number of FMT clinical trials and the diversity of indications being studied.¹⁶ In 2013, researchers registered 21 trials, with the large majority (17/21) focusing on *C. difficile* or IBD. By 2017 this number had more than tripled to 76 trials with less than a third (24/76) studying *C. difficile* or IBD.

In contrast to clear responses seen in patients with recurrent *C. difficile*, clinical response to FMT used for other indications have generally been heterogenous with a subset of patients showing promising results while the remainder have little or no response.^{15,17,18} This heterogeneity may be due to several inter-related factors:

Association vs Causation: Motivation for evaluating FMT as a potential treatment for the indications listed above comes from studies showing that such illnesses are associated with changes in the microbiome. However, such associations do not eliminate the possibility that changes in microbiome composition may be a consequence of an indication rather than a causative factor.

Complexity of the Indication: *C. difficile* is a relatively simple illness where pathogenic bacteria colonize a portion of the large intestine for several weeks or months. After an FMT, a donor's community of bacteria can help return the recipient's microbiome and large intestine to a more normal baseline.^{3,19}

In contrast, other indications such as obesity or autism may occur over a longer period that may overlap with critical windows of development. Because of this, it may be more difficult or impossible to reverse disease progression. Additionally, some indications may affect multiple organ systems in complex ways. The immune system, in particular, relies on intricately choreographed communication between several cell types that are affected by many factors including a patient's age, diet, previous exposure to pathogens, overall health, and genetic factors. Given the complexity of some indications, it is understandable that FMT may have divergent outcomes in a patient population.

Finally, FMT or other microbiome-based treatments may be more effective or only have an effect when used in combination with other treatments. As an example, children with moderate acute malnutrition recovered body weight more quickly after consuming a microbiome-directed complementary food supplement alongside the standard treatment of nutrient dense ready-to-use supplementary food rather than the supplementary food alone.²⁰

Proper Dosing and Donor Selection: Treating a wide range of indications may require different dosing and donor selection protocols that have been used for *C. difficile*. Instead of a single FMT, which resolves between 80-90% of recurrent *C. difficile* infections, patients with other indications may require multiple FMTs or a single FMT followed by multiple smaller maintenance doses.

In addition to dosing, optimally matching a stool donor to an FMT recipient may affect clinical response. Data from OpenBiome demonstrate that donor selection does not affect treatment of *C. difficile*; stool from any healthy donor is equally effective at resolving infections.²¹ In contrast, application of FMT for other indications may benefit from matching donors to recipients.²² This approach may be particularly effective if the patient microbiome is altered in a specific way such as missing a species of bacteria or missing a group of bacteria that fulfills a particular function.

Examples of rational donor selection or donor response:

- A clinical trial for hepatic encephalopathy selecting donors with high abundance of *Lachnospiraceae* and *Ruminococcaceae* taxa, which were previously found to be depleted in patients with hepatic encephalopathy.²³
- A clinical trial in HIV selecting donors with high abundance of *Faecalibacterium*—a group of bacteria that produces butyrate—as well as high butyrate concentrations in their stool. Butyrate, a short-chain fatty acid produced by intestinal bacteria, had been previously shown to play a role in systemic inflammation underlying the severity of HIV infection.²⁴

Closely tied to the aim of expanding the use of FMT, is better understanding the therapeutic mechanisms of fecal transplants to engineer more defined therapies.

FMT is a unique therapy because it is not only a treatment but also a discovery tool. If FMT is effective for treating a particular indication, then a more defined microbiome therapy will likely also be effective. If FMT is ineffective, a more defined therapy may still be beneficial for the patient but developing such a therapy will be more complicated and involve more risk.¹²

One approach to engineering more defined therapies is to transplant a consortium of rationally selected bacteria rather than the entire microbiome.¹² This strategy has been pursued by multiple pharmaceutical companies whose drug candidates comprise purified spores from specific bacterial strains that may play an outsized role in clearing *C. difficile* infections.²⁵ Use of a defined cocktail of bacteria helps mitigate the risk of pathogen transmission from stool donor to FMT recipient and creates a more standardized treatment.

Moving beyond bacteria, it may also be possible to reduce the therapeutic properties of FMT to a group of small molecules.¹² This approach would eliminate the need for stool donors and introducing bacteria into patients as well as create a treatment more similar to standard drug products. As an example, researchers are exploring whether administration of secondary bile acids—a metabolite produced by the microbiome that kills *C. difficile*—could be used to treat *C. difficile* infections or used prophylactically to reduce the chance of infection.^{2,3,26}

Overall, efforts to expand on the success of FMT with *C. difficile* have the potential to create a new and diverse class of microbiome-based therapeutics ranging from minimally processed stool to small molecules capable of addressing a wide-range of difficult-to-treat indications.

Conclusion

Dating back to 300 AD China, Fecal Microbiota Transplantation (FMT) has a long history of use for gastrointestinal disorders that is now entering a period of rapid development.

FMT was adopted by Western Medicine relatively recently, with the first published use in 1958 and first randomized clinical control trial in 2013. Building on clinical trial results, the use of FMT to treat *C. difficile* expanded after 2013, in part due to two key factors: the FDA's policy of enforcement discretion as well as the founding of stool banks that helped overcome the logistical limitations of screening and processing stool. The success of FMT with *C. difficile* has established a new field of microbiome-based medicine exploring whether minimally processed stool, rationally selected consortium of bacteria, and small molecules can treat a wide range of illnesses that have resisted standard therapies.

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