

Foundation Position Statement (Patients): Fecal Bacterial (Microbial) Transplantation

Position: Clostridium difficile infection (also called *C. difficile*, *Clostridioides difficile* infection, or CDI) recurs in 20-30% of patients after treatment of the initial infection.ⁱ Antibiotics are known to be an important risk factor for acquiring CDI, but antibiotics are also first-line therapy for recurrent infection. Given the relationship between antibiotic use and CDI, use of fecal microbiota transplantation (FMT) has been implemented.

The gastrointestinal tract, especially the colon, normally contains over ten trillion microscopic organisms (bacteria, fungi, and viruses), known scientifically as the microbiota.ⁱⁱ There are at least several hundred bacterial species living in the human gut which exist in a mutually beneficial relationship with the human host (this relationship is known as symbiosis). The number of species of bacteria is also known as bacterial or microbial diversity. Gut bacteria contribute to good health by producing vitamins, processing carbohydrates, providing nutrients to the cells lining the colon, suppressing harmful bacteria and helping the immune system develop normally.

The usually finely balanced microbiome can be disrupted; this can particularly occur after using antibiotics which may destroy part of the normal gut bacteria. There has likely been a decrease in the different types of bacteria over time particularly in the Western world, possibly related to sanitation, increased public hygiene and indiscriminate antibiotic use. This change in the composition of human gut bacteria is thought to be a possible contributor to the increasing frequency of inflammatory bowel disease (Crohn's disease and ulcerative colitis) worldwide and especially in the developed and developing countries.

One common and most obvious consequence of microbial disturbance for an individual is infection with the *Clostridioides difficile* bacteria. This infection can cause severe illness, including diarrhea and abdominal pain. Often, but not always, CDI occurs after antibiotics have suppressed the normal bacteria residing in the gastrointestinal tract. This infection has become a major problem for inflammatory bowel disease patients, posing challenges for both diagnosis and therapy. CDI can be very difficult to eliminate and may require the administration of more antibiotics. In cases where antibiotic treatment fails, surgical resection has traditionally been recommended. The use of fecal microbial transplantation (FMT), can now be implemented to help these patients void extensive antibiotic use and surgery. This process involves transferring bacteria from the stool of a healthy donor to a patient with recurrent CDI. The donor is screened for a variety of infections including CDI, HIV and other infectious organisms. The donor's fecal bacteria are then transferred to the patient's gastrointestinal tract by colonoscopy, enema, or a tube inserted through the nose into the upper gastrointestinal tract. Several studies from different health care centers indicate that this can be a safe and effective treatment for refractory, unmanageable and recurrent CDI. Although there may be risks

involved in this procedure, there is increasing consensus that fecal microbial transplantation is an acceptable treatment for recurrent, difficult cases of *CDI* – if performed at a healthcare center with established expertise.

A more challenging question is whether fecal microbial transplantation can be a treatment for inflammatory bowel disease, in the absence of *CDI*. It is known that the gastrointestinal microbiome of inflammatory bowel disease patients contains different bacteria from that of people without IBD or those with IBD in remission. These observations suggest that FMT may be a possible treatment for IBD.

The use of FMT for treatment of ulcerative colitis has been evaluated in a small number of randomized controlled trials, which have generally recruited patients with mild to moderate disease. These trials vary widely in their study design, route and frequency of FMT administration, and stool donor selection. In most of these studies, clinical symptoms and endoscopic inflammation improved in patients receiving FMT as compared with placebo. Adverse events were mild and self-limiting and did not differ from the placebo group. Other studies reveal similar short-term positive data. A recent study evaluated treatment of ulcerative colitis using antibiotics and FMT administered by colonoscopy, followed by fecal enema five days per week for 8 weeks. A proportion of patients achieved clinical remission, suggesting that this may be an effective treatment for ulcerative colitis, but larger studies are needed.ⁱⁱⁱ Overall, current evidence suggests that FMT might have a role in the treatment of mild to moderate ulcerative colitis. But uncertainty remains due to the small number of trials, differences in study design, short follow up periods, lack of long-term safety data, and small numbers of patients treated with this therapy. There are limited high quality studies that have demonstrated FMT to be curative for the treatment of Crohn's disease, but clinical studies are currently ongoing. More randomized-controlled studies, with larger patient samples are needed to evaluate the use of FMT for treatment of IBD. In summary, there is currently no definitive evidence that FMT is a cure for IBD, nor that it induces sustained remission in well-controlled trials.

In 2013, the Food and Drug Administration (FDA) issued a draft decision to consider a regulatory approach to FMT therapy for the treatment of *CDI* that has not been responsive to standard therapy.^{iv} The potential decision will consider implementation of a regulatory process for FMT that is similar to that of drug approvals. While regulation will establish a process for the clinically validated safety and efficacy of this therapy, including long-term adverse effects, it is important to have a discourse on potential effects on patient access and the advancement of continued research to further understand FMT's role in IBD.

On June 13, 2019, the FDA informed patients and health care providers of potential serious or life-threatening infections with the use of FMT, after bacterial infections

caused by multi-drug resistant organisms (MDROs) occurred during investigational FMT, resulting in the death of one individual. After this event, the FDA issued new requirements for FMT providers including the requirement for additional screening and testing procedures for donor stool to detect MDROs.^v In addition, studies published in 2020 have found that there can be fecal transmission of infections of E.coli, and SARS-CoV-2, therefore it is important for patients to understand and discuss the risks of FMT with their providers.

In November 2022, the FDA finalized the requirements and guidance for the use of FMT to treat C. difficile infection that does not respond to therapies (“Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies” dated July 2013 (July 2013 guidance).

There has been growing investment interest from various commercial entities, medical researchers, and other types of investors to further advance FMT as a therapy. Considerations on safety and the effects of this approach will need consideration from multiple stakeholders, including patients, physicians and researchers, and the FDA, among others.

Crohn's & Colitis Foundation Patient Education Committee

July, 2023

ⁱ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4128635/>

ⁱⁱ Backhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A. & Gordon, J. I. Host–bacterial mutualism in the human intestine. *Science* 307, 1915–1920 (2005) and Sender, R., Fuchs, S. & Milo, R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell* 164, 337–340 (2016)]

ⁱⁱⁱ Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet*, 2017. 389: 1218–28

^{iv} <https://www.fda.gov/media/86440/download>

^v Website: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation>]

^{vi}Yin Lai, C., Sung, J., Cheng, F., Tang, W., Wong, S., Chan, P., Kamm, M., Sung, J., Kaplan, G., Chan, F., Ng, S. Systematic review with meta-analysis: review of donor features, procedures and outcomes in 168

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clinical studies of faecal microbiota transplantation. *Alimentary Pharmacology & Therapeutics*; Volume 49, Issue 4, January, 2019.

^{vii} [Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies | FDA](#)