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FMT: The New Revolutionary Treatment Modality

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ABSTRACT

The human gastrointestinal tract is home to the most diverse microbial ecosystem in the human body and is made up of bacteria, viruses and eukarya. Collectively known as the gut microbiota. There is emerging evidence that gut microbiota plays a pivotal role in both health and disease. Perturbations to the structure and function of the gut microbiota are known to be associated with certain disease states. Therefore, manipulating the gut microbiota in an attempt to restore structure and function represents a promising therapeutic strategy. Recently, there has been a surge in clinical and scientific interest in manipulating the gut microbiota using a method called fecal microbiota transplantation (FMT). This increase in interest has gathered after it was shown in randomized controlled trials to be highly effective in treating recurrent *Clostridium difficile* infection (CDI).

Keywords: *Clostridium difficile* infection (CDI), Microbiota, Fecal microbiota transplantation (FMT)

INTRODUCTION

The gut microbiota provides an intestinal biological barrier against pathogens and has a pivotal role in the maintenance of intestinal homeostasis and modulation of the host immune system [1]. The specific changes in the composition of gut microbiota, termed dysbiosis, have been associated not only with many gastrointestinal (GI) diseases but also with metabolic diseases, autoimmune diseases, allergic disorders, and neuropsychiatric disorders [2]. Restoring a healthy microbial community is, therefore, a promising therapeutic strategy for diseases related to gut dysbiosis [3]. Fecal microbiota transplantation (FMT), also called stool/fecal transplantation or fecal bacteriotherapy, is the new revolution and answer to the above disorders.

CDI is one of the most common hospital-acquired infections and represents a major health problem in the United States. Among the most vulnerable populations susceptible to CDI are HSCT (hematopoietic stem cell transplant) recipient where the incidence of CDI is as high as 25% [3].

Vancomycin, metronidazole and fidaxomicin are the first-line therapies for CDI; however, for hematopoietic cell transplantation patients, recurrent infection is common on cessation of antibiotic therapy, with severe cases being accompanied by a high incidence of mortality. Probiotic therapy, particularly using the yeast *Saccharomyces boulardii* in combination with high-dose antibiotic therapy, has been used for recurrent CDI (RCDI), although with limited success [3].

Fecal microbiota transplantation (FMT) is the infusion of liquid filtrate feces from a healthy donor into the gut of a recipient to cure a specific disease. A fecal suspension can be administered by nasogastric or nasoduodenal tube, colonoscopy, enema, or capsule. The high success rate and safety in the short term reported for recurrent *Clostridium difficile* infection have elevated FMT as an emerging treatment for a wide range of disorders. There are many unanswered questions regarding FMT, including donor selection and screening, standardized protocols, long-term safety and regulatory issues that are yet to be uncovered.

HOW SUCCESSFUL IS IT?

An effective treatment against recurrent *C. difficile* infection is not available. Generally, repeated and extended courses of vancomycin are prescribed which disrupts the natural environment of the microbiome. Infusion of feces from healthy donors has been reported as an effective treatment for recurrent *C. difficile* infection. Various studies and trials have proven the effectiveness of FMT not only recurrent *C. difficile* infections but also in other diseases.

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A study was conducted, in which donor feces were infused [4] in patients with recurrent *C. difficile* infection and compared with conventional 14 day vancomycin treatment, with and without bowel lavage. Randomly assigned patients received one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary endpoint was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

Of 16 patients in the infusion group, 13 (81%) had a resolution of *C. difficile* associated diarrhea after the first infusion [4]. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($P<0.001$ for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity.

Another successful study was conducted in five years. All patients who received FMT for recurrent recurrence within 8 weeks of the previous treatment) or refractory CDI from 2013 through 2017 in all the five medical centers in Israel currently performing FMT was studied. Stool donors were screened according to the Israeli Ministry of Health guidelines [5].

Fecal microbiota transplantation (FMT) emerged as a promising treatment for *Clostridium difficile* infection (CDI). The aim was to summarize the national Israeli experience in FMT. 111 patients with CDI underwent FMT, 37 (35%) of which via oral capsules and 50 (45%) via colonoscopy. The overall success rate was 87.4%, with no difference between the administration routes.

FMT TECHNIQUES

FMT is an effective and robust strategy for treating recurrent CDI. Several FMT techniques are used in the process of fecal transplantation. FMT involves the restoration of the colonic microflora by introducing healthy bacterial flora through the infusion of stool, e.g. via colonoscopy, enema, orogastric tube or by mouth in the form of a capsule containing freeze-dried material, obtained from a healthy donor. Out of this, the colonoscopy method has been found out to be the most effective. The major advantage that colonoscopy offers over other modalities is the ability to visualize the entire colon [6]. It also enables reliable delivery of stool to affected segments of the bowel [6,7] and possibly better retention of stool. Furthermore, colonoscopy can deliver larger amounts of stool per transplant procedure associated with higher success rates. Bowel preparation before the procedure is suggested to increase the likelihood of resolution of CDI by decreasing the number of spores and residual organisms [7].

Upper gastrointestinal routes are typically faster, less expensive and better tolerated compared to colonoscopy, though not as aesthetically pleasing to some patients [8]. The most recently developed mode of stool delivery is in the form of oral capsules [9,10]. It involves the delivery of stool mixed with a cryoprotectant, most commonly glycerol and double- or triple-encapsulated to protect the stool from stomach acidity. Capsules are minimally invasive, convenient, and eliminate the risk of perforation by endoscopic procedures. Additionally, capsules are more aesthetically pleasing, as patients have shown a preference for this mode of delivery over others [11]. Based on current data, colonoscopy is supposed to be the most effective strategy. However, capsule FMT offers patients a more convenient and aesthetically pleasing option.

COST-EFFECTIVENESS

The first cost-effective analysis compared three types of FMT (colonoscopy, duodenal infusion and enema) and standard antibiotic therapy in the US. They found that FMT via colonoscopy was cost-effective compared to vancomycin and dominant (both cheaper and more effective) compared to the other therapies [12]. Cost-effectiveness models comparing these various approaches support the use of fecal transplant using colonoscopy over antibiotic therapy for treating recurrent CDI. However, there remains a knowledge gap regarding the cost-effectiveness of capsule FMT.

FMT AND ITS ADVERSE EFFECTS

Commonly reported immediate adverse events after FMT include abdominal discomfort, bloating, flatulence, diarrhea, constipation, vomiting and transient fever [13]. Most of these symptoms are self-limiting and disappear within 2 days after FMT. However, very little information is available regarding the long-term immunologic effects of FMT.

In July 2013, The Food and Drug Administration (FDA) is informed the health care providers and patients of the potential risk of serious or life-threatening infections with the use of fecal microbiota for transplantation (FMT). The agency is now aware of bacterial infections caused by multi-drug resistant organisms (MDROs) that have occurred due to the transmission of MDRO from the use of investigational FMT.

DONOR SCREENING AND ADDITIONAL PROTECTIONS FOR INVESTIGATIONAL USE OF FMT

Donor screening is focused on risk reduction. Consensus guidance published by Cammarota et al. [14] recommends that donors are extensively screened by a medical questionnaire before undergoing blood and stool testing. The medical questionnaire is usually designed to elicit information regarding risk factors for transmittable pathogens and conditions and diseases that could potentially be microbiome-mediated [14]. As a general rule, prospective donors with active infection or who disclose risk factors for infection should be excluded. Because of serious adverse reactions that occurred with investigational FMT, FDA has determined that additional protections are needed for any investigational use of FMT. Special donor screening methods are to be taken into considerations:

1. Donor screening must include questions that specifically address risk factors for colonization with MDROs and individuals at higher risk of colonization with MDROs must be excluded from donation. Examples of persons at higher risk for colonization with MDROs include:
    a. Health care workers.
    b. Persons who have recently been hospitalized or discharged from long term care facilities.
    c. Persons who regularly attend outpatient medical or surgical clinics.
    d. Persons who have recently engaged in medical tourism.
2. FMT donor stool testing must include MDRO testing to exclude the use of stool that tests positive for MDRO. The MDRO tests should at a minimum include extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). The culture of nasal or peri-rectal swabs is an acceptable alternative to stool testing for MRSA only. Bookend testing (no more than 60 days apart) before and after multiple stool donations is acceptable if stool samples are quarantined until the post-donation MDRO tests are confirmed negative.
3. All FMT products currently in storage for which the donor has not undergone screening and stool testing for MDROs as described above must be placed in quarantine until the donor is confirmed to be not at increased risk of MDRO carriage and the FMT products have been tested and found negative. In the case of FMT products manufactured using pooled donations from a single donor, stored samples of the individual donations before pooling must be tested before the FMT products can be administered to subjects.
4. The informed consent process for subjects being treated with FMT products under your IND going forward should describe the risks of MDRO transmission and invasive infection as well as the measures implemented for donor screening and stool testing.

USE OF FMT BEYOND CDI

Preliminary studies seem promising for various gastrointestinal disorders, yet RCTs are needed to determine if FMT truly is an effective treatment modality for IBS, chronic constipation or other GI disorders.

FMT can also be used to treat diseases other than GI disorders in which the gut microbiota is disturbed. There are preliminary reports on the use of FMT therapy in a wide range of disorders including Parkinson's disease, fibromyalgia, chronic fatigue syndrome, myoclonus dystonia, multiple sclerosis, obesity, insulin resistance, metabolic syndrome and childhood regressive autism [15].

Vrieze et al. [16] performed RCT of FMT in 18 male patients with metabolic syndrome. Patients who received fecal microbiota infusion from lean male donors reported a marked increase in insulin sensitivity helping people with obesity and other metabolic issues.

FUTURE PROSPECTS OF FMT

FMT is an effective treatment for recurrent CDI regardless of the route of delivery and method of preparation and storage. The use of encapsulated and orally administered fecal microbiota will expand access for patients and simply the design of placebo-controlled trials. Short-term follow-up suggests that FMT appears to be a relatively safe treatment, with the majority of side effects being mild and self-limiting.

There is emerging evidence suggesting that FMT may have a treatment utility beyond recurrent CDI, although further RCT evidence is required before wide-scale adoption may occur for these indications [17].

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