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Fecal Microbiota Transplant for Recurrent *Clostridium difficile* Infection: A Primary Care Perspective

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Clostridium difficile infection (CDI) has surpassed methicillin-resistant *Staphylococcus aureus* as the leading cause of health care-associated infections in the United States, with an estimated annual cost of $1 billion.[1] Up to 25% of patients with CDI will experience recurrence within 30 to 90 days, with some experiencing multiple recurrences.[1] Fecal microbiota transplant (FMT) has been in the news for the last few years as an effective though cringe-inducing treatment for recurrent severe CDI. Also known as stool transplant, it was first reported in 1958 for the treatment of pseudomembranous colitis.[1,2] FMT involves the infusion of a fecal suspension from a healthy donor into the gut of a patient with CDI. This article provides a brief outline of a procedure that is often mysterious to the average primary care provider but denotes a paradigm shift in the understanding of the importance of intestinal microbes.

What are the indications?

According to the FMT workgroup guidelines published in 2011, the primary indications for FMT are: 1) recurrent or relapsing CDI (i.e. three or more episodes of mild to moderate CDI and failure of a six- to eight-week taper with vancomycin with or without an alternative antibiotic), 2) moderate CDI not responding to standard therapy (vancomycin) for at least a week, and 3) severe or fulminant CDI with no response to standard therapy after 48 hours.[3]

How does it work?

The imbalance of commensal intestinal flora, also known as microbiota, is known as dysbiosis and can lead to recurrent CDI. These organisms help maintain a balanced and protective immunologic gut physiology. Antibiotics can breach this protective barrier and encourage colonization by *C. difficile*. It appears that abnormally low levels of intestinal *Bacteroides* and *Firmicutes* species may predispose a patient to recurrent CDI, although other organisms are likely involved.[1] As stool is biologically active, FMT from a healthy donor has been proven to correct dysbiosis, restore the normal bacterial milieu, eradicate *C. difficile*, and prevent recurrence.[1]

What is the evidence?

There is growing evidence of the effectiveness of FMT. Case series, systematic reviews, meta-analyses, and a single randomized controlled trial (RCT) have demonstrated that FMT is a highly effective treatment for recurrent CDI. In an RCT done in Amsterdam, patients with recurrent CDI were randomized to either FMT versus a standard two-week treatment with vancomycin.[4] The former group had an 81% resolution with one infusion and 94% after a second infusion among those who had recurrence. In the latter group, only 31% in the vancomycin group ($p < 0.001$) achieved resolution. Of note, a second randomized trial is ongoing. Another multicenter study designed for long-term follow-up revealed a primary cure rate of 91% and a secondary cure rate of 98% for a mean follow-up of 17 months.[2]

How is it done?

A fresh stool sample less than six hours old is recommended. In a blender provided by the patient, the donor stool is blended with non-bacteriostatic saline. After a proper slurry-like consistency is achieved, the mixture is filtered through gauze pads to remove particulate matter. The liquefied stool is then collected in 60 cc catheter tipped syringes. The stool is introduced into the recipient in either of two ways: 1) the upper GI tract via a nasogastric or nasoduodenal tube or 2) directly into the lower GI tract, via colonoscopy or retention enema, which can be self-administered. For lower GI tract administration, a colon lavage prior to the procedure is usually recommended, and patients are encouraged to take two tablets of loperamide an hour prior to help retain the donor stool. For colonoscopy, a minimum of 50 grams is recommended, as patients who received less that 50 grams of stool had higher recurrence rates of CDI.[5] For upper GI tract administration, smaller amounts are typically used. Prior to FMT, all antibiotics need to be stopped for a minimum of two days. After FMT is performed, it is important that the recipient remain off antibiotics, indefinitely if possible. It should be noted that the optimal protocol for FMT has yet to be determined, and further research is needed in this area.

Choice of Donor

Donors have to be carefully screened for transmissible infections such as hepatitis B and C, HIV, and syphilis. Donor stool is cultured and tested for ova and parasites as well as *C. difficile* to screen for asymptomatic carriers. Other exclusion criteria used to screen potential stool donors include: antibiotic use in the last three months, high-risk sexual behaviors, recent incarceration, and recent body pierc-

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ings/tattoos. Relative exclusion criteria include history of inflammatory bowel disease, intestinal malignancy, and immunosuppression because such patients have increased risk of underlying dysbiosis.

The donor may be a close relative or an unknown volunteer—there is no significant difference in the resolution rates. Patients may designate their donor and even, on occasion, self-administer the fecal sample. It typically takes five to seven days for donor testing to be completed. It should be noted that the cost of screening the donor is approximately $500, which may not be covered by health insurance plans. An alternative is to use a stool bank, where volunteer donors may be reimbursed for their sample.

Stool Bank and Cost of Treatment

Donor stool specimens are available through stool banks, which carefully screen donors and prepare stool samples for FMT. Massachusetts General Hospital in Boston has its own stool bank. Commercial stool banks like OpenBiome provide stool samples for the general medical community. Through OpenBiome, samples can be ordered for overnight delivery in urgent situations. Each frozen stool sample costs $250 and must be stored in a proper medical freezer prior to use. Once the sample is thawed, it can be used in the same manner as a freshly prepared stool sample. The cost of obtaining frozen samples from a stool bank may or may not be reimbursed by health insurance. Future steps include the development of a standardized frozen preparation and the use of a universal donor, both of which are underway. The Food and Drug Administration (FDA) is currently considering whether the patient and physician need to know the demographics of the donor.

Safety Issues

In July 2013, the FDA labeled FMT as an investigational new drug (IND), which usually requires an IND application. After much uproar from the medical community, concerns were raised that requiring an IND would make this potentially life-saving treatment out of reach for many patients. Subsequently, the FDA decided that it would exercise enforcement discretion for recurrent CDI. Physicians would be able to proceed with FMT without filing for an IND, provided appropriate informed consent was obtained and documented. Patient safety remains a concern, especially in the immunosuppressed, although recent studies have shown that it may not be as dangerous as initially thought. Short-term adverse events include diarrhea, cramping, belching, and constipation.[5] Rarely there may be a flare of underlying chronic inflammatory diseases like ulcerative colitis. Long-term follow up has confirmed the benign nature of the procedure without significant negative outcomes.[1,3] Careful informed consent must be obtained and documented. Patients must be made aware that although FMT is very effective, it is still an investigational treatment. Given the complexity of fecal microbiota, the possibility of unforeseen consequences must be discussed.

Our Experience and Future Possibilities

At Henry Mayo Newhall Hospital in Santa Clarita, a 238-bed community hospital affiliated with the University of California, Los Angeles, nine patients have undergone this procedure of which eight achieved complete cure. This 90% success rate is consistent with literature reports. The ninth patient had a relapse initially treated with prolonged vancomycin followed by another severe relapse and a repeat emergency stool transplant. Despite initial clinical improvement, the patient eventually died from his many concurrent illnesses.

In our experience, FMT is an effective life-saving procedure that is affordable and can be performed at community hospitals with significant success. In a recent open label feasibility study published from Massachusetts General Hospital, frozen encapsulated inoculum from unrelated donors (the stool pill) was found to be effective and safe.[6] Patients with recurrent CDI were treated with 15 capsules on two consecutive days and followed for up to six months. This breakthrough treatment modality addresses practical barriers and safety concerns associated with conventional FMT and will hopefully be widely available as standard therapy for recurrent CDI in the future. Formal guidelines are needed to ensure the best possible outcomes and minimal adverse events in a multidisciplinary approach.

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