CRITICAL VIEWS IN GASTROENTEROLOGY & HEPATOLOGY

Fecal Microbiota Transplantation: Where Is It Leading?

Fecal microbiota transplantation (FMT) has gained a great deal of interest in the past year, and controversy briefly hit the news when the US Food and Drug Administration stated, in May of 2013, that an investigational new drug application would be required to perform FMTs and then softened its stance a month later to allow the use of FMT in cases of recurrent or refractory *Clostridium difficile* infection. *Gastroenterology & Hepatology* spoke separately with 2 experts in the field on the topic of FMT and regulation issues: Eamonn M. M. Quigley, MD, professor of medicine and human physiology at the University College Cork in Ireland, and chief of the Division of Gastroenterology and Hepatology at Houston Methodist Hospital and Weill Cornell Medical College in Houston, Texas, and Stacy Kahn, MD, assistant professor of pediatrics at the University of Chicago Medicine in Illinois. These thought leaders were in alignment yet brought their unique insights to the discussion presented below.

Fecal microbiota transplantation (FMT) was recognized millennia ago as a useful therapeutic modality[1] and, only in recent years, has entered the medical mainstream, bringing with it both promise and controversy. FMT, practiced today in the traditional medical setting, is the delivery of stool from a healthy, extensively prescreened donor to another person with the intent of repopulating the normal, healthy commensal bacteria of that other person. FMT can be delivered through a nasogastric or nasoduodenal tube, an upper endoscopy, colonoscopy, or enema.

Although much of the data on FMT come from case reports, the evidence of the efficacy and safety of FMT for refractory or relapsing *Clostridium difficile* infection (rCDI) has been so convincing that the US Food and Drug Administration (FDA) reversed its stance on requiring an investigational new drug (IND) application for FMT for this indication.[2] Promising yet insufficient data exist to support more widespread use of FMT. Theoretical long-term issues also exist, according to Dr Quigley. Because the microbiome plays a role in obesity, metabolic syndrome, and other conditions, FMT might theoretically put a person at risk for disease down the road. For this reason, some specialists in the field reject donors who, for example, have a family history of colon cancer or a high body mass index (BMI).

At minimum, donors must have no history of gastrointestinal disease or other serious comorbid illnesses. They must be extensively screened for community-acquired diseases such as HIV, hepatitis A, B, and C, and syphilis, and their stool must be tested for pathogens such as *C difficile,* flagella, *Escherichia coli, Campylobacter,* ova and parasites, and *Salmonella.* The disease being treated also may dictate the screening requirement. For example, Dr Kahn suggested that stool meant for a patient with inflammatory bowel disease (IBD) should be tested for cytomegalovirus (CMV) during the screening process to avoid potential transmission of CMV colitis through FMT.

BMI and food allergies are also important issues in the donor screening process, according to Dr Kahn. Because microbiota influences metabolism, a BMI of less than 30 kg/m^2 has been recommended, she said, and although there has yet to be a report of a transmission of a food allergy via FMT, erring on the side of caution might be the reasonable thing to do. While Dr Kahn notes that screening protocols vary among institutions, many are based on the guidelines published by the FMT Workgroup.[3] Dr Quigley noted that a workable systematic methodology has been published in the May 2012 issue of the *American Journal of Gastroenterology* in which donor stool, which is frozen and stored, comes from a pool of screened volunteers.[4]

> Evidence of the efficacy and safety of FMT for refractory or relapsing Clostridium difficile infection has been so convincing that the FDA reversed its stance on requiring an IND.

Long-term safety persists as a major concern as increasingly more FMT procedures are performed, considering that only 30% of the thousands of microbes inhabiting the human gut can be detected by culture-based techniques.[5] Both Dr Quigley and Dr Kahn reiterated that unknowns

persist about whether FMT opens up the risk of transmission of cancer or metabolic or autoimmune diseases.

Further adding to the dynamic of the evolution of FMT is its coverage in the lay media in which the procedure is portrayed as a natural, do-it-yourself remedy. Interest is high among the lay public, noted Dr Kahn.

> Patients are willing to try FMT, but they do not always have a balanced and educated perspective . . . . Many of them do not recognize that significant safety concerns and risks are associated with FMT.
> — Dr Stacy Kahn

She and her team receive multiple e-mail inquiries weekly. "Patients are willing to try FMT, but they unfortunately do not always have a balanced and educated perspective about the procedure. Many of them do not recognize that significant safety concerns and risks are associated with FMT," she explained. The importance of medical evaluation and a proper diagnosis for patients considering FMT cannot be stressed more, she added. The medical profession can play a role in educating patients about appropriate indications for FMT and can protect vulnerable patients from the already looming industry of alternative health practitioners who have begun charging exorbitant fees for FMT procedures.

Current guidance for the industry is that FMT can be performed without an IND provided that the indication is rCDI, informed consent is acquired, and the donor and donor stool are duly screened.[6] This policy, however, does not extend to other uses of FMT. The FDA states in its most recent draft guidelines: "Data related to the use and study of FMT to treat diseases or conditions other than *C difficile* infection are more limited, and study of FMT for these other uses is not included in this enforcement policy."[6]

Dr Quigley conjectured that the FDA's original stance to require an IND for FMT was generated, at least in part, to protect patients from abuse and arbitrary use of the procedure. Alternative methods to regulate the procedure and protect public health are needed and may be challenging to develop. "Quality control is going to fall on medical centers and FMT specialists. Without standardization, however, there is a grave risk that FMT could be used for anything sans appropriate evidence for use, which will lead to misfortune," he said. Still, Dr Quigley said that the FDA's decision to recommend rather than require an IND to perform FMT for rCDI[2] was a good move. "The idea of having to obtain an IND was very daunting and put a halt to research for a while," he said.

These sentiments were acknowledged in the FDA's most recent guidelines.[6] Dr Kahn said that the FDA's initial stance on the IND requirement presented a challenge but added that it was well understood that public safety was at the core of the decision. "Although the lay community is frustrated, feeling that progress is slow, I know, through having had multiple conversations with the FDA, that it very much recognizes the potential benefits of FMT and is working to adapt to the changing situation," said Dr Kahn. "Although the FDA initially required an IND and had a public workshop to address the issue, the FDA really listened to practitioners in the field." Within a month, the FDA acknowledged that credible evidence existed about the value of FMT for rCDI and also conceded that, although it would like more evidence on FMT's efficacy and safety, requiring an IND for FMT of every case of rCDI was not necessarily reasonable.[2]

This kind of responsiveness from a regulatory agency is remarkable in Dr Kahn's view. According to Dr Kahn, the FDA has been very open to ongoing discussions with the American Gastroenterological Association's Human Microbiome Project, headed by Gary D. Wu, MD, of the University of Pennsylvania in Philadelphia, as well as the Pediatric FMT Task Force that Dr Kahn cochairs and is headed by Athos Bousvaros, MD, MPH, who is president of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and is affiliated with the Boston Children's Hospital in Massachusetts. "The FDA has been incredibly approachable, very interested in dialogue, and very willing to engage in planning for future studies as well as protocol developments," she said.

> The field should be moving beyond fecal transplants to identifying the particular organisms that are essential in a particular indication and then providing those organisms in a much simpler fashion than FMT.
> — Dr Eamonn M. M. Quigley

Indeed, Dr Kahn and her team at the University of Chicago Medicine have been diligent in keeping the FDA in the loop regarding a pilot study of FMT in adults with

ulcerative colitis as well as their use of FMT in pediatric patients with rCDI. "We want to do this in the safest, most methodical manner and want the public to understand the value of proceeding this way," she said. "When a patient does the procedure at home and then is admitted to the hospital because of complications, it certainly slows down progress, and this needs to be communicated."

As for indications for FMT beyond treatment of rCDI, IBD is a target, considering that evidence suggests that the gut microbiota is involved in IBD. "We have known for decades that the microbiome is important in IBD pathogenesis because diversion procedures, practiced in patients with IBD long ago, demonstrated that IBD could be healed by diverting the fecal stream from the affected part of the bowel. Once the continuity of the fecal stream was restored, relapse occurred," explained Dr Quigley. Still, the role of FMT in IBD is beset with questions that require randomized controlled trials to answer, he said.

The field should be moving beyond fecal transplants to identifying the particular organisms that are essential in a particular indication and then providing those organisms in a much simpler fashion than FMT, according to Dr Quigley. "If we are still doing fecal transplants in 5 years' time, we have failed," he said, explaining that, in his view, the field will be advancing rapidly such that FMT will likely become obsolete fairly quickly. Controversies regarding INDs, regulations, and abuse of FMT will then be moot. "We will probably move into a situation in which a patient would be given a specific cocktail of organisms in a highly quality-controlled context. The requirement for an IND will be much more appropriate in this setting, and the pharmaceutical industry will carry research forward."

References

1. Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? *Am J Gastroenterol.* 2012;107(11):1755; author reply 1755-1756.

2. Guidance for industry: enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat *Clostridium difficile* infection not responsive to standard therapies. U.S. Department of Health and Human Services Food and Drug Administration. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm361379.htm. Accessed March 11, 2014.

3. Bakken JS, Borody T, Brandt LJ, et al; Fecal Microbiota Transplantation Workgroup. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol.* 2011;9(12):1044-1049.

4. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *Am J Gastroenterol.* 2012;107(5):761-767.

5. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. *Science.* 2005;308(5728):1635-1638.

6. Draft guidance for industry: enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat *Clostridium difficile* infection not responsive to standard therapies. U.S. Department of Health and Human Services Food and Drug Administration. http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm387023.htm. Accessed March 21, 2014.