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Fecal Transplants Bring Hope to Patients, Challenge the FDA

Janis C. Kelly | December 15, 2014

A Surprisingly Effective Treatment

At first glance, fecal microbiota transplant (FMT) appears more like gardening than clinical medicine, involving as it does the "replanting" of normal microorganisms into the gastrointestinal tract. However, FMT's nearly 90% cure rate for patients with recurrent *Clostridium difficile* infection (CDI) verifies its surprising new role in contemporary gastroenterology—namely, as the most effective treatment available for this indication, far surpassing that of antibiotics. The success of FMT has catalyzed a surge of new approaches to replacing gut microbes and a dramatic revision to the US Food and Drug Administration's (FDA) initial regulatory approach.

FMT is defined as "infusion of a fecal suspension from a healthy individual into the gastrointestinal tract of another person to cure a specific disease."[1] The procedure can be done using fresh stool transplants, frozen stool transplants (capsules are a subtype), or biosynthetic combinations of organisms derived from normal fecal microbiota. The regulatory environment for these approaches is still unsettled and has been further roiled by the ease with which FMT can be self-administered by patients at home.

CDI: Patients' Perspective and Causes

Devastating Impact

The attraction of FMT, despite its unappealing aesthetic aspects, is clear once one considers how recurrent CDI affects patients. At a May 2013 workshop on FMT, Colleen R. Kelly, MD, assistant professor of medicine at Brown University's Warren Alpert Medical School in Providence, Rhode Island, read from a patient's email describing the experience: "Imagine having frequent diarrhea, out-of-control diarrhea, can't get to the bathroom in time diarrhea, and imagine not having any warning. You might be in bed, eating a meal, taking a walk, going for a ride in the car. Imagine how you feel as you soil yourself, your clothing, your bedding, your home. Imagine how you feel as a family member helps to clean you up."[2]

"The presence of *C difficile* infection also at least doubles mortality," said Lawrence J. Brandt, MD, professor of medicine and surgery at Albert Einstein College of Medicine and emeritus chief, Division of Gastroenterology at Montefiore Medical Center in Bronx, New York.

Mortality is about 4% in primary CDI and 12% in secondary CDI, compared with 2% in the absence of CDI. Furthermore, CDI is associated with a mean total treatment cost of $32,198.[3]

Antibiotic Overuse

According to John G. Bartlett, MD, professor emeritus, Department of Medicine, Johns Hopkins Hospital in Baltimore, Maryland, whose research team identified *C difficile* as the major cause of antibiotic-related diarrhea and pseudomembranous colitis in 1978,[4] the three major risks for CDI are antibiotic exposure, advanced age, and hospitalization. The antibiotics most often linked to CDI reflect prescribing practices, beginning with clindamycin in the 1970s, then later to ampicillin or amoxicillin, and now currently to broad-spectrum cephalosporins and fluoroquinolones.[5] The Infectious Diseases Society of America (IDSA) guidelines for CDI note that it can be associated with almost any antimicrobial agent if *C difficile* strains resistant to that drug are present, and that CDI risk increases with longer antimicrobial exposure as well as with exposure to multiple antimicrobials.[6]

Dr Brandt said that hospitalization rates related to *C difficile* infection began to rise significantly after 2001, and the approximately 700,000 new cases per year in the United States now account for about 10% percent of infections.

Dr Kelly added that the overuse of antibiotics is a major contributor to this increasing incidence of *C difficile* infection. "Many of the cases of *C difficile* I have seen developed as a result of inappropriate use of antibiotics—for example, to treat 'sinus infections' or prophylaxis around dental procedures," she said. "I encourage physicians to carefully consider every course of antibiotics they prescribe. I've seen patients die as a result of *C difficile* that resulted from courses of unnecessary antibiotics."

Standard Treatment Strategies

Faulty Logic Behind Antibiotic Treatment

CDI is defined in the American College of Gastroenterology (ACG) guidelines as "acute onset of diarrhea with documented toxigenic *C difficile* or its toxin and no other documented cause for diarrhea."[7] Standard treatment guidelines focus on discontinuing the offending antibiotic and treating with other antibiotics.

The rationale behind FMT as treatment is that CDI often develops after conventional antibiotic therapy has disrupted the normal gut microbiome. Dr Brandt said that FMT using feces from a healthy donor is intended to reintroduce normal bacteria into the colon, restore phylogenetic diversity, and make the patient more resistant to colonization by *C difficile*.

Elaine O. Petrof, MD, associate professor of medicine, Queen's University School of Medicine in Kingston, Ontario, Canada, and Emma Allen-Vercoe, PhD, associate professor of molecular and cellular biology at the University of Guelph, Ontario, Canada, developed a synthetic stool transplant for treating *C difficile*. They commented, "The treatment of a disease that is largely caused by the effects of antibiotic exposure with yet more antibiotics is counterintuitive, akin to attempting to remove weeds from a lawn by setting fire to the grass. In this light, it is not surprising that the standard therapies for CDI are failing and that the incidence of recurrent CDI is rising. A more insightful approach to the management of the disease would involve the replenishment or replacement of the protective gut microbiota; crowding out the dandelions with healthy new turf."[8]

Current Treatment Recommendations

For an initial case of CDI, the ACG recommends[7] discontinuing the contributing antimicrobial agent and treating mild to moderate cases with metronidazole. For severe CDI or for patients not responding to metronidazole, the ACG recommends vancomycin. Recommended treatment for a first recurrence of CDI is to repeat the regimen used for the initial episode unless the CDI is severe, in which case the patient should be switched to vancomycin. For a second recurrence, the ACG recommends a pulsed vancomycin regimen. For a third recurrence after this, the ACG recommends considering FMT.

The IDSA guidelines, which are currently under revision, are similar but do not include FMT.[6]

According to Dr Brandt, the ACG guidelines are effective in most CDI cases, but recurrence rates are still 15%-35%, and risk increases with each subsequent recurrence. After a second recurrence, the risk for a third recurrence rises to 65%.

Seeking Alternatives to Antibiotic Treatment for CDI

FMT's Quick Emergence

The high failure rate of antibiotic therapy led to contemporary interest in FMT. Although some form of fecal transfer was used in the fourth and 16th centuries by early medical practitioners Ge Hong and Li Shizhen, respectively,[9] interest notably increased after publication of a proof-of-concept paper by Silverman and colleagues in 2010.[10] They described successful self-administered FMT (performed at home) using low-volume enemas by seven patients who had chronic relapsing CDI that was refractory to other treatment. None of the patients had recurrent CDI after the FMT (including the three patients who later required antibiotics for urinary tract infection or perioperative prophylaxis for hip replacement), and there were no adverse effects.

Recipients and donors were instructed to use one bottle of normal (nonbacteriostatic) saline, a standard 2-quart enema bag kit, and a standard 1-L blender. Stool from the donor (50 mL) was obtained less than 30 minutes before administration, added to 200 mL of normal saline in the blender, and mixed to a "milkshake" consistency. The mixture (about 250 mL) was poured into the enema bag and administered to the patient, who was instructed to lie on the left side and hold the infusate as long as possible.

The authors commented that the success of low-volume enema FMT showed that repopulation of the colon with normal flora could be done without colonoscopy or nasogastric intubation.[10]

Brandt and colleagues[11] later reported a multicenter long-term follow-up study in 77 of 94 patients who had colonoscopic FMT for recurrent CDI. Diarrhea resolved in 74% and 84% of patients within 3 and 5 days after FMT, respectively. There was a primary cure rate of 91%, and no definite FMT-related adverse effects.

van Nood and colleagues[12] also reported that FMT was three times more effective than vancomycin in treating recurrent *C difficile* infection in a randomized study of 43 patients. This interim analysis brought the trial to an early halt. The only significant differences in adverse events were mild diarrhea and abdominal cramping in the infusion group on the day of infusion. The authors reported that after FMT, fecal bacterial diversity in the patients became similar to that in healthy donors.

Mainstream Acceptance

In the wake of such encouraging studies, patients with recurrent *C difficile* began to approach gastroenterologists and infectious disease specialists, seeking FMT; the specialists in turn began to offer the procedure. Catherine Duff, a patient with *C difficile,* set up The Fecal Transplant Foundation after undergoing a self-administered FMT at home with her husband's stool and the help of a physician who had it tested for safety. Patients also set up The Power of Poop, an informational website.

By the end of 2012, dozens of clinicians in several countries were administering FMT, with researchers experimenting with both frozen stool in capsules and biosynthetic preparations based on organisms found in normal, healthy stool. Private companies began offering testing of donor stool samples (about $800 per sample, usually not reimbursable by insurance).

Industry Takes Notice

At the same time as clinical acceptance took hold, researchers began to seek alternatives to the admittedly unaesthetic home-blender enema FMT. These included manufactured FMT products, stool banks, use of frozen rather than fresh stool, and biosynthetic alternatives.

Rebiotix, Inc., developed RBX2660, a standardized "microbiota suspension" derived from fresh stool, which received fast-track status from the FDA. Researchers led by Erik Dubberke, MD, from the Division of Infectious Diseases at Washington University School of Medicine in St Louis, Missouri, reported phase 2 safety data in early October 2014, showing no serious treatment-related adverse events and an overall efficacy rate of 87.1%.[13]

Clinicians who want to perform FMT without the hassle of preparing stool can turn to a nonprofit stool bank, such as OpenBiome. Dr Kelly said, "OpenBiome has shown that they can provide material to a large number of clinicians and researchers at a reasonable cost ($250 per dose). This is very advantageous for patients, who may not be able to identify a suitable donor or who may end up reimbursing their donors for laboratory testing that is not always covered, and for physicians, who may spend hours on the donor identification/screening process.

"OpenBiome is arguably safer as well," Dr Kelly continued. "They monitor donors carefully at and between donations, quarantine all material for 30 days until donors can be rescreened, and preserve safety aliquots on all material."

Other institutions are setting up their own stool banks. Herbert L. DuPont, MD, director of the Center for Infectious Diseases at the University of Texas Health Science Center in Houston, Texas, who is helping set up a bacteriotherapy or FMT service for two hospitals at the Texas Medical Center, advised physicians to work with the blood-banking facilities at their hospitals to set up donor screening and sample storage.[2]

Ilan Youngster, MD, from the Division of Pediatric Infectious Diseases, Boston Children's Hospital and Massachusetts General Hospital in Boston, and colleagues[14] reported that frozen capsules prepared from the stool of healthy donors produced complete resolution of diarrhea in 70% of 20 patients with CDI after a single 15-capsule treatment and in 90% after a second treatment.[14]

Dr Youngster said, "With the caveat of this being a small study, it seems as if oral administration of frozen fecal capsules is well tolerated, safe, and has success rates comparable to other modes of administration of FMT. Since the study was published, we have treated another 20 patients, with similar results."

The need to harvest, test, and prepare stool from donors for FMT would be obviated if the key organisms in stool could be identified, cultured, and packaged in a synthetic form. Drs Petrof and Allen-Vercoe have developed and hold the patent on "RePOOPulating" the gut. Their proof-of-principle study in three patients with recurrent *C difficile* in whom at least three courses of metronidazole or vancomycin had failed showed that all were symptom-free within 2-3 days after receiving RePOOPulate via colonoscopy and remained so for 6 months thereafter.[15]

According to the patent application, the synthetic stool preparation comprises a mixture of bacterial strains isolated and purified from a healthy donor who had not received antibiotics in the past 5 years. Strains known to be pathogenic, to have an unfavorable antibiotic resistance profile resistant to imipenem or vancomycin (or both), and those considered difficult to culture or that grow unreliably were not included.[16]

The FDA Takes On FMT

As FMT receives increasing attention from the development sector, concerns surrounding its safety have begun to escalate. In April 2013, the FDA stunned some in the clinical community by announcing that it had begun regulating human feces as an unapproved drug and that all FMT procedures and clinical trials would require Investigational New Drug (IND) approval. The agency's reasoning

was that fecal microbiota were both a biologic product and a drug used in FMT to "prevent, treat, or cure a disease or condition" or "intended to affect the structure of any function of the body of man."[17]

This regulatory move was met by a surge of concern from clinicians, researchers, and patient support groups. In response, on May 3, 2013, the FDA's Center for Biologics Evaluation and Research partnered with the National Institute for Allergy and Infectious Diseases to hold a public workshop on scientific and regulatory issues regarding fecal microbiota for transplantation.[2] The workshop included presentations by some of the more experienced clinicians and researchers working with FMT. These experts said that the approximately 700 published cases of FMT showed notably few adverse effects and 90% efficacy in curing CDI diarrhea, with several of the presenters expressing their fears that the IND requirement would make FMT all but unavailable to many patients.

Ms Duff later told Medscape that "As someone who had *C difficile* eight times between 2005 and 2012, my only options by 2012 were a total colectomy or FMT. People with CDI who don't respond to repeated and prolonged antibiotic therapy experience isolation, depression, personal and financial ruin, as well as the continued damage to their gut microbiome that repeated antibiotic use can cause. Ensuring that FMT is readily available will save lives, and what could be more important than that?"

A New Stance

In the wake of the May 2013 workshop, the FDA kept the IND requirement in place but stopped enforcing it.[18] An FDA spokesperson told Medscape that the agency still considers FMT an unapproved new drug and an unlicensed biological product requiring an IND approval, but as delineated in the agency's July 2013 guidance, has adopted an interim policy of exercising "enforcement discretion" regarding the use of FMT to treat *C difficile* infection not responsive to standard therapies.

The FDA intends to continue exercising discretion while they further consider the issue. Clinicians performing FMT for treatment of *C difficile* infection are not required to first obtain an IND approval, but should obtain "adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products." Consent should include a statement that the use of FMT products to treat *C difficile* is investigational, along with offering a discussion of its potential risks. Physicians who have questions about the use of FMT or about submission of an IND are encouraged to contact the FDA at 1-800-835-4709 or 240-402-8010, or by email to OCOD@fda.hhs.gov.

According to an FDA spokesperson, the agency has the authority to regulate stool banks, does not distinguish between FMT obtained from stool banks and FMT obtained from individual donors, and expects to exercise "enforcement discretion" when several conditions are met. These include that the FMT product is obtained from a donor known to either the patient or the treating licensed healthcare provider. FDA is currently considering comments on the 2014 draft guidance, which was written to facilitate access to FMT for patients with treatment-resistant *C difficile* who have few or no other treatment options.

Another way around the regulatory dilemma might be for the FDA to regulate FMT as a tissue/transplant, similar to the rules governing transplants of hematopoietic stem cells derived from cord blood.

Dr Kelly noted that stool is a heterogeneous substance, composed primarily of bacteria and water, but also containing viral and fungal organisms, metabolic products of these organisms, undigested foods, bile, bilirubin, cholesterol, inorganic salts, dead cells, and mucus from the lining of the intestinal wall. "The colonic microbiome functions in a symbiotic relationship in the human body at a level of complexity akin to an organ or tissue. FMT takes whole stool from one person and infuses it into the gastrointestinal tract of another person with the goal of transplanting the entire community of physiologic gastrointestinal flora. The replacement of this highly complex whole community of microorganisms cannot be regulated as a 'drug,' per se. It is not possible to provide exact dosing/colonization data for this substance, which is highly variable among individual donors," she said.

The Future of FMT

There is widespread agreement among researchers that FMT can provide effective and safe treatment of recurrent CDI that has not responded to conventional antibiotic regimens. The current FDA guidance provides what amounts to a temporary amnesty for individual physicians who use FMT with patients who have given adequate informed consent.

New FMT formulations, such as frozen stool capsules and biosynthetic preparations, are expected to join conventional stool preparations in the FMT armamentarium within the next few years. Meanwhile, the American Gastroenterological Association Center for Gut Microbiome Research and Education provides up-to-date information and physician resources, as well as a directory of practitioners who perform FMT.

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