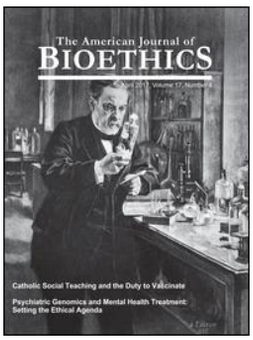

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Eline M. Bunnik, Nikkie Aarts & Lea Ann Chen

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Physicians Must Discuss Potential Long-Term Risks of Fecal Microbiota Transplantation to Ensure Informed Consent

Eline M. Bunnik, University Medical Centre Rotterdam
Nikkie Aarts, University Medical Centre Rotterdam
Lea Ann Chen, New York University Langone Medical Center

Fecal microbiota transplantation (FMT) for patients with multiply recurrent *Clostridium difficile* (*C. difficile*) infections despite standard medical treatment is considered both effective, with approximately 90% cured (Aroniadis et al. 2016), and acceptable regarding short-term safety concerns. Doctors who perform FMT often also receive requests for the treatment from patients suffering from a range of other conditions, including irritable bowel syndrome and inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis. Sometimes patients request FMT prior to accepting standard treatment options, and thus seem to prefer it to standard of care. Other patients request FMT for non-gastrointestinal disorders, in which disease etiology and activity may be more tenuously linked to gut bacteria. These examples highlight the growing popularity of FMT, which in turn gives rise to concerns regarding appropriate informed consent for the procedure. For patients who qualify for FMT, doctors should explain the investigational nature of the treatment, ensure a discussion of its potential long-term risks as part of the informed consent process (Food and Drug Administration 2013), and at minimum discuss all U.S. Food and Drug Administration (FDA)-approved treatment alternatives.

Address correspondence to Eline M. Bunnik, PhD, Erasmus MC, University Medical Centre Rotterdam, Department of Medical Ethics and Philosophy of Medicine, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands. E-mail: e.bunnik@erasmusmc.nl

The FDA has chosen to regulate human feces as a drug—specifically, as a biological product (e.g., vaccines, blood products), but has not yet approved FMT for any medical indication. However, in light of the growing rate and severity of *C. difficile* infections (CDIs) and the promising early data from FMT, in 2013 the FDA announced its decision to exercise enforcement discretion when doctors provide FMT for CDIs that do not respond to standard treatment (typically interpreted as multiply recurrent and refractory CDIs). For all other indications, FMT can only be used under an investigational new drug (IND) application (i.e., in the context of a clinical trial).

In being condoned by the FDA for the treatment of certain CDIs and gradually adopted by physicians, the use of FMT has resembled the way in which some surgical techniques are introduced in clinical practice: not based on large-scale clinical trial data, but rather on accumulating experience and case reports. In cases of recurrent and refractory CDIs, FMT can be considered in the "transition zone" (Schwartz 2014) between experimental research and standard of care. Although innovative interventions are usually regulated less stringently than new drugs or biological products, their "experimental" nature does imply special ethical requirements for informed consent. While there are no formal standards for the content of informed consent for "transition zone" interventions, it is generally accepted that such discussions should include the following elements: the innovative nature of the procedure, the provider's experience with the procedure, the risks and benefits including unknown risks, the (lack of) evidence, and alternatives to the innovative intervention (Broekman, Carrière, and Bredenoord 2016). As the FDA states in its enforcement policy: "The consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks" (FDA 2013). We are concerned that these standards for informed consent may not be consistently met in clinical practice.

Yonghui Ma and colleagues (2017), likewise, identify informed consent as one of the main ethical issues in FMT, but do so for the wrong reasons. They argue that it would be "extremely difficult" to obtain informed consent for FMT from patients with inflammatory bowel disease (IBD)—"prime candidates for this treatment"—as patients with IBD are sometimes young and often confronted with a poor quality of life and/or stress due to their disease. Yonghui Ma and colleagues state that a "patient's autonomy may be compromised by their stress and desperation, affecting their ability to give informed consent." We challenge the idea that the capacity to consent of "desperate" or vulnerable patients would be compromised regarding FMT decisions. With an appeal to the principle of respect for patients' autonomy, patients are usually presumed capable of providing informed consent unless demonstrated otherwise. There is no reason to believe that patients suffering from IBD lack understanding, appreciation, reasoning, or decisional capacities related to the specific task of deciding for or against a treatment offer. Clinicians routinely treat patients suffering from—arguably—more severe and/or life-threatening diseases, who are perfectly capable of giving (presumed) informed consent, and researchers legitimately include these patients in research studies based on their voluntary informed consent.

Informed consent generally presupposes three elements: capacity to consent, voluntariness, and information (Bunnik, Janssens, and Schermer 2013). It is not capacity to consent but inadequate information that may pose difficulties in regard to FMT. Despite the description of FMT in ancient medical texts and its documented uses in veterinary medicine, the utilization of FMT in modern health care is relatively recent. Its clinical demand has greatly outpaced the understanding of its risks and benefits that would have typically developed through multiple phases of clinical trials required to bring a drug to market. Data regarding its long-term safety in humans are particularly lacking.

While FMT may seem "natural" and safe (Kahn, Gorawara-Bhat, and Rubin 2012), and possibly even "frugal," researchers are concerned about lasting effects that donors' intestinal microbes may have on FMT recipients. For example, the gut microbiota has been shown to be a likely transferrable agent of risk or phenotype in multiple disorders, including obesity (Turnbaugh et al. 2006), cardiovascular disease, and autoimmune disorders, such as type 1 diabetes. Also, the gut microbiota has been found to interact with the central nervous system and to affect brain chemistry and behaviors (Bercik et al. 2011). Theoretically, FMT could entail the transmission of anxiety and depression, autism, or neurological conditions, such as Parkinson's disease. However, most of these effects have only been examined in preclinical (i.e., animal) studies.

Though all risks should be disclosed during the informed consent process, we question whether in practice most doctors offering FMT for recurrent CDIs refer to preclinical research, including animal studies, when discussing potential long-term risks of FMT with patients. The risks of FMT may be inadequately appreciated by clinicians who are not familiar with preclinical studies, and thus by their patients as well.

Over the next couple of years, it is imperative that data on potential long-term safety risks of FMT are gathered. This can be done at relatively low cost through data registries, such as the national registry that is being spearheaded by the American Gastroenterological Association to track the long-term benefits and risks of FMT, compare the effectiveness of various modes of FMT delivery (e.g., colonoscopy, enema, nasogastric tube), and develop standards of care (Kelly et al. 2017). There is broad international support for the development and maintenance of local, regional, national, and international registries to trace potential long-term side effects from FMT, and to provide more (short- and long-term) information about the clinical use and utility of FMT. Complementary to clinical trials, data registries can support the wider clinical implementation of FMT for the treatment of CDIs, and in the future possibly also for other indications.

Until that time, we encourage treating clinicians to underline the investigational character of the treatment, inform patients about other treatment options that are FDA approved, and to discuss the implications of basic and translational studies to potential FMT patients to ensure informed consent. In the informed consent process, health professionals should counter the seemingly frugal and risk-free image of FMT by clearly indicating the unknowns and possible risks. While we agree with Yonghui Ma and colleagues that desperation of patients should not be a basis for treatment decisions about FMT, we do contend that—on the condition of proper informed consent—it can be perfectly reasonable for some patients with CDI to pursue FMT. ■

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