Fecal Microbiota Transplantation — An Old Therapy Comes of Age

Ciarán P. Kelly, M.D.

In 1958, doctors in Denver administered feces by enema to their patients with fulminant, life-threatening pseudomembranous enterocolitis. The goal of this infusion of donor feces (also termed fecal microbiota transplantation [FMT]) was to “re-establish the balance of nature” within the intestinal flora to correct the disruption caused by antibiotic treatment. They reported “immediate and dramatic” responses and concluded that “this simple yet rational therapeutic method should be given more extensive clinical evaluation.” During the ensuing 50 years, the association between Clostridium difficile infection and pseudomembranous enterocolitis was established, and effective antimicrobial treatments were identified. Despite these advances, C. difficile became the most commonly identified cause of nosocomial infectious diarrhea in the United States. During the past decade, there has been an alarming increase in the incidence and severity of this disorder, with associated increases in mortality and economic cost.

Although most patients with C. difficile infection have a response to antimicrobial therapy, approximately 25% have a recurrence after the initial treatment course. Patients with a first recurrence of C. difficile infection are more likely to have a second recurrence (risk, 35 to 45%), and for patients with multiple recurrences, the subsequent recurrence rates surpass 50%.^2^4^ Only patients with the most recalcitrant cases of C. difficile infection are likely to undergo FMT, usually out of desperation after multiple treatment approaches have failed. Yet, systematic review reveals that the reported efficacy of FMT in treating recurrent C. difficile infection is greater than 90%. So why has FMT not become routine therapy for C. difficile infection during the past 50 years? There are three main reasons: it is aesthetically unappealing, it is logistically challenging (in terms of harvesting and processing suitable donor material), and there is a lack of efficacy data from randomized, controlled trials.

The last impediment is addressed in a report on a randomized, controlled trial by van Nood et al., now in the Journal. In this study, investigators compared the duodenal infusion of donor feces after vancomycin therapy and bowel lavage with vancomycin therapy either alone or with bowel lavage. The study was unblinded and imperfect. Nonetheless, the outcome favors FMT (81% response) above vancomycin therapy either alone (31%, P<0.001) or with bowel lavage (23%, P<0.001) in patients with relapsed C. difficile infection in whom standard therapy with vancomycin has failed. The trial was closed to new enrollment by its data and safety monitoring board after only 43 of a planned 120 patients had undergone randomization because almost all patients in the two control groups had a recurrence. The finding that FMT was effective in 81% of patients with recurrent C. difficile infection is consistent with a systematic review of uncontrolled case series in which FMT through the stomach or small intestine showed an overall response rate of 80%; the anecdotally reported overall response rate for FMT through colonoscopy or enema is 92%. Thus, this study and the previous case series yield consistent, strongly positive results.

The study by van Nood et al. is an important confirmation of the efficacy of FMT for recurrent C. difficile infection. Their findings will provide added stimulus to the ongoing efforts to address...
the other main impediments to the routine and widespread use of FMT. Natural antipathy toward fecal therapy can be reduced by banking suitable material from anonymous, screened donors. Such a system would both distance the recipient from the stool donation and provide physicians with readily accessible, quality-controlled treatment materials. Ultimately, the use of feces may be eliminated in favor of defined mixtures of cultured bacteria that confer colonization resistance against *C. difficile*, an approach that was pioneered by Tvede and Rask-Madsen in 1989 and is now being examined afresh. The later approach can also assuage concern regarding the inadvertent transmission of disease-causing pathogens through FMT. These advances can make intestinal microbiota therapy acceptable and accessible to most patients and their physicians. It will also facilitate the “more extensive clinical evaluation” of FMT for severe, refractory *C. difficile* infection, as first advocated in 1958.

The significance of the study by van Nood et al. goes far beyond the treatment of recurrent or severe *C. difficile* infection. The burgeoning field of microbiome research, initially made possible by technologies to identify bacterial 16S ribosomal RNA in complex biologic samples, has alerted us to the abundant, diverse, and influential nature of the gut microbiota. Microbiome research has been expanded and complemented by methods to characterize the protein composition (proteomics) and metabolic processes (metabolomics) of the intestinal contents and those from other body sites. The results of this study represent a clear precedent in which planned therapeutic manipulation of the human intestinal microbiota can lead to demonstrable, clinically important benefits, thereby bringing FMT to the mainstream of modern, evidence-based medical practice. The study by van Nood et al. will encourage and facilitate the design of similar trials of intestinal microbiota therapy for other indications, such as inflammatory bowel disease, irritable bowel syndrome, prevention of colorectal carcinoma, and metabolic disorders, to name just a few. As such, it heralds the delayed adolescence of a broad and exciting new branch of human therapeutics.

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From the Division of Gastroenterology, Beth Israel Deaconess Medical Center, and Harvard Medical School — both in Boston. This article was published on January 16, 2013, at NEJM.org.


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