Fecal Microbiota Transplantation: What We Know and What We Need to Know

Recurrent *Clostridium difficile* infection (CDI) is the recurrence of infection and symptoms after successful initial therapy for *C. difficile* with resolution of symptoms. The risk for a first recurrence is 10% to 20%, but the rate increases to 40% to 60% after 1 recurrence. Recurrent CDI is difficult to treat, even with pulsed antibiotic regimens and probiotics. Patients who have several recurrences become debilitated and discouraged, and some believe that they may never get rid of the infection. Fecal microbiota transplantation (FMT) has emerged as an excellent therapy for these patients when all other options are unsuccessful.

Fecal microbiota transplantation is the term used to describe delivery of stool from a healthy donor into a patient via enema, colonoscopy, or upper gastrointestinal tract. Since 2000, many published case reports and case-series studies of FMT have reported success rates of 83% to 90%. The landmark randomized, controlled trial (RCT) published in 2013 demonstrated the efficacy of FMT via the nasoduodenal route in patients with recurrent CDI; the study was stopped early because of the effectiveness of FMT compared with standard vancomycin therapy (1). Practice guidelines from both the American College of Gastroenterology and European Society of Clinical Microbiology and Infectious Diseases now recommend FMT for recurrent CDI (2, 3). In this issue, Drekonja and colleagues (4) offer a new systematic review of FMT, incorporating the 2 published RCTs. It gives us several important insights.

First, after reviewing the available evidence, the authors concluded that overall efficacy of FMT for recurrent CDI is 85%, albeit with low-strength evidence and few short-term adverse effects but few data on potential late events. This is reassuring and supports previous meta-analyses and systematic reviews as well as clinical experience with reported success rates of 83% to 100% (5, 6).

Second, although this article includes 2 RCTs, the authors point out the need for further controlled studies. In fact, a third RCT has just been published using FMT to treat patients with recurrent CDI. This study, which included several patients with pseudomembranous colitis, was also stopped early due to its 90% efficacy in the FMT group compared with 26% in the vancomycin group (7). Other trials are also under way, and we will see more as newer products are developed. As the review points out, various methods are used to perform FMT and screen donors. The U.S. Food and Drug Administration has not clarified what it considers essential. OpenBiome is a stool bank that screens for 17 pathogens and offers frozen stool from healthy donors for $250 plus shipping (www.openbiome.org).

Third, the authors conclude that there is insufficient evidence of efficacy for treatment of a first episode or refractory CDI. The use of the terms "recurrent" and "refractory" are sometimes erroneously used interchangeably in literature and can be confusing. A recurrence (sometimes called relapse) occurs after initial successful therapy; a refractory infection is one that does not completely respond to treatment. Some patients with refractory CDI have disease that is severe and complicated and may be critically ill in the intensive care unit and at risk for death. This is important because there may be pressure to perform FMT in such patients as a last-ditch effort to prevent surgery, but FMT is not yet the standard of therapy (surgery is the standard—either colectomy or loop ileostomy). Although there are many case reports of successful therapy for these severe cases, FMT should be considered on a case-by-case basis, weighing the risks against the possible benefits. If the patient who is critically ill dies, the practitioner would have no way of knowing whether FMT played a role or whether more expeditious and definitive surgical treatment would have been more beneficial.

From available evidence, we know that FMT is effective and provides durable cures by all routes of administration. A cost–benefit analysis of FMT for recurrent CDI showed a cost savings of $17 000 per patient (8). However, there is much that we do not know.

Are there long-term consequences of changing the microbiota? Although 1 long-term retrospective case-series study suggests safety and few long-term adverse effects, several patients developed immune-related diseases (9). A prospective registry would be the best way to collect long-term data.

How should FMT be regulated? There must be regulatory oversight because there are risks for infection and possible microbiome-related conditions, such as the metabolic syndrome. Regulations should standardize screening, preparation of material, and long-term follow-up. Human stool is currently classified as a drug and biologic by the U.S. Food and Drug Administration.

Why and how does it work? This is almost as exciting and interesting as the fact that it does work. Fecal microbiota transplantation for recurrent CDI has been very important in demonstrating some of the functions of the colon microbiota. Abnormal microbiota in recurrent CDI was demonstrated in studies of the fecal microbiome in 3 healthy persons and 7 with CDI, of whom 3 developed recurrent CDI (10). The microbiota was markedly different in the patients with recurrent CDI than in control participants and those with a single episode of CDI. Overall, stools of patients with recurrent CDI had less diversity and a decrease in the normally dominant anaerobes of the *Bacteroidetes* and *Firmicutes* phyla and an increase in others, such as *Proteobacteria*. We know that the recipient's stool microbiota may resemble that of the donor for at least 1 month, but we need to know much more. Which bugs are key? Are their bacterial metabolites important? Is there a defined

microbial consortium of microbiota that could be used in place of whole-stool FMT? Are there other diseases that might get better with FMT? There are ongoing trials of FMT in inflammatory bowel disease and enthusiasm around the potential of FMT in other conditions associated with dysbiosis. Well-designed clinical trials are necessary before adopting this therapy for other diseases.

The excitement about FMT is justified given its high efficacy in treating recurrent CDI, relative availability and simplicity, and favorable cost profile compared with other therapies. Finally, FMT gives us insight into the importance of the gut microbiota in maintaining health and the therapeutic potential therein.

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-0609.

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Ann Intern Med. 2015;162:662-663. doi:10.7326/M15-0609

References

1. **van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al.** Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368:407-15. [PMID: 23323867] doi:10.1056/NEJMoa1205037

2. **Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al.** Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. Am J Gastroenterol. 2013;108:478-98. [PMID: 23439232] doi:10.1038/ajg.2013.4

3. **Debast SB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases.** European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect. 2014;20 Suppl 2:1-26. [PMID: 24118601] doi:10.1111/1469-0691.12418

4. **Drekonja D, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, et al.** Fecal microbiota transplantation for *Clostridium difficile* infection. A systematic review. Ann Intern Med. 2015;162:630-8. doi:10.7326/M14-2693

5. **Kassam Z, Lee CH, Yuan Y, Hunt RH.** Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. Am J Gastroenterol. 2013;108:500-8. [PMID: 23511459] doi:10.1038/ajg.2013.59

6. **Bagdasarian N, Rao K, Malani PN.** Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. JAMA. 2015;313:398-408. [PMID: 25626036] doi:10.1001/jama.2014.17103

7. **Cammarota G, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, et al.** Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. Aliment Pharmacol Ther. 2015. [PMID: 25728808] doi:10.1111/apt.13144

8. **Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN.** Cost-effectiveness of competing strategies for management of recurrent *Clostridium difficile* infection: a decision analysis. Clin Infect Dis. 2014;58:1507-14. [PMID: 24692533] doi:10.1093/cid/ciu128

9. **Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, et al.** Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. Am J Gastroenterol. 2012;107:1079-87. [PMID: 22450732] doi:10.1038/ajg.2012.60

10. **Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM, et al.** Decreased diversity of the fecal Microbiome in recurrent *Clostridium difficile*–associated diarrhea. J Infect Dis. 2008;197:435-8. [PMID: 18199029] doi:10.1086/525047