

Fecal Microbiota Transplantation in *Clostridium difficile* Infection: Evidence and Indications

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In 2011, nearly half a million patients in the United States had a symptomatic *Clostridium difficile* infection, and 29,000 died within 30 days after diagnosis.¹ The clinical spectrum of *C. difficile* infection stretches from asymptomatic or mild diarrhea to a fulminant, life-threatening colitis that can require emergency colectomy. Initial antibiotic treatment for mild to moderate infection consists of metronidazole (Flagyl), whereas oral vancomycin is recommended for complicated or severe disease.^{2,3} Rates of initial treatment success are high, particularly in mild disease, with a clinical cure rate greater than 90%.^{3,4} However, rates of recurrence after initial infection are also high at 15% to 30%, and they increase to 40% and 50% with second and third recurrences.^{5,6}

Because disruption of the gut microbiota mediates the susceptibility to and recurrence of *C. difficile* infection, fecal microbiota transplantation, which aims to rapidly restore the normal diverse colonic microbiota by delivering a large inoculum of typical gut organisms, makes intuitive sense. Over the past 15 years, fecal microbiota transplantation has become an increasingly used treatment for *C. difficile* infection, particularly to prevent recurrent disease. In a recent systematic review, two randomized controlled trials (RCTs) and 28 case series evaluated fecal microbiota transplantation for *C. difficile* infection.⁵ The quality of the evidence was low, with only one of the two RCTs using a non-fecal microbiota transplantation control group. The effect sizes, however, were striking. Overall success rates were 85% for recurrent disease and 55% for refractory disease. There was much less evidence for initial treatment of *C. difficile* infection—only seven cases from two case series.

Fecal microbiota transplantation appears to be safe. The two RCTs reported mild, self-limited diarrhea, cramping, belching, nausea, abdominal pain, fever, and dizziness.⁵ However, there is little evidence on the long-term safety of fecal microbiota transplantation.

Although public and scientific interest in fecal microbiota transplantation continues to grow, many scientific, regulatory, and logistical challenges remain. Transplantation is most commonly performed at referral medical centers under the supervision of a gastroenterologist or infectious disease physician and requires informed consent. Donors can be anonymous or known to the patient, and are subjected to rigorous infectious disease screening, similar to that used for blood donation. Donors with recent antibiotic use are typically excluded, as are those with any of a long list of conditions that may be mediated by the gut microbiota. The optimal route of administration is unknown. Studies have described instillation into the gastrointestinal tract via nasogastric tube, esophagogastroduodenoscopy, enemas, and colonoscopy. Recent reports of successful administration via oral capsules containing frozen or lyophilized (freeze-dried) stool demonstrate a noninvasive and convenient delivery option.⁶

The direct cost of formulations ranges from \$400 to \$800 per treatment, but the total cost can be thousands of dollars if a colonoscopy is involved or if multiple treatments are needed. Patients usually pay out of pocket because there is minimal or no coverage by most insurance providers. The U.S. Food and Drug Administration (FDA) currently regulates fecal microbiota transplantation as a drug, requiring an Investigational New Drug application for transplantation research; however, the FDA exercises enforcement discretion, exempting treating physicians from this requirement when transplantation is used clinically to treat recurrent *C. difficile* infection that does not respond to standard therapies.

Editorials

The regulatory uncertainty has been a deterrent to widespread use in clinical practice, because it requires adequate documentation of indication, justification for use, informed consent, and several levels of approval in most medical centers.

There is intense interest in harnessing certain components of the full microbiota for the treatment or prevention of *C. difficile* infection. These include development of various synthetic stool mixtures containing only a few strains that are thought to mediate the protective effects of fecal microbiota transplantation, and other innovations, such as a capsule containing only a mixture of bacterial spores from a donor stool.^{7,8} However, given the complexity of the full colonic microbial community, it is likely that full-spectrum transplantation will continue to be useful going forward.

Fecal microbiota transplantation is a safe and effective treatment to prevent further recurrences of *C. difficile* infection and should be considered in individuals who have experienced one or more recurrent episodes of moderate to severe infection. Nevertheless, because of the uncertainty regarding long-term safety and effectiveness, and the high burden of recurrent *C. difficile* infection, large, blinded RCTs are needed.

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