PERSPECTIVE

Treating *Clostridium difficile* Infection With Fecal Microbiota Transplantation

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***Clostridium difficile* infection is increasing in incidence, severity, and mortality. Treatment options are limited and appear to be losing efficacy. Recurrent disease is especially challenging; extended treatment with oral vancomycin is becoming increasingly common but is expensive. Fecal microbiota transplantation is safe, inexpensive, and effective; according to case and small series reports, about 90% of patients are cured. We discuss the rationale, methods, and use of fecal microbiota transplantation.**

Keywords: Clostridium difficile; Transplantation; Microbiota; Fecal Enema; Recurrent Infection; Diarrhea.

During the last 15 years, *Clostridium difficile* infection (CDI) has become epidemic and continues to gain momentum, with greater incidence, morbidity, and mortality than in past decades. In the United States, the National Hospital Discharge Survey revealed doubling of CDI diagnoses from 31/100,000 in 1996 to 61/100,000 in 2003.[1] This rise has been accompanied by increasing rates of colectomy and mortality during the same time period.[2] In 2010, the yearly incidence of CDI was estimated at 500,000, with mortality at 15,000–20,000,[3–5] and the cost of managing CDI was estimated to be at least $1 billion per year in the U.S. alone.[6] One major reason for this growing problem is the emergence of newer, more virulent, and more antibiotic-resistant strains including North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis group BI, and polymerase chain reaction (PCR) ribotype 027 (NAP1/BI/027) among others.[7,8] Although acquisition of CDI still occurs most commonly in health care facilities, it is increasingly recognized that CDI can also be acquired in the community by young, healthy individuals without prior exposure to antibiotics or hospitals. Furthermore, patients at greater risk are no longer just elderly people but also patients with inflammatory bowel disease, compromised immune systems, and peripartum women.[5,8]

As the *C difficile* epidemic continues to grow, the numbers of failed treatments and patients who experience relapses or recurrences also are increasing. Metronidazole and vancomycin are the first-line agents for *C difficile* treatment; however, recent data suggest that metronidazole is losing its efficacy, and expert opinion is shifting toward the use of vancomycin as first-line therapy.[9] Furthermore, the rates of recurrent and severe CDI continue to increase despite the efficacy of these agents. Recurrent CDI has been documented to occur in as many as 15%–30% of patients after an initial bout of CDI, and up to 65% of patients who experience 1 recurrence will have subsequent recurrences after antibiotic therapy is stopped.[10,11] Recurrent CDI can turn into a chronic, recalcitrant disease in which repeated bouts of infection can continue for years, leading to persistent use of antibiotics, repeated hospitalizations, and even death.

The basic pathophysiology of recurrent CDI is not completely understood. Antibiotics suppress and disrupt the distal bowel microbial communities that normally keep expansion of *C difficile* populations in check. Because *C difficile* spores are largely resistant to antibiotics, they can germinate back into vegetative forms after antibiotic treatment has been discontinued. If residual normal intestinal microbiota cannot restrain the infection, *C difficile* bacteria proliferate and once again produce toxins that cause destruction of colonic epithelial cells and return of inflammation with resultant disease symptoms. Although spores are thought to play a role in the pathophysiology of recurrent CDI, some patients might become reinfected

Abbreviations used in this paper: **CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; FDA, Food and Drug Administration; FMT, fecal microbiota transplantation; GI, gastrointestinal; HAV, hepatitis A virus; HCT/Ps, human cell tissues and cellular tissue-based products; HIV, human immunodeficiency virus; IBS, irritable bowel syndrome; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction.**

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with different strains. In 1 series of patients with recurrent CDI, molecular analysis showed that 6 of 18 (33%) had a new strain.[12]

Different treatment options exist for recurrent CDI, most of which focus on further antibiotic management. Tapered and/or pulsed courses of vancomycin therapy are favored during a traditional 10-day to 14-day course of therapy. Patients from the placebo arm of 2 studies evaluating a probiotic adjunct to standard antibiotics for recurrent CDI were analyzed for recurrence rates. The overall recurrence rate was 44.8%. However, those who had a tapering course of vancomycin had a recurrence rate of 31%; those who received pulsed dosing of vancomycin had an even lower recurrence rate of 14%.[11] Although vancomycin regimens are widely used and effective in many patients, the use of antibiotics represents a double-edged sword by suppressing both the pathogen as well as the protective microbiota. Indeed, the repeated and chronic use of antibiotics to treat recurrent infection has an adverse effect on the intestinal flora. Vancomycin is a broad-spectrum antimicrobial agent with activity against almost all gram-positive aerobic and anaerobic organisms and thus might ultimately increase susceptibility to CDI by maintaining a persistently altered state of bowel flora.

Alternative antibiotics are being investigated, but their efficacy in patients with recurrent disease is unknown.[13] Fidaxomicin had a lower rate of recurrences compared with vancomycin in 2 studies, but its role in the therapy of recurrent CDI has not been established. *Clostridium difficile* toxin-binding resins are not curative and are best used as adjunctive agents to vancomycin.

The only currently available immunologic approach to treat CDI is administration of pooled intravenous immunoglobulin (IVIG). However, the role for this therapy in CDI remains unclear because the results of studies, all retrospective so far, have been equivocal at best.[14]

An alternative approach to treatment of recalcitrant CDI is to restore the damaged microbial intestinal communities. The efficacy of the probiotic *Saccharomyces boulardii* as an adjunct to antibiotics has been tested in 2 trials. Although it did not decrease recurrence rates in those with their first episode of CDI (19% compared with 24% with placebo), it did decrease the frequency of relapses in those with recurrent CDI (34.6% vs 64.7% with placebo).[10] However, a second trial showed *S boulardii* had efficacy only in the subset of patients who were given high-dose vancomycin (2 g/d) (16.7% compared with 50% with placebo). No significant benefit was seen in those given metronidazole or lower-dose vancomycin.[15] Although the probiotic *Lactobacillus* GG showed promise in case reports, recurrence rates were worse than placebo (37.5% vs 14.3% with placebo).[16] In a controlled, albeit underpowered, trial of *L plantarun* 299v as an adjunct to metronidazole in 11 patients with recurrent CDI, the probiotic arm had a lower recurrence rate (36%) compared with placebo (66%).[17] The data to date indicate that probiotics might have a role in treatment, but their efficacy is less than ideal.

In contrast, fecal transplantation, also known as fecal bacteriotherapy, is proving to be an effective alternative intervention. Case reports and small case series to date suggest that recurrent CDI can be cured with a single treatment. The material is readily available and very inexpensive. Because the exact agent or combination of agents that might affect the cure is unknown, the terms *fecal transplantation* and *fecal bacteriotherapy* will henceforth be replaced with the new term *fecal microbiota transplantation* (FMT). The rationale behind FMT is simple; antibiotics and other factors disrupt the normal balance of colonic flora and reduce "colonization resistance," allowing pathogenic *C difficile* strains to grow, leading to the typical clinical presentations of diarrhea and pseudomembranous colitis; by reintroducing normal flora via donor feces, the imbalance can be corrected, the cycle can be interrupted, and normal bowel function can be reestablished.

The idea of FMT has parallels in the veterinary world, where the practice of transfaunation has been used for centuries to treat ruminants with severe ruminal acidosis and other gastrointestinal disorders and for the treatment of equine diarrhea.[18] In humans, the first use of FMT dates back at least to a 1958 case series of 4 patients with pseudomembranous enterocolitis.[19] Of note, 3 of 4 patients reported in the 1958 series were in a critical state when fecal enemas were administered, and in all patients, symptoms resolved within hours of FMT. The first documented case of confirmed CDI treated with FMT, a 65-year-old woman who had "prompt and complete normalization of bowel function, was reported in 1983 by Schwan et al.[20] At follow-up 9 months later, the patient remained asymptomatic. Up until 1989, retention enemas had been the most common technique for FMT. However, alternative methods subsequently included fecal infusion via duodenal tube in 1991, rectal tube in 1994, and colonoscopy in 1998. FMT for recurrent CDI has been reported to be successful whether given via colonoscopy,[21–23] nasogastric tube,[24,25] or enemas administered at home.[26] No clear superiority of one method over another has yet been demonstrated. However, of the approximately 200 cases reported, regardless of route, a mean success rate of 96% has been achieved.[27]

It is now well-appreciated that intestinal microbiota constitute a microbial organ that is integral to overall host physiology, including pivotal roles in metabolism and immune system function.[28] So far, recurrent CDI appears to represent the clearest known example of near-complete disruption of the intestinal microbiota resulting in gastrointestinal dysfunction. Until recently, the intestinal microbiota has been generally inaccessible to scientific study because most of its constituents could not be easily cultured in the laboratory. In part this is because individual microorganisms are highly specialized and exist in structured community networks that become disrupted in attempts at single cell cloning.

Chang et al[29] constructed 16S rRNA-encoding gene clone libraries from the fecal material of 4 patients with first-time CDI and 3 patients with recurrent CDI, performed phylogenetic analyses, and compared them with normal control samples. They found that the microbiomes of patients with an initial episode of CDI were largely intact at the phylum level, ie, the majority of sequences belonged to Bacteroidetes and Firmicutes, the 2 dominant bacterial phyla in the colon. However, major reduction and even disappearance of Bacteroidetes were noted in patients with recurrent CDI and were accompanied by markedly increased proportions in other phyla that normally are only minor constituents of fecal microbiota. Khoruts et al[30] compared the microbiota of a patient with recurrent CDI before and after FMT by using terminal-restriction fragment length polymorphism and 16S rRNA gene sequencing approaches. Before transplantation, the patient's microbiota were deficient in members of Bacteroidetes. Instead, they were composed of atypical bacterial populations such as *Veillonella, Clostridium, Lactobacillus, Streptococcus*, and unclassified bacteria similar to