REVIEW

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Fecal Microbiota Transplantation in the Treatment of *Clostridium difficile* Infections

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ABSTRACT

In recent years, *Clostridium difficile* infections have become more frequent, more severe, more refractory to standard treatment, and more likely to recur. Current antibiotic treatment regimens for *Clostridium difficile* infection alter the normal gut flora, which provide colonization resistance against *Clostridium difficile*. Over the past few years, there has been a marked increase in the knowledge of the gut microbiota and its role in health maintenance and disease causation. This has, fortuitously, coincided with the use of a unique microbial replacement therapy, fecal microbiota transplantation, in the treatment of patients with multiple recurrent *Clostridium difficile* infections. We briefly review current knowledge of the gut microbiota's functions. We then review the indications for use of fecal microbiota transplantation in *Clostridium difficile* infection, the techniques employed, and results of treatment. Fecal microbiota transplantation has been shown to be efficacious for patients with multiply recurrent *Clostridium difficile* infections (reported cure rates of 90%), with an excellent short-term safety profile, and has been included in the American College of Gastroenterology treatment guidelines for this troublesome disease.

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Clostridium difficile is a ubiquitous, anaerobic, Gram-positive, cytotoxin-producing bacillus first described by Hall and O'Toole in 1935 by isolating it from healthy neonates.[1] Bartlett et al described the pathogenic role of *Clostridium difficile* in 1978.[2] The spore-forming bacteria release toxins A and B that cause colon epithelial damage, inflammation, and pseudomembrane formation that manifests in diarrhea and colitis.[2,3] Before the identification of *Clostridium difficile* as the causative agent, Tedesco reported in 1974 that patients receiving antibiotics were the group at highest risk of pseudomembranous colitis.[4] This discovery fostered future research on the importance of the fecal microbiota in health and disease. It has become clear that commensal bacteria in the colon are an important defense mechanism against the proliferation of *Clostridium difficile* and may have complex immunoprotective effects.[5]

Clostridium difficile infections once were limited to nosocomial infections in the elderly but now are the cause of severe morbidity and mortality even in the healthy ambulatory patient with no recent antibiotic exposure.[6] The rate of *Clostridium difficile* infections was level in the 1990s but nearly tripled from 1996 to 2005.[3,6] A new strain of *Clostridium difficile* called NAP1/027 was identified that produces a binary toxin that has contributed to the increase in prevalence and virulence. This discovery came as a result of virulent *Clostridium difficile* infection outbreaks first identified in Quebec and 8 US sites.[3,7] As a result, *Clostridium difficile* infections are now the leading cause of hospital-associated gastrointestinal illness.[8-11] Once an infection occurs, it typically requires treatment with antimicrobials that target *Clostridium difficile*. While initial response rates are high, the recurrence rate for *Clostridium difficile* infections in the 1-8

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weeks after treatment can be as high as 35%, with subsequent recurrences after retreatment occurring in 50%-65% of patients.[12,13] Multiple recurrences are associated with increasing disability (diarrhea, weight loss, weakness) and the potential for colectomy or death.[12,13] The presence of *Clostridium difficile* infections in hospitalized patients has an overall mortality rate as high as 23% at 30 days.[13] *Clostridium difficile* infection management was estimated in 2010 to cost $1 billion in the US.[6]

CLINICAL SIGNIFICANCE

- *Clostridium difficile* infections can have severe recurrent cases that are not effectively treated with current antibiotic treatment.
- Antibiotics kill the bacteria but also destroy the gut microbiota that serves as a vital part of colon health, immunity, and metabolic function.
- Fecal microbiota transplantation replaces the altered gut flora to allow colonization resistance.
- Transplantation has >90% efficacy in resolving recurrent *Clostridium difficile* infections.

TREATMENT PARADIGMS

Initial therapy for *Clostridium difficile* infection includes stopping all antibiotic therapy if possible, followed by the use of metronidazole or vancomycin based on illness severity and comorbidities.[11] Metronidazole is the first-line agent in treatment for mild to moderate *Clostridium difficile* infection, although the failure rate appears to be increasing, with one study indicating an increase in failure rates from 2.5% to 18% after the year 2000.[3] Vancomycin is used initially for severe infections and also for recurrent disease, sometimes in a pulsed or tapered therapy.[11,14] Vancomycin is active against all gram-positive aerobic and anaerobic organisms. Vancomycin, along with other antimicrobials used for *Clostridium difficile* infection, suppresses the growth of *Clostridium difficile*, but also suppresses some normal bowel flora that provide colonization resistance.[6,13] A newly Food and Drug administration (FDA)-approved antibiotic, fidaxomicin, was compared with vancomycin in a multicenter randomized control trial. Cure rates were equivalent to vancomycin, but fidaxomicin had a lower recurrence rate (15% vs 25%).[8,15] Despite these results, its use has been limited, as a 10-day course costs $2800.[16] *Clostridium difficile* exists in both a vegetative form, the toxin-producing replicative state, and a spore form. The latter is particularly resistant to destruction even with antiseptics. This allows the organism to persist in the gut and the environment. If the gut microbiota remains disturbed after *Clostridium difficile* infection therapy, the spores can germinate to the vegetative form, resulting in recurrent disease.

Microbiota refers to the inhabitation of a particular region of the body by a community of microorganisms. The intestine commensal bacterial environment is termed the gut microbiota.[17] In order to eradicate chronic *Clostridium difficile* infection, most believe that the gut microbiota needs to be restored to protect the intestinal lining and help eliminate or prevent residual spores from causing recurrent disease.[13] For this reason, nonantibiotic treatment has gained much interest in recent years, including vaccine development, intravenous immunoglobulin, and fecal microbiota transplantation.[13] Most nonantibiotic treatments have yet to be proven efficacious. However, fecal microbiota transplantation has been shown to resolve recurrent *Clostridium difficile* infection in >90% of patients. Given its high cure rate, fecal microbiota transplantation is now being used in some centers for *Clostridium difficile* infection patients with refractory disease, as well as for second recurrence if one or more of the initial episodes was severe enough to require hospitalization.[11] The goal of fecal microbiota transplantation is to break the cycle of imbalance of intestinal flora. By introducing donor feces, there is almost immediate restoration of bacterial diversity and *Clostridium difficile* colonization resistance.[6]

Transplantation of enteric flora for gastrointestinal disease began in veterinary medicine in the 17th century. It was termed transfaunation by the Italian anatomist Fabricius Acquapendente.[12] The goal of the original human fecal transplant in 1958 was to "re-establish the balance of nature" when fecal enemas were used in 4 patients to successfully treat fulminant, life-threatening pseudomembranous enterocolitis.[18,19] Fecal retention enemas were the administration technique for fecal microbiota transplantation for many years, but administration through duodenal tube began in 1991, via colonoscopy in 1998, and by self-administered enemas in 2010.[6,12,20,21]

While there are no professional society guidelines regarding fecal microbiota transplantation, there are working guidelines written by the Fecal Microbiota Transplantation Workgroup.[6] In addition, multiple studies have described the technique using similar methodologies with some slight variations. In general, patients receive a course of antibiotics leading up to the transplant to decrease inflammation and *Clostridium difficile* spore burden. The antibiotics are stopped 2-3 days before the transplant. A bowel preparation is administered the day before transplant.[6] Stool donor screening varies somewhat among investigators, but should include, at a minimum, ova and parasites, *Salmonella*, *Shigella*, *Campylobacter*, and *C. difficile* toxin by polymerase chain reaction. Serum studies include hepatitis A, B, and C, syphilis, and human immunodeficiency virus. Many investigators similarly screen the patient's blood, so as to identify preexisting conditions that might manifest posttransplantation.[10] Once a donor is "cleared," the transplantation procedure is scheduled. Fresh donor feces are then collected within a few hours of the actual transplantation procedure. Stool is mixed with water, preservative-free saline, or milk, and blended or