Evaluating the Role of Fecal Microbiota Transplant in the Treatment of Clostridium Difficile Infection

Anh Dao Le
Ohio Northern University

Olivia Henton
Ohio Northern University

Shane Bogusz
Ohio Northern University

Brian Heilbronner
Ohio Northern University

Jessica Hinson
Ohio Northern University, j-hinson@onu.edu

Follow this and additional works at: https://digitalcommons.onu.edu/paw_review

Part of the Digestive System Diseases Commons, Gastroenterology Commons, and the Other Pharmacy and Pharmaceutical Sciences Commons

This Article is brought to you for free and open access by the ONU Journals and Publications at DigitalCommons@ONU. It has been accepted for inclusion in Pharmacy and Wellness Review by an authorized editor of DigitalCommons@ONU. For more information, please contact digitalcommons@onu.edu.
Evaluating the Role of Fecal Microbiota Transplant in the Treatment of Clostridium Difficile Infection

Anh Dao Le, Olivia Henton, Shane Bogusz, Brian Heilbronner, Jessica Hinson, PharmD

Abstract
Fecal microbiota transplant (FMT) therapy is an increasingly prevalent treatment option for Clostridium difficile infection (CDI). Clostridium difficile infection is an aggressive and potentially fatal disease state, and antibiotic therapy often fails to resolve the disease state effectively. Clostridium difficile infection occurs most commonly subsequent to the use of antimicrobial agents that disrupt the natural bacterial flora of the gastrointestinal (GI) tract. Since disease state pathophysiology operates in this way, researchers have experimented with ways to restore GI flora to a natural state in which nonpathogenic bacteria can proliferate. Probiotic agents do not impose an acute enough response to recreate typical GI tract flora, which has led to experimentation with direct supplementation of GI bacteria, thus underlying the purpose of FMT therapy. Presently, FMT has demonstrated unparalleled efficacy in resolving CDI and is poised to become first-line therapy as the body of evidence supporting its use continues to grow. This review examines the mechanism of action for FMT therapy and evaluates the results of clinical trials that have tested FMT therapy. Finally, the potential role for pharmacists in the management of patients with CDI will be discussed. Research has supported both the expanded use of FMT therapy in CDI and the establishment of standard practices for administering FMT therapy in hospitals treating larger numbers of CDI patients. Furthermore, additional clinical trials that could supplement existing support for FMT therapy are currently recruiting patients.

Key Terms
Clostridium Difficile; Fecal Microbiota Transplantation; Gastrointestinal Microbiome; Metronidazole; tcdA protein; toxB protein; Vancomycin

Background
The gastrointestinal (GI) tract comprises more than 500 species of intestinal microbiota, serving the functions of protection, structural support and metabolism to maintain homeostasis.1 Antibiotics are utilized to treat infectious diseases states; however, long-term use of antibiotics poses the risk of causing digestive adverse effects such as cramping, gas or diarrhea, due to nonselective eradication of bacteria and protective intestinal microbiota.2 Overutilization of antibiotics may also increase the risk of Clostridium difficile infection (CDI).3 Clostridium difficile infection is caused by Clostridium difficile (C. difficile), a gram positive, rod-shaped, spore-forming bacteria that is transmitted via the fecal-oral route through direct and indirect contact. Subsequent to their inadvertent ingestion, C. difficile spores survive gastric acid and proceed to the small intestine where they colonize and rapidly proliferate under anaerobic conditions. Proliferation and subsequent CDI may be further exacerbated by the coadministration of antibiotics, which additionally displace and eradicate the homeostatic functions of normal GI flora.

The infectious symptomatology of C. difficile originates from the bacterial spore which releases specific toxins. Toxin A and Toxin B, that progress to GI cells.1-3 Toxin A is an enterotoxin which alters GI mucosal epithelium cell permeability, allowing fluid secretion, whereas Toxin B is a cytotoxin that induces mucosal inflammation in the colon. The inflammation causes increased GI permeability and motility, which allows more granulocytes and fluid in the GI tract, resulting in antibiotic-induced diarrhea. Alterations in cellular function and structure from the toxins also initiate cellular response and apoptosis, further damaging the GI tract.

According to the guidelines for diagnosis, treatment and prevention of C. difficile infections, diagnostic testing for confirmation of CDI should occur prior to treatment for patients who do not present strong pre-test suspicion for CDI.3 Diagnostic techniques include testing the suspected patient's stool using laboratory tests and diagnostic imaging, the most common of which include toxin enzyme immunoassays, toxicogenic cultures, nucleic acid amplification tests and the C. difficile cytotoxin neutralization assay.4 GI structural remodeling can be observed by diagnostic colonoscopy and computed tomography of the abdomen and pelvis.

The recommended first-line treatment for mild CDI is metronidazole 500 mg three times daily for 10 to 14 days.2 If resolution of symptoms does not occur within five to seven days, oral vancomycin 125 mg four times daily for 10 days should be administered. Patients who experience recurrence of CDI within eight weeks of therapy are classified as having recurrent infection (RCDI), and approximately 20 percent of CDI patients in mid-pharmacologic therapy for CDI treatment experience a recurrence of the infection within six months of therapy. For patients with RCDI, treatment with metronidazole or a vancomycin pulse regimen (every two to three day dosing) is initially recommended. Fecal microbiota transplant (FMT) is then recommended after three recurrences of infection within six months after discontinuing therapy. The use of FMT is to establish normal GI flora composition, metabolism and upregulate immune responses in the mucosa. Fecal microbiota transplant is used due to its safety, efficacy and perceived cost-effectiveness.

Fecal Microbiota Transplant: Treatment Procedure, Efficacy and Safety
Fecal microbiota transplant is a procedure during which stool from a healthy patient is infused into a patient with
RCDI. The rationale behind the treatment is based on RCDI and the loss of homeostasis of GI flora, and the stool from healthy patients can reintroduce normal flora to reestablish homeostasis. The procedure calls for a stool sample from a healthy donor to be prepared with normal saline and administered into the GI tract of the patient with CDI. Patients should be placed in the right lateral recumbent position and hold this position throughout the implantation in order to facilitate the optimum permanence of the fecal solution into the colon. The procedure lasts about 10 minutes. The tube is then removed, but patients are monitored during recovery for approximately two hours.

Various methods of FMT administration exist, including nasogastric tube, naso-duodenal tube, colonoscopy, oral fecal capsules and self-administered enemas. The most common and advantageous route is via colonoscopy due to its ability to spread the stool throughout the length of the colon extensively. Accessing the colon also allows the physician to observe abnormalities in the colon. This route has yielded 86 percent to 100 percent successful outcomes.

Given the limited understanding of the short-term and long-term effects of FMT, there are only a few studies that have investigated the potential effects of transplanted microbiota on recipient patients. In one cohort study by Song and colleagues at the University of Maryland’s School of Medicine, 14 RCDI patients underwent FMT along with their respective healthy donor as subjects. The fecal specimens of both populations were analyzed before FMT, as well as one week and one year post-FMT to determine if the recipient’s recovered intestinal microbiota would mirror that of the donor’s after an extended period of time. Patients recovered symptomatically within two to three days of undergoing FMT and were classified as asymptomatic based upon resolution of diarrhea.

The fecal specimens of RCDI patients collected prior to FMT displayed low diversity in microbial species when compared to the samples given by healthy donors. The species present in each sample were determined using rarefaction analysis of operational taxonomic units, a method that utilizes DNA to determine the presence of types of species. One week after FMT, patients displayed an increase in microbial species, determined using Shannon diversity index calculations, a set of calculations used to determine how proportional a multiple species are in a given environment. Furthermore, the study discovered that species diversity and species richness remained constant over time: fecal specimens collected one year after FMT illustrated constant Shannon diversity scores.

More specifically, recipient microbiota not only increased in diversity but also matched the composition of the donor in most patient cases. However, multiple subjects did experience a transient return to a microbiota composition that resembled the patient’s pre-FMT specimen collection. Despite this regression on a microbial level, all patients experienced a resolution of symptoms. One patient relapsed one month after the initial FMT following antibiotic treatment for a urinary tract infection but underwent a second, successful FMT. This data suggests that asymptomatic patients are still more susceptible to a C. difficile infection than healthy individuals following administration of antibiotics despite an evolved microbiota. This study supported FMT for treatment of C. difficile infections presenting evidence that FMT treatment improved the microbiota composition of RCDI patients.

Another cohort study that investigated a similar parameter was conducted by researchers of Wright State School of Medicine. Three RCDI patients received fecal matter from the same healthy donor and fecal specimens were collected from the three subjects as well as the donor prior to the FMT procedure. Specimens subsequently were collected from patients on days three and seven following the treatment and throughout a four month post-FMT period. Similar to the results found by Song and colleagues, all three patients experienced a resolution of symptoms characteristic to a C. difficile infection only days after FMT. Two of the three patients reported to have a firm bowel movement on day three following the FMT procedure. The same two patients remained free of infection for approximately two years following FMT; the third patient, who also suffered from ulcerative colitis, experienced an infection of C. difficile 1.5 years following treatment after taking antibiotics for an unrelated urinary tract infection. Specimens obtained from patients prior to FMT illustrated low species diversity. The composition of the healthy donor was diverse, and the abundance of organisms was even with regard to each species. The study found a pattern in the type of species that existed in patients pre-FMT compared to that found in the donor. The three recipients had specimens containing high levels of organisms belonging to the classes gammaproteobacteria and bacilli. These microbial classes are able to withstand the presence of oxygen as C. difficile infections often lead to an infiltration of reactive oxygen species. In contrast, the study reported that the donor’s fecal matter were dominated by bacteria in Clostridia, Actinobacteria, Erysipelotrichi and Bacteroidia, classes that typically comprise the GI tract of a healthy human. Following FMT, the three patients displayed an increase in bacteria from classes Bacteroidia and Clostridium which remained stable over the four month period following treatment. The patients’ pre-FMT fecal compositions were reportedly variable and distinct from each other. Following FMT, however, the three subjects’ samples paralleled the donor sample. This study concluded that the composition of the subjects’ microbiota prior to FMT did not affect the outcome or microbial makeup following treatment and confirmed the efficacy of FMT on a long-term basis. This finding provides clinical significance in the outcome of FMT; the change in microbial makeup parallels the patients’ reduction of symptoms, including diarrhea.

Comparison of Fecal Microbiota Transplant, Antibiotics and Combination Therapy in Treating Clostridium Difficile Infection

Several studies and randomized control trials have evaluated the efficacy of FMT in comparison to traditional pharmacologic treatment modalities, specifically comparing FMT alone or as an adjunct therapy with antibiotics to antibiotic monotherapy. Catholic University School of Medicine conducted an open-label, randomized clinical trial comparing the thera-
pies of FMT via colonoscopy in patients with recurrent CDI versus pharmacologic vancomycin therapy. Twenty patients diagnosed with C. difficile were treated with 125 mg vancomycin tablets four times a day for three days, followed by one or more infusions of feces until the conclusion of 10 weeks. Nineteen patients were treated with 125 mg vancomycin four times a day for 10 days, followed by pulse therapy of 125 to 500 mg/day every two to three days for at least three weeks. Results showed 18 of the 20 patients treated by FMT with vancomycin short term pretreatment no longer suffered from diarrhea. Only five of the 19 patients treated with vancomycin alone (P < 0.0001) were treated successfully. The researchers concluded that FMT via colonoscopy is more effective than vancomycin therapy in treatment of CDI.

Another randomized, control trial compared traditional antibiotic use with FMT. Els van Nood and colleagues conducted a study using duodenal infusion of feces versus a typical 14 day vancomycin treatment for CDI. Three dependent groups in the trial were included: patients who were given an initial vancomycin regimen of 500 mg orally four times a day for a duration of four days then underwent a bowel lavage, followed by infusion fecal; patients who were given the standard vancomycin regimen followed by bowel lavage; and patients who were just given the standard vancomycin regimen. Patients were randomly assigned to one of these groups with the primary end point of curing RCDI with absence of relapse within 10 weeks. Sixteen patients were in the infusion group and 13 patients (81 percent) met the primary end point. The remaining three patients who did not show resolution underwent a second infusion, and two patients had successful resolution (P < 0.001). The group that received the bowel lavage had three successful resolutions within 13 patients (23 percent). The group that only received standard vancomycin regimen yielded four successful resolutions out of 13 patients (31 percent). Researchers concluded that infusion donor feces is more efficacious in comparison to vancomycin in RCDI treatment.

Researchers of the Harvard School of Public Health conducted a retrospective review of the long-term effects of multiple FMT treatments in patients with RCDI. The review involved 94 RCDI patients total; 45 subjects were cured (defined as having not experienced diarrhea incidents for six consecutive months) after one single FMT treatment. The remaining patients received multiple FMTs, the highest number of which was 10 FMTs. Patients receiving multiple FMTs were given antibiotics between each treatment which resulted in a 5.3 percent increase in the resolution rate; thus, the subsequent treatment was more successful. Patients considered cured following FMT were reported to be free of C. difficile infection for an additional period of six to 24 months. The study resulted in an absence of adverse events as a result of FMT therapy. The authors reported a 92 percent cure rate among patients who underwent FMT with additional antibiotic therapy. Researchers concluded that FMT is an effective treatment for RCDI not resolved by antibiotic therapy and is safe when completed multiple times on a single patient.
certain PPIs are available over-the-counter, the patient’s physician may not be aware of this medication use. Pharmacists should counsel patients taking PPIs for extended periods of time, and should remain vigilant for cases of patients on high-risk antibiotics taking either prescribed or over-the-counter PPIs.11

Conclusion
Fecal microbiota transplant exerts its therapeutic action by restoring intestinal nonpathogenic bacteria to produce a state more closely resembling the GI flora of the fecal matter donor. Preliminary research suggests a superiority of FMT over antibiotic therapy in treatment of C. difficile infection. Though comparative trials between the two therapies are limited in scope and number, FMT produced disease state resolution in 81 percent and 90 percent of patients, while antibiotic therapy attained such success in only 26 percent and 23 percent of patients, respectively.9 When the two therapies were combined, with intermittent antibiotics administered between multiple FMTs, a synergistic effect was produced by the combination therapy with a successful treatment rate of 92 percent. Additional trials are currently recruiting patients to increase the strength of the evidence supporting increased use of FMT in treating CDI, but the direction of preliminary research indicates that FMT is a safe, effective treatment with superiority to antibiotics alone.

References
11. Frary JA, Winsett RP. The association between proton pump inhibitors and Clostridium difficile infection: reducing risk. MEDSURG Nursing. 2015 Dec;4:6-.