Fecal Microbiota Transplantation: A Promising Treatment to Eliminate Refractory Clostridium Difficile Enteritis

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BACKGROUND

Over the last 15 years, Clostridium difficile infection (CDI) in the United States has continued to gain momentum with a greater incidence, morbidity, and mortality than in decades past. 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 over the same time period. Treatment options are still limited. Recurrent treatment regimes of antibiotics, toxin binding agents, and probiotics appear to be losing their efficacy. Recurrent disease is especially challenging due to increasingly required, yet expensive, extended treatments with oral vancomycin and other agents.\(^2\) Fecal microbiota transplantation (FMT) is safe, effective and less expensive than the current recommended regimen based on a series of reports summarized in a recent review.\(^3\) We present a case of an El Pasoan woman who underwent successful FMT at our Gastroenterology center at University Medical Center with elimination of her refractory Clostridium difficile. In this report, we will discuss the procedure, rationale, and methods for this technique, which could be beneficial for the patients in El Paso and the region.

CASE PRESENTATION

A 78 year old Hispanic female was originally hospitalized for community acquired pneumonia, which was subsequently treated with antibiotics. Unfortunately, her hospital stay was complicated by CDI. She was treated with metronidazole and discharged home to complete a six week course. Two weeks after she finished her treatment, she presented to the hospital again with abdominal pain and watery diarrhea. *Clostridium difficile* was identified as the offending agent and this episode of CDI was treated with a six week course of metronidazole and vancomycin in an outpatient manner. When she completed this regimen, she was symptom-free for about 2 weeks, but again presented to the hospital with severe dehydration secondary to diarrhea. Once again, CDI was documented to be positive.

Based on her refractoriness to the management of the CDI relapses by the standard approach, the patient and her daughter elected to pursue the FMT procedure as a new option.

After appropriate testing of the donor’s fecal and blood status, the donor fecal matter was collected and mixed with 500cc of normal saline. 250cc of this mixture was then introduced into the patient via a colonoscopy technique (see discussion for details) without any complications. Within the following 3 days, the patient showed marked improvement with resolution of her CDI symptoms. She was then discharged home with no antibiotics on a lactulose-free, low fiber diet. Loperamide was given to prolong contact of the stool transplant with the colonic mucosa and a scheduled follow-up visit was requested in 2 weeks. On follow-up, the patient has remained asymptomatic and has not had any problems or flare ups of CDI for over 6 months.

DISCUSSION

Fecal transplantation is not commonly performed for *Clostridium difficile* infection, but interest in this procedure is growing rapidly. Approximately 450 cases of fecal transplantation for treatment of *Clostridium difficile* infection have been reported worldwide.

The clinical use of FMT dates back to 1958, although the bulk of published work, which is still limited, is from the last 2 decades.\(^3,4\) Initially, retention enemas were the most common technique for FMT, but fecal infusion by duodenal and rectal tubes has also been reported. Although colonoscopy is now the most popular route for delivering the transplantation, differences in opinion still exist on the exact technique to perform FMT. The colonoscopic approach is now favored over the fecal enema, largely because enemas only reach the splenic flexure;\(^5\) whereas, colonoscopy can elucidate the extent and severity of the disease while the treatment is being administered.\(^6\)

The methodology of FMT is as follows. After giving informed consent, the patient undergoes standard colonoscopy to the cecum under sedation, and biopsy specimens are obtained if necessary. Approximately 20mL of stool suspension homogenized from the donor stool is drawn up in a syringe and injected via the biopsy channel of the colonoscope every 5 to 10 cm as the endoscope is slowly withdrawn from the right colon to the rectum, for a total volume of 250 to 500mL.\(^7,8\) The patient is advised to refrain from defecating for 30 to 45 minutes after fecal microbiota transplantation.\(^9\)

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This approach allows direct visualization of the entire colon, as well as the instillation of stool suspension throughout the colon, including certain areas where *Clostridium difficile* may predominate or hide (e.g., in diverticuli). One disadvantage to this route of administration is the risk of colon perforation, especially if the patient has toxic colitis. Hence, the procedure should not be conducted when there is very active disease and certainly when there is concern for toxic megacolon.

Who should not be a donor? It is the responsibility of the physician performing the fecal microbiota transplantation to make sure that the possibility of transmitting disease to the recipient is minimized. History-taking and physical examination must never be omitted, since not all diseases or conditions can be detected by laboratory screening alone, especially if testing was done during the early stage or window period of a given disease. Nevertheless, the donor’s blood and stool should be screened for transmissible diseases, such as human immunodeficiency virus (HIV), hepatitis, syphilis, enteric bacteria, parasites, and *Clostridium difficile*. The recipient has the option to be tested for transmissible diseases such as HIV and hepatitis in order to avoid any concerns about transmission after fecal microbiota transplantation. A positive screening test must always be verified with confirmatory testing.

The Fecal Therapy to Eliminate Associated Long-standing Diarrhea (FECAL) trial, currently underway in Norway is the first randomized trial to assess the efficacy of fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection. Such clinical trials will address continuing doubts about the efficacy of fecal microbiota transplantation and hopefully pave the way for its application in the near future.

The patients are learning to overcome the “yuck factor” associated with fecal microbiota transplantation once they understand the safety and benefits of this procedure. Moreover, the Human Microbiome Project is attempting to identify specific organisms in stool that may specifically treat *C. difficile* infection, hence eliminating the need for whole-stool transplantation in the near future. Although fecal microbiota transplantation is still in its infancy, its low cost, safety, and effectiveness in treating recurrent *C. difficile* infection will likely lead to the procedure becoming widely adopted in mainstream clinical practice.

In a recently published randomized controlled trial in the New England Journal of Medicine, patients were randomly assigned to receive one of three therapies: an initial vancomycin regimen (500mg orally 4 times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500mg orally 4 times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks. It was concluded that the infusion of donor feces was significantly more effective for the treatment of recurrent *C. difficile* infection than the use of vancomycin.

Based on a small series of case reports, a successful outcome is anticipated in about 90% of cases. Our patient is an example of a good outcome, which leads us to strongly advocate the use of FMT for the treatment of refractory CDI. This therapy is not only straightforward to perform, it is well tolerated by the patient and it is also inexpensive. In the future, other pathological processes will be targeted including ulcerative colitis, Crohn's disease, irritable bowel syndrome, and idiopathic constipation, with current studies being initiated in these areas. Although no adverse effects associated with this procedure have been reported, longer term follow-up is crucial.

The US Food and Drug Administration (FDA) initially mandated Investigational New Drug (IND) approval for all fecal transplantations prior to performing the procedure. Subsequent workshops and discussions led to modification of this policy. FDA now states that no IND will be required for FMT for the treatment of refractory CDI. FDA emphasized that IRB approval at the medical institution as well as informed consent are minimum requirements. Patients should be provided with adequate explanation about the procedure and its potential risks, and fully educated and informed before electing to pursue this treatment. Currently, investigators are in the process of securing IND approval in order to perform a controlled trial of fecal transplantation for the treatment of CDI. Further guidelines are expected in the future.

In summary, this case report highlights an innovative procedure that is available in our Gastroenterology Center, thus providing a new treatment modality for refractory *Clostridium difficile* infection for physicians and patients in El Paso.

REFERENCE


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