

A Report of Fecal Transplantation for Refractory Clostridium Difficile Colitis in an Orthotopic Liver Transplant Recipient

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ABSTRACT

A 61 year old woman received an orthotopic liver transplant for nonalcoholic steatohepatitis. Two months after her transplant she developed diarrhea that was found to be caused by Clostridium Difficile. Her colitis was refractory to antibiotic therapy. Fecal transplantation was used via a nasojejunal route with immediate clinical improvement. She redeveloped symptoms and Clostridium toxin positivity weeks later after broad spectrum antibiotics were given for presumed pneumonia. This colitis was refractory to another round of antibiotics, and a second fecal transplant was performed with similarly positive results.

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Key words: Clostridium Difficile; Liver Transplant; Fecal Transplant; infection

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INTRODUCTION

The diagnosis of Clostridium Difficile (CD) colitis is of major importance in solid organ transplant recipients, because of increasing incidence, prevalence, and risk for morbidity and mortality. In this population, rates of diagnosis have risen from 4.5% in 1999 to 9.5% in 2010^[1]. The prevalence in liver transplant patients has been reported to be three times than the general population (2.7% vs 0.9%)^[2]. Medical treatment is typically effective, but refractory patients may require colectomy. CD colitis has also been associated with increased graft complications or loss^[3]. The risk of mortality is also significantly increased (5.5% vs 3.2%)^[2]. The following is a report of CD colitis refractory to medication that was safely and successfully resolved with fecal transplantation.

CASE REPORT

SL is a 61 year old woman who was found to have non-alcoholic steatohepatitis induced liver cirrhosis in the spring of 2013. She was transplanted on 9/11/13, with a MELD score of 18. The donor allograft was a CDC increased risk due to donor lifestyle issues and positivity for hepatitis B core antibody. There were no intraoperative complications. She had an uneventful postoperative course. She was discharged to a rehabilitation center on postoperative day 16.

On December 4, she represented to the emergency room complaining of profuse diarrhea, inability to tolerate oral intake, fatigue, and malaise. She had a low grade fever and a slightly elevated leukocytosis. A CT scan performed suggested colitis, and she was found to be CD positive. She was started on oral metronidazole and vancomycin, but her symptoms did not improve. She was then converted to oral fidaxomicin which improved her symptoms within 48 hours. Upon discharge on December 15, she had only one bowel movement in the last 24 hour period.

She represented to the emergency room three days later with nausea, vomiting, diarrhea, and malaise. Repeat PCR screening

for CD was negative. She was readmitted and continued on her previously prescribed antibiotics. Her symptoms persisted over the course of the next month despite adjustment of diet, supplementary enteral tube feeding changes, and motility agents. She was also given a second full course of fidaxomicin. Flexible sigmoidoscopy performed showed erythematous mucosa in the sigmoid colon that showed benign colonic mucosa with pseudomembranous necrotizing ulcerations and focal mucosal erosion. She had three negative CD cultures drawn this admission, but her clinical picture appeared to be caused by chronic CD infection. On January 28 she underwent stool transplantation administered through a nasojejunal tube. Her husband volunteered to donate and was tested appropriately. Her symptoms markedly improved on post-operative day 1. Within a week, she regained a significant amount of energy and was able to participate in physical therapy. She was then discharged back to rehab on February 5.

During the first few days during her stay at rehab, she developed acute dyspnea and was started on broad spectrum antibiotics. Her dyspnea was due to an asthma exacerbation, which was then complicated by acute renal insufficiency and recurrence of her diarrhea and malaise. Over the next week her diarrhea persisted despite medical therapy. On February 25 she had a second stool transplantation performed via nasojejunal tube, with almost immediate resolution of her symptoms. She was discharged March 4 back to rehab and has not had any recurrence of diarrhea, has improved energy, and is progressing well with physical therapy.

DISCUSSION

Clostridium Difficile (CD) colitis is a common cause for nosocomial watery diarrhea, and has been associated with exposure to broad spectrum antibiotics. The solid organ transplant recipient patient is particularly vulnerable because of the medically induced immunosuppression used in order to protect the allograft from the recipient. As a result, antibiotics are typically initiated if any of the warning signs for bacteremia present, since delay or failure to treat could lead to lethal sepsis. Empiric antibiotics were given and withdrawn for short courses multiple times throughout our patient's hospital stay. This was likely the etiology for the recurrence of CD after her first stool transplant. When she was transferred to rehab she was started on three antibiotics for an overnight fever; within 72 hours she tested positive again for CD.

Many studies have reported associations between CD colitis and other postoperative complications, including intra-abdominal bleeding, biliary complications, systemic infections, graft dysfunction, and even graft loss^[3,4]. CD can progress to toxic megacolon and lead to septic shock that necessitates an urgent subtotal colectomy^[5]. Our patient did not meet criteria for urgent operative intervention, namely toxic megacolon, perforation, or necrotizing colitis. Diverting loop ileostomy^[6] with colonic lavage has been shown to be effective and less invasive solution for fulminant CD. Elective operation was considered, but her poor overall, functional, and nutritional status created a high perioperative risk that led us to explore fecal transplantation as our next line of therapy.

Standard treatment of CD colitis includes oral metronidazole or oral vancomycin. Oral fidaxomicin has been shown^[7] to be noninferior to oral vancomycin, with a lower recurrence reinfection rate. In our patient the standard treatment proved to be ineffectual, but the first doses of fidaxomicin seemed to be highly successful. It was discovered at the time of readmission that she did not finish her antibiotics on discharge, which likely led to the recurrence of her

symptoms leading to her second admission. The failure of the second regimen may be attributed to possible microbial resistance, however no testing was performed to confirm this hypothesis.

Fecal transplantation is a developing modality for refractory CD colitis. CD colitis frequently occurs when the microbiota of the colon is disrupted, and the clostridium bacteria is allowed to propagate unchecked. Even with satisfactory antimicrobial administration, there is a probable risk of recurrence if the microbial balance is not restored. Fecal transplantation is a means of directly reintroducing normal flora into the colon. It has been described in uncontrolled studies and case reports with positive results^[8-11]. Recently the FDA created regulations regarding the use of fecal transplantation, and coordination with the gastroenterology service allowed an exception against their protocol for its use on this patient. An exclusion criterion for their protocol includes the immunocompromised patient, since the consequences of creating a bacteremia from the procedure could be potentially life threatening. After an extensive care conference between the family, transplant team, and gastroenterology service, this risk seemed more favorable than the morbidity of an operative intervention.

This case illustrates one of the many challenges of liver transplantation, antimicrobial use, and opportunistic infection. Increasing resistance of *Clostridium Difficile* to conventional antibiotics has given rise to novel therapies that were successful in our patient, but further studies are needed.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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