CLINICAL VIGNETTE

Fecal Microbiota Transplantation in a Patient with Severe Clostridium *difficile colitis*

Michael Jean, MD and Sittiporn Bencharit, MD

Case

A 55-year-old female presented to the emergency department (ED) with severe diarrhea. She had two previous hospitalizations for Clostridium difficile infection (CDI), four and five months prior to presentation. Both of the hospitalizations required admission to the intensive care unit (ICU) secondary to sepsis and the need for vasopressor support. During both hospitalizations, she was treated with oral vancomycin and intravenous metronidazole. Each hospitalization lasted 10 to 14 days, during which she gradually recovered and was discharged home.

Two weeks prior to the most recent admission, she had urinary tract infection and was started on a 3-day course of oral ciprofloxacin. Three days prior to admission, she had an upper endoscopy with dilation of an obstructing distal esophageal stricture. One day prior to admission, she started to have loose stools, which rapidly progressed to severe diarrhea.

Significant past medical history included systemic lupus erythematosus, scleroderma, and steroid dependent asthma, which required a chronic maintenance dose of prednisone 5mg a day. She also had been on chronic dose of pantoprazole 40mg a day for years, given her history Barrett's esophagus and a recurrent esophageal stricture. Vital signs in the ED included a temperature of 38°C, pulse of 106, respiratory rate of 22, blood pressure of 94/59, and an oxygen saturation of 99% on room air. Her body mass index was 33. The patient appeared fatigued and flushed. Other significant physical findings included chronic moon fascies and abdominal striae. Abdominal exam revealed mild diffuse abdominal discomfort without rebound or guarding. Significant laboratory values showed a white blood cell count (WBC) of 18,500 with 56% neutrophils. The magnesium (1.5 mEq/L) and albumin (2.9 grams/dL) levels were both low. Computed tomography (CT) of the abdomen and pelvis revealed a diffusely thickened colon with the development of mild ascites (Fig. 1-3).

The patient was placed empirically on oral liquid vancomycin and intravenous metronidazole. She was admitted to the intensive care unit after developing hypotension, requiring vasopressor support. Intravenous stress dose steroids were started by the hospitalist team. The Clostridium difficile cytotoxin stool assay was positive later that evening.

During the first several days of hospitalization, there was a gradual clinical improvement with her liquid diarrhea decreasing from 20 times a day, to 4-5 times a day. However, on hospital day number 5, there was a worsening of the patient's clinical status. The WBC increased to 23,800, and the patient developed worsening of her diffuse abdominal pain. Surgery was consulted and the options of a loop ileostomy with colonic lavage versus a subtotal colectomy were discussed. The patient absolutely declined any surgery intervention, and requested medical treatment only. The option of a fecal microbiota transplant (FMT) was discussed with the patient and she was willing to proceed, realizing it was an experimental treatment. A frozen stool sample was ordered from a commercially available stool bank (OpenBiome, based in Somerville, MA). On hospital day number 7, a fecal microbiota transplant (FMT) was delivered via an endoscopically placed nasoduodenal tube. The distal esophageal stricture was dilated to 12mm to allow passage of the nasoduodenal tube. Of note, her oral and intravenous antibiotics were stopped 36 hours prior to FMT.

There were no immediate complications after FMT, and the patient reported clinical improvement the following day. Her WBC and clinical status gradually improved (Fig. 4), and eventually she was discharged on hospital day 23. She has had no subsequent recurrences of CDI over a 3 and ½ year follow up period.

Discussion

Clostridium difficile is a gram-positive, spore forming bacteria. It is one of the most common healthcare-associated infections in the United States.[1,2] In the US, there are an estimated 500,000 cases of CDI a year, causing death in an estimated 29,000 patients a year. The estimated healthcare cost of CDI is $1-3 billion dollars a year, and comprises of up to 1% of hospitalizations in the US.[2] Increasing infection rates have been noted in the past two decades. From 1996 to 2003, CDI prevalence doubled in the US.[3]

CDI is likely caused by dysbiosis, or the decrease in fecal microbiota diversity. Our patient had multiple risk factors for recurrent CDI and dysbiosis, including recent prolonged hospital stays, immunosuppression from chronic steroids, recent antibiotics, and the chronic use of proton pump inhibitors.[4] FMT is the process of introducing a diverse colonic microbial

population from a healthy donor via colonoscopy, nasoenteric tube, upper endoscopy, or by the ingestion of capsules. A diverse colonic microbiota likely provides resistance against Clostridium difficile infection.

FMT was first described in the medical literature in 1958, when fecal enemas were used to treat patients with pseudomembranous colitis.[5] It has been subsequently shown that FMT is an effective treatment for recurrent CDI.[6] While FMT has been shown to be effective in patients with recurrent CDI, there has been less data on the effectiveness on patients who present with severe or fulminant CDI. While in the past there has not been a consensus definition on how to define severe CDI, recent guidelines used the following definition: Severe CDI is defined as a patient with a WBC >15,000 cells/mL or a serum creatinine level >1.5 mg/dL. Fulminant colitis is described as hypotension or shock, ileus, or toxic megacolon.[7]

One of the largest published experiences of FMT with patients with severe or severe-complicated CD enrolled 57 patients from 2013 to 2016.[8] At 1 month, 91% of the patients were successfully treated and cured. A single FMT was needed in 30 patients (52.6%), 2 FMTs in 16 patients (28.1%), 3 FMTs in 4 patients (7%), and 4-5 FMTs in 2 patients (3.5%). In this study, the authors noted that there were 2 phenotypes that were not well suited for FMT. First were the patients with multiorgan system failure (refractory to supportive treatment) who had concomitant severe acidosis (pH<7.2). Second, were patients with toxic megacolon and signs of impending perforation (patients with intraluminal colonic air).

Conclusion

Our case is one of the few cases of severe, fulminant colitis secondary to CDI that has been successfully treated with FMT. While surgical resection is currently the standard of care for patients with fulminant colitis, FMT may be an option in carefully selected patients. Patients that are poor surgical candidates may be considered for FMT, given the high morbidity and mortality of surgery. There is likely a point where FMT is unlikely to be of benefit (impending perforation). Further research needs to be done to identify which patients with severe fulminant CDI colitis will benefit from FMT.

REFERENCES

1. **Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America**. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010 May;31(5): 431-55. doi: 10.1086/651706. PubMed PMID: 20307191.
2. **Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, Farley MM, Holzbauer SM, Meek JI, Phipps EC, Wilson LE, Winston LG, Cohen JA, Limbago BM, Fridkin SK, Gerding DN, McDonald LC**. Burden of Clostridium difficile infection in the United States. *N Engl J Med*. 2015 Feb 26;372(9):825-34. doi:10. 1056/NEJMoa1408913. PubMed PMID: 25714160.
3. **Heinlen L, Ballard JD**. Clostridium difficile infection. *Am J Med Sci*. 2010 Sep;340(3):247-52. doi: 10.1097/MAJ. 0b013e3181e939d8. Review. PubMed PMID:20697257; PubMed Central PMCID: PMC2935936.
4. **Ananthakrishnan AN**. Clostridium difficile infection: epidemiology, risk factors and management. *Nat Rev Gastroenterol Hepatol*. 2011 Jan;8(1):17-26. doi: 10.1038/ nrgastro.2010.190. Epub 2010 Nov 30. Review. PubMed PMID: 21119612.
5. **Eiseman B, Silen W, Bascom GS, Kauvar AJ**. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery*. 1958 Nov;44(5):854-9. PubMed PMID: 13592638.
6. **Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C**. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. *Am J Gastroenterol*. 2012 Jul;107(7):1079-87. doi: 10.1038/ ajg.2012.60. Epub 2012 Mar 27. PubMed PMID: 22450732.
7. **McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH**. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018 Mar 19;66(7):987-994. doi: 10.1093/cid/ciy149. PubMed PMID: 29562266.
8. **Fischer M, Sipe B, Cheng YW, Phelps E, Rogers N, Sagi S, Bohm M, Xu H, Kassam Z**. Fecal microbiota transplant in severe and severe-complicated Clostridium difficile: A promising treatment approach. *Gut Microbes*. 2017 May 4;8(3):289-302. doi: 10.1080/19490976.2016.1273998. Epub 2016 Dec 21. PubMed PMID: 28001467; PubMed Central PMCID: PMC5479393.

Figures

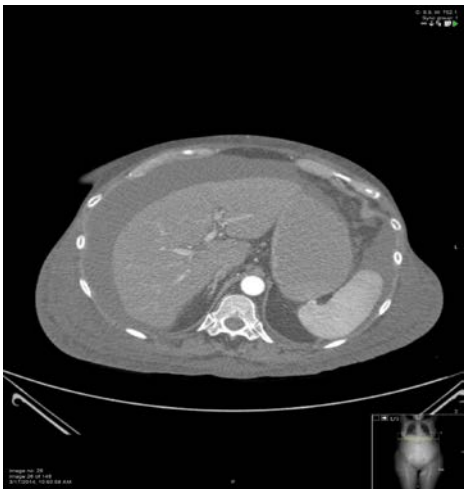

Figure 1. CT scan demonstrated peri-hepatic ascites

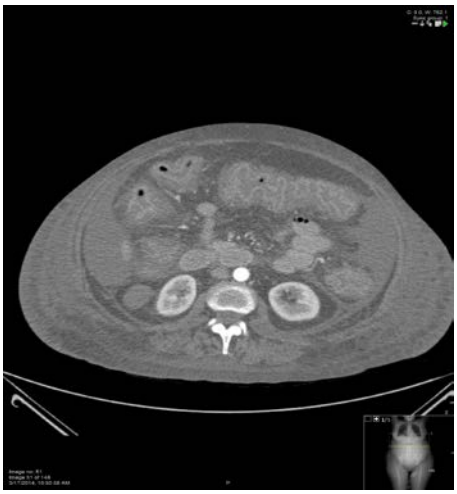

Figure 2. CT scan demonstrated markedly thickened transverse colon.

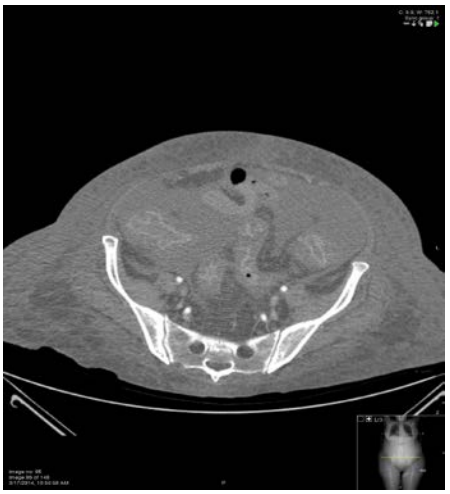

Figure. 3. CT scan demonstrated markedly thickened sigmoid colon.

FMT

HD 1	HD 3	HD 4	HD 5	HD 5	HD 6	HD 7	HD 8	HD 9	HD10
18.5	17.2	16.0	17.8	23.8	26.1	45.1	37.5	30.2	17.8

HD11	HD12
18.6	9.9

Figure 4. WBC = White Blood Cell Count**,** HD = Hospital Day**,** FMT= Fecal Microbiota Transplant.

Submitted May 24, 2018