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Clostridium difficile Enteritis Treated with Fecal Microbiota Transplant

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Background	*Clostridium difficile* (*C. difficile*) enteritis is less common than colitis and is associated with a mortality rate of 30 percent. *C. difficile* enteritis presents more frequently in patients with a history of inflammatory bowel disease or total abdominal colectomy. After an ileostomy, ileal mucosa may undergo an adaptive transformation, making the small bowel biome similar to that of colonic flora, increasing susceptibility to *C. difficile*. Others suggest that the ileocecal valve may prevent *C. difficile* from colonizing the small bowel, thus placing patients who have undergone ileocecal resections at higher risk for *C. difficile* enteritis. This report describes a remarkable case of *C. difficile* enteritis diagnosed at the time of total abdominal colectomy for *C. difficile* colitis.
Summary	The patient is a 39-year-old male with a remote history of sigmoid resection for perforated diverticulitis, small bowel obstruction requiring resection, and complex ventral herniorrhaphy with synthetic extraperitoneal mesh. He presented with fever and watery diarrhea. Stool and endoscopic examination revealed pseudomembranous colitis, negative for *Clostridium difficile*. He was discharged against medical advice, returning four weeks later with worsening abdominal pain and ileus. Repeat stool testing for *C. difficile* toxin was positive. Still, he was nonadherent with maximal inpatient medical management and required exploratory laparotomy due to the development of rebound tenderness, fever, and leukocytosis. A total abdominal colectomy, jejunal resection with primary anastomosis, and end-loop ileostomy were completed. Pathologic examination demonstrated pseudomembranous enterocolitis involving the jejunum and predominantly the right colon. Intravenous metronidazole, vancomycin per stoma, and vancomycin enemas were continued postoperatively, but antibiotic treatment failed. Because of persistent enteritis and lack of clinical improvement, he underwent esophagogastroduodenoscopy and fecal microbiota transplant with prompt resolution of tachycardia, ileus, and leukocytosis.
Conclusion	We demonstrate a rare case of *Clostridium difficile* enteritis with jejunal perforation and without a known diagnosis of inflammatory bowel disease or previous total abdominal colectomy. Surgeons should be aware of the manifestations of small bowel complications and be prepared to treat the enteritis component of *C. difficile* enterocolitis. Physicians should not underestimate the utility of fecal microbiota transplant and its potential role in the first-line treatment of *C. difficile* enteritis, as well as refractory and recurrent cases.

Key Words	*Clostridium difficile* enteritis; *Clostridium difficile* infection; fulminant *Clostridium difficile*

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Case Description

The patient is a 39-year-old man who had sigmoid resection for diverticulitis in 2005. He developed multiple subsequent adhesive small bowel obstructions and eventually underwent laparotomy with small bowel resection and mesh repair of an incisional hernia in 2017. In December 2019, he presented to the emergency department (ED) with one week of abdominal pain, non-bloody postprandial diarrhea, and 15-pound weight loss. He had a normal colonoscopy one year prior. Computed tomography (CT) of the abdomen/pelvis was unremarkable, but his white blood cell count was elevated at 15,000 cells/mm^3. He subjectively improved with intravenous fluids, declined hospital admission, and was discharged home with plans for gastroenterology follow-up.

He re-presented a week later to the ED with persistent symptoms. Repeat CT of the abdomen/pelvis demonstrated mild wall thickening throughout the entire colon and rectum as well as splenomegaly. He was admitted to the medicine service and started on intravenous ceftriaxone and Flagyl® for empiric treatment of colitis. Gastroenterology was consulted. Colonoscopy with biopsies demonstrated friable mucosa and yellow pseudomembranes with exudate extending from the rectum to the ascending colon, consistent with diffuse active colitis with some features of chronicity. *Clostridium difficile* (*C. difficile*), glutamate dehydrogenase (GDH) antigen, and toxin immunoassays were negative. The patient refused inpatient management and left the hospital against medical advice with a prescription for 14 days of oral vancomycin that he subsequently claimed to complete.

He returned to the hospital four weeks later with persistent diarrhea, worsening weight loss, and dehydration. Repeat CT of the abdomen/pelvis demonstrated wall-thickening of the cecum, ascending colon, and rectum concerning for colitis. Multiple loops of the small bowel in the pelvis also demonstrated mild wall thickening. White blood cell count was mildly elevated at 12,000 cells/mm^3. The patient again declined hospital admission and was instructed to follow up with gastroenterology. *C. difficile* GDH antigen and toxin immunoassays were available after discharge and were found to be positive. The ED notified the patient, and he subsequently returned to the hospital for admission and medical management of *C. difficile* colitis.

The patient was admitted to the medicine service for treatment with oral and rectal vancomycin in combination with intravenous metronidazole. CT of the abdomen/pelvis obtained two days after admission demonstrated small bowel dilation to 3 cm. Two days later, a repeat CT of the abdomen/pelvis showed worsening small and large bowel dilation concerning for ileus (Figure 1). A nasogastric tube was placed with some improvement in nausea. After ten days of inpatient medical management of C. difficile colitis, he was transferred to the surgical service. He then developed worsening abdominal distension, tachycardia, fever, and decreased urine output. He was transferred to the surgical intensive care unit and offered operative intervention.

Exploratory laparotomy revealed dense adhesions requiring four hours of difficult enterolysis. In addition to total abdominal colectomy (TAC), a jejunal resection was needed for an unavoidable iatrogenic enterotomy. Because of sepsis with increasing intraoperative vasopressor requirements, no anastomosis or stoma was constructed, and a negative pressure dressing was placed. The patient returned to the operating suite multiple times for subsequent abdominal washouts, further resection of nonviable jejunum with ultimate primary anastomosis, repair of ileal enterotomy, and end-loop ileostomy. Pathologic examination demonstrated *C. difficile* enterocolitis involving the jejunum and, predominantly, the right colon and pseudomembranes throughout the entire colon.

Postoperatively, antibiotic treatment included intravenous metronidazole, vancomycin per nasogastric tube, vancomycin per stoma, and vancomycin enemas. However, due to persistent ileus and significant bowel dysfunction, it is unlikely that the medicine was reaching and being absorbed by areas of the small bowel affected by *C. difficile*. Because of persistent *C. difficile* enteritis (CDE) and lack of clinical improvement, fecal microbiota transplant (FMT) was considered. He underwent esophagogastroduodenoscopy and FMT in the distal duodenum. FMT is typically completed using 50 grams of donor stool (fresh or frozen) emulsified in 250 mL of sterile saline. Particles are typically reduced to 1 to 2 mm in width to prevent obstruction of the insertion tube. Approximately 250 mL of donor stool emulsion was instilled in the fourth portion of the duodenum. Antibiotics were held for at least seven days after the transplant, and his tachycardia, ileus, and leukocytosis slowly resolved.

He returned to the operating room on the same day as the FMT for abdominal wound closure with biologic mesh. His postoperative course was complicated by the development of an enterocutaneous (EC) fistula through the mesh, which was treated nonoperatively with bowel rest and total parenteral nutrition. The patient was advanced to a liquid diet and discharged to a long-term acute care facility for nonoperative management of the fistula and close outpatient follow-up. He was referred to a large academic quaternary center for operative management of the EC fistula. Approximately seven months following his original operation for *C. difficile* colitis, he underwent complex EC fistula takedown with ileorectal anastomosis, loop jejunostomy, and primary fascial closure. It has been approximately two months since this procedure. Per chart review, the patient is recovering well, although he remains on total parenteral nutrition. He has not had any recurrence of the EC fistula.

Discussion

The initial differential diagnosis for this patient included infectious colitis, inflammatory colitis, and ischemic colitis. He had an unknown antibiotic history before presentation and was not immunocompromised. *C. difficile* testing was originally negative, despite visualization of pseudomembranes on flexible sigmoidoscopy. Testing for infectious colitis, including stool cultures and ova and parasite evaluation, was negative.

The most recent Infectious Diseases Society of America Clinical Practice Guidelines recommend *C. difficile* testing with GDH antigen and toxin.[1] The *C. difficile* toxin test varies in sensitivity and may have a high rate of false negatives. Nucleic acid amplification testing should be used if the GDH antigen and toxin enzyme immunoassays provide contradictory results. Repeat testing should not be performed for at least seven days following a negative result.[1]

Although pseudomembranes in the colon suggest *C. difficile* colitis, there are other causes, such as Behcet's disease, collagenous colitis, inflammatory bowel disease (IBD), ischemic colitis, drugs, and toxins.[2] Patients with IBD are at an increased risk for concomitant *C. difficile* colitis.[3] The patient had no personal or family history of IBD, and the final pathologic examination of the surgical specimen did not suggest IBD. The patient did not have extraintestinal symptoms or known exposures to drugs or toxins. It is possible that the patient initially presented with infectious colitis, received intravenous ceftriaxone and Flagyl®, and then four weeks later developed *C. difficile* colitis. A study evaluating the relationship between cumulative antibiotic exposure and risk of *C. difficile* infection demonstrates increasing risk with increasing dose, a number of antibiotics, and days of antibiotic exposure.[4] He did have a history of regular ranitidine use, dating back to September 2018. Ranitidine has been associated with cases of recurrent *C. difficile* in both pediatric and adult populations.[5,6]

The clinical spectrum of *C. difficile* infection ranges from asymptomatic to life-threatening fulminant colitis. The patient described in this vignette is best categorized as having *Clostridium difficile* colitis complicated first by patient nonadherence and then by medical management failure. Although success rates of initial treatment for *C. difficile* are high, especially in mild cases, this patient failed routine pharmacotherapy.[7] After treatment with oral and rectal vancomycin combined with intravenous metronidazole for ten days, he required emergent operative intervention.

Postoperatively, the patient had persistent ileus that likely impaired the effectiveness of oral and per stoma vancomycin. FMT was considered after postoperative medical management failed for persistent refractory enteritis. Other options for recurrent or refractory *C. difficile* infection include fidaxomicin. This drug is associated with lower recurrence than vancomycin (15.4% versus 25.3%), but a ten-day regimen of oral therapy costs approximately $2,800.[8] Studies do not support the use of IV metronidazole as an adjunct in patients with refractory or recurrent *C. difficile* enterocolitis.[9,10]

FMT is best described for treating recurrent disease, defined as *C. difficile* recurring within eight weeks of successful medical management.[11] Recurrence rates for standard oral vancomycin after an initial *C. difficile* infection range from 15 to 30% but increase to 40 to 50% with more than two recurrent episodes.[7] Risk factors associated with recurrent disease are concomitant antibiotic use, elderly patients, presence of comorbidities, use of proton pump inhibitors, and severe initial disease. The American College of Gastroenterology recommends the management of the first recurrence with vancomycin, and FMT should be considered for the third recurrence.

Although the optimal route of FMT instillation has not yet been determined, options include enema therapy, nasojejunal tube delivery, or endoscopic introduction using a gastroscope or colonoscope. FMT capsules are noninferior to FMT delivery by colonoscopy but are not recom-

mended in patients with persistent ileus.[9,10] The protocol for FMT delivery by endoscopy is not yet standardized. Smaller volumes and slower rates are utilized to decrease the risk of aspiration, the most common complication.[12] Across all transplantation modalities, FMT is cost-effective and clinically effective, with a *C. difficile* colitis resolution rate of 87 to 92%.[8] There is no standardized minimum washout period between antibiotic therapy and treatment with FMT. However, studies have demonstrated that vancomycin-treated patients maintained concentrations of vancomycin in their stool for four to five days following treatment, whereas metronidazole is only detected during treatment.[13] Most FMT protocols recommend patients stop taking antibiotics for 24 to 48 hours before the procedure.[12] Antibiotics should be held for at least seven days after FMT instillation.

Guidelines released in 2018 by the British Society of Gastroenterology and Healthcare Infection Society recommended the use of FMT for both recurrent and refractory CDE.[14] We suggest that FMT be considered a treatment option in patients with ileus, for whom delivery of oral vancomycin to the affected areas of the small and large bowel may not be possible. Small studies suggest the efficacy of FMT as a first-line treatment for *C. difficile* infection, but these results have yet to be confirmed in more extensive trials.[15]

Although the role of FMT in recurrent and refractory *C. difficile* infection is still evolving, multiple clinical trials are in progress to evaluate safety and efficacy. A multicenter, randomized, placebo-controlled clinical trial assessing the effectiveness of microbiota-based treatments for recurrent *C. difficile* is currently entering stage three.[16] Another clinical trial evaluating the utility of FMT in cases of recurrent, severe, and refractory *C. difficile* is in the recruitment stage.[17]

Conclusion

This is a rare case of CDE with jejunal perforation and without a known diagnosis of IBD or previous TAC. Surgeons should be aware of the manifestations of small bowel complications and be prepared to treat the enteritis component of *Clostridium difficile* enterocolitis. Physicians should not underestimate the utility of FMT and its potential role in refractory and recurrent cases of CDE.

Lessons Learned

Surgeons should be aware of and be prepared to treat the enteritis component of *Clostridium difficile* enterocolitis. Fecal microbiota transplant is a cost-effective therapeutic option and highly effective in treating refractory *Clostridium difficile* enterocolitis.

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