CLINICAL VIGNETTE

Fulminant *Clostridioides difficile* Infection in a 50-Year-Old Male

Rahul Vasavada, MD and Shelley Schwartz, MD

Introduction

Clostridioides difficile (*C. difficile*) causes nearly 500,000 infections annually with clinical severity ranging from mild disease to fulminant colitis. Fulminant infection is a rare but life-threatening condition with high mortality rates.[1] Appropriate management requires an understanding of disease pathophysiology, risk factors as well as disease severity. This patient progressed to fulminant *C. difficile* colitis and highlights the management of patients with severe and/or recurrent disease as well as fulminant infection.

Case Presentation

A 56-year-old male with Crohn's disease, nephrolithiasis, hypertension, and major depressive disorder presented to the emergency room (ED) with three days of abdominal pain associated with nausea, chills, and diarrhea. The patient reported that he went camping a few days prior, and subsequently developed bilateral lower quadrant colicky abdominal pain. He reported associated watery, non-bloody diarrhea as well as nausea without emesis. He had poor recent oral intake and chills without fevers. The patient increased his prednisone dose after symptoms started, but ran out of prednisone the past two days.

His Crohn's disease was initially diagnosed at the age 20. He reports three prior small bowel resections, (last occurring over ten years ago). He has been maintained on adalimumab and low dose prednisone. He had two recent hospitalizations for increased abdominal pain six months and six months prior to his current presentation. His recent hospitalization included colonoscopy which showed minimal erythema of the ileocolonic anastomosis and normal visualized ileal and colonic mucosa. He was treated for a urinary tract infection with five-days of levofloxacin.

In the ED, the patient was afebrile, and normotensive, but tachycardic in the low 100 range. Physical examination was notable for bilateral lower quadrant abdominal tenderness without rebound or peritoneal signs as well as dry mucous membranes. Laboratory results were remarkable for an acutely elevated creatinine of 4.7 mg/dL (baseline of 1.0), and markedly elevated white blood cell (WBC) count of 26.5 x 10^3/µL, erythrocyte sedimentation rate of 113 mm/hr and C-reactive protein (CRP) of 53.8 mg/dL. CT of the abdomen and pelvis revealed pancolitis with diffuse colonic wall thickening, with initial concern for infection versus inflammatory bowel disease flare. Gastroenterology was consulted.

Stool testing revealed positive for both Norovirus as well as *Clostridioides difficile* toxin B by PCR. The patient was started on oral vancomycin and intravenous fluid resuscitation. Despite rapid improvement in kidney function, his WBC count continued to increase to a peak of 30 x 10^3/µL. Watery diarrhea and abdominal pain continued. Infectious disease recommended switching antibiotics from oral vancomycin to fidaxomicin. Following this change his WBC count gradually decreased to 23-25 x 10^3/µL with ongoing but improved lower quadrant pain and with about five daily loose stools.

On hospital day seven, he developed a fever to 101F with tachycardia and increasing WBC to 27.8 x 10^3/µL. CRF increased to 266 mg/dL. Blood cultures and lactic acid levels returned negative, and intravenous metronidazole was added. The patient experienced progressively worsening lower quadrant abdominal pain with nausea and guarding. Stat CT abdomen/pelvis revealed worsening pancolitis with increased severe wall thickening of the transverse colon and increased dilation of the transverse colon (measuring 7 cm) concerning for toxic megacolon. Colorectal surgery consulted, and after risk - benefit discussion, the patient was taken urgently to the operating room. He underwent exploratory laparotomy with successful open total abdominal colectomy and end ileostomy. Following definitive surgical management of fulminant *C. difficile* colitis and adequate post-operative recovery, the patient was discharged.

Discussion

Clostridioides difficile (formerly termed *Clostridium difficile*) was first identified in 1935. Gram-positive, anaerobic, toxin-producing bacteria cause antibiotic-associated colitis.[1] Following disruption of the colonic microbiome (often due to antibiotics), *C. difficile* is able to colonize the colon inducing intestinal mucosal inflammation and injury by releasing exotoxins A and B.[2] Stool toxin levels correlate with disease severity. Toxin B has more than ten times virulence as toxin A.[2] Interestingly, a minority of patients with nontoxogenic *C. difficile* strains (not secreting A or B) have colonization without any pathogenic effects.

C. difficile is transmitted via fecal-oral ingestion, with high incidence of nosocomial transmission. Studies have shown handwashing with soap and water is more effective than alcohol-based hand sanitizers for removal of *C. difficile* spores.[1] Strict contact precautions with thorough hand hygiene is recommended. Entities that disrupt the colonic microflora raise the risk of developing *C. difficile* infection. Antibiotics are the most clearly associated. Clindamycin, cephalosporins, broad-spectrum penicillins, and fluoroquinolones are the most frequently implicated antibiotics.[1] In addition, advanced age, chemotherapy, inflammatory bowel disease, gastric acid suppression, and hospitalization are strong risk factors predisposing to *C. difficile* infection.[3] The incidence of *C. difficile* infection is approximately 147 per 100,000 people, while carrier rates are approximately three percent of healthy adults and up to ten percent of hospitalized patients.[1,4] Since the early 2000s, *C. difficile* prevalence has increased significantly, with more severe disease. The general increase in antibiotic resistance may be a factor in the rising disease severity as well as emergence of a hyper-virulent *C. difficile* strain, ribotype 027, which was identified in the early 2000s.[1,4]

C. difficile causes a wide spectrum of disease severity, which categorized as non-severe infection, severe infection, and fulminant colitis. Severe disease cases are characterized by WBC count greater than 15 x 10^3/μL and creatinine greater than 1.5 mg/dL, while fulminant infections are associated with shock, ileus, and toxic megacolon.[5] According to the 2021 Infectious Diseases Society of America (IDSA) treatment guidelines, both severe and non-severe cases of *C. difficile* infection should be treated with either fidaxomicin 200 mg twice daily or vancomycin 125 mg four times daily orally for ten days.[5] If these antibiotics are unavailable, metronidazole can be used, but has higher treatment failure rates. Studies have reported similar cure rates with oral fidaxomicin and vancomycin. Patients treated with fidaxomicin have reduced recurrent infections.[5]

Recurrence is common in *C. difficile* infection and current treatment regimens can include a pulse tapered oral vancomycin regimen as well as extended courses of fidaxomicin. Patients with more than one recurrence, IDSA guidelines recommend administration of the monoclonal antibody bezlotoxumab. This is administered as a single infusion binding *C. difficile* toxin B. Randomized studies have shown efficacy in reducing recurrence of *C. difficile* infection.[5] For patients with three or more *C. difficile* infections or those with severe disease unresponsive to antibiotic therapy, are recommended for fecal microbiota transplant (FMT). FMT involves implanting stool microbiota from a healthy donor into patients with *C. difficile* infection. This can be administered orally, via nasojejunal tube, or via colonoscopy.[6] FMT has high cure rates ranging from 70-90% after 18 weeks, though there is risk of disease transmission and procedural complications.[7] FMT is not recommended in patients with inflammatory bowel disease or those who are significantly immunocompromised.[6]

Patients with fulminant *C. difficile* colitis manifesting with shock, ileus and/or toxic megacolon require more aggressive treatment, often including definitive surgery. Fulminant infection is rare, reported in approximately 3% of patients. Poor prognostic factors include WBC count greater than 20 x 10^3/μL, fever, hypotension, ileus, lactic acidosis, and failure to improve after three days of maximal medical therapy.[8] Mortality rates in fulminant *C. difficile* colitis are as high as 80%.[8,9] Patients with worsening sepsis, end-organ failure, peritonitis +/- perforation, colonic ischemia, and WBC count greater than 50 x 10^3/μL require surgical intervention. Either total abdominal colectomy in patients' perforation, abdominal compartment syndrome or necrosis or diverting loop ileostomy, in less severe cases.[9] Fortunately, multiple studies have shown improved mortality outcomes when early surgical consultation is obtained with severe and fulminant infection.[10,11] Stewart et al. reviewed patients with fulminant *C. difficile* colitis reported reduced mortality in patients undergoing surgery. Pooled adjusted odds ratio for mortality was 0.70 in patients undergoing surgery compared to medical management.[11] Early surgical intervention should be strongly considered in patients with concern for fulminant disease.

Conclusion

C. difficile infection causes a wide spectrum of disease severity, ranging from non-severe infection to fulminant colitis. Treatment options depend on disease severity as well as infection recurrence. Although rare, patients with *C. difficile* infection not responsive to maximal medical therapy or demonstrating evidence of end-organ failure, should have early surgical consultation, to reduce mortality associated with fulminant disease.

REFERENCES

1. **Guh AY, Kutty PK**. Clostridioides difficile Infection. *Ann Intern Med*. 2018 Oct 2;169(7):ITC49-ITC64. doi: 10.7326/AITC201810020. PMID: 30285209; PMCID: PMC6524133.
2. **Lyras D, O'Connor JR, Howarth PM, Sambol SP, Carter GP, Phumoonna T, Poon R, Adams V, Vedantam G, Johnson S, Gerding DN, Rood JI**. Toxin B is essential for virulence of Clostridium difficile. *Nature*. 2009 Apr 30;458(7242):1176-9. doi: 10.1038/nature07822. Epub 2009 Mar 1. PMID: 19252482; PMCID: PMC2679968.
3. **Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, Toye B, Beaudoin A, Frost EH, Gilca R, Brassard P, Dendukuri N, Béliveau C, Oughton M, Brukner I, Dascal A**. Host and pathogen factors for Clostridium difficile infection and colonization. *N Engl J Med*. 2011 Nov 3;365(18):1693-703. doi: 10.1056/NEJMoa1012413. PMID: 22047560.
4. **Guh AY, Mu Y, Winston LG, Johnston H, Olson D, Farley MM, Wilson LE, Holzbauer SM, Phipps EC, Dumyati GK, Beldavs ZG, Kainer MA, Karlsson M, Gerding DN, McDonald LC; Emerging Infections**

Program Clostridioides difficile Infection Working Group. Trends in U.S. Burden of *Clostridioides difficile* Infection and Outcomes. *N Engl J Med*. 2020 Apr 2;382(14):1320-1330. doi: 10.1056/NEJMoa1910215. PMID: 32242357; PMCID: PMC7861882.

5. **Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, Wilcox MH**. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. *Clin Infect Dis*. 2021 Sep 7;73(5):e1029-e1044. doi: 10.1093/cid/ciab549. PMID: 34164674.
6. **Peery AF, Kelly CR, Kao D, Vaughn BP, Lebwohl B, Singh S, Imdad A, Altayar O; AGA Clinical Guidelines Committee**. Electronic address: clinicalpractice@gastro.org. AGA Clinical Practice Guideline on Fecal Microbiota-Based Therapies for Select Gastrointestinal Diseases. *Gastroenterology*. 2024 Mar;166(3):409-434. doi: 10.1053/j.gastro.2024.01.008. PMID: 38395525.
7. **Kassam Z, Lee CH, Yuan Y, Hunt RH**. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. *Am J Gastroenterol*. 2013 Apr;108(4):500-8. doi: 10.1038/ajg.2013.59. Epub 2013 Mar 19. PMID: 23511459.
8. **Adams SD, Mercer DW**. Fulminant Clostridium difficile colitis. *Curr Opin Crit Care*. 2007 Aug;13(4):450-5. doi: 10.1097/MCC.0b013e3282638879. PMID: 17599017.
9. **Butala P, Divino CM**. Surgical aspects of fulminant Clostridium difficile colitis. *Am J Surg*. 2010 Jul;200(1):131-5. doi: 10.1016/j.amjsurg.2009.07.040. Epub 2010 Apr 21. PMID: 20409527.
10. **Hall JF, Berger D**. Outcome of colectomy for Clostridium difficile colitis: a plea for early surgical management. *Am J Surg*. 2008 Sep;196(3):384-8. doi: 10.1016/j.amjsurg. 2007.11.017. Epub 2008 Jun 2. PMID: 18519126.
11. **Stewart DB, Hollenbeak CS, Wilson MZ**. Is colectomy for fulminant Clostridium difficile colitis life saving? A systematic review. *Colorectal Dis*. 2013 Jul;15(7):798-804. doi: 10.1111/codi.12134. PMID: 23350898.