A 31-year-old, HIV-Positive Man Presenting with Emesis and Bloody Diarrhea

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A 31-year-old man with a history of HIV-seropositivity with a last known CD4 count of 136/mm$^3$, hypertension, and hepatitis B presented to the emergency department with a chief complaint of emesis for 2 days and bloody diarrhea for 2 weeks. The patient had been seen earlier in the day by his primary care physician who referred him to the emergency department. He also complained of fever, chills and abdominal pain, and reported a 40-pound weight loss over six months. At the time of presentation, the patient was experiencing severe, dull, diffuse, nonradiating abdominal pain that was relieved with defecation. He noted up to 15 episodes of small volume bloody diarrhea daily. His appetite was decreased. He had no dysphagia or odynophagia.

The patient reported a recent hospitalization for treatment of *Pneumocystis jiroveci* pneumonia. The patient denied any significant surgical history or family medical history. Medications included abacavir/lamivudine/zidovudine, didanosine, clotrimazole troches, hydrochlorothiazide, felodipine, clindamycin, primaquine, and trimethoprim/sulfamethoxazole. The patient had no known drug allergies. He denied tobacco, alcohol, or illicit drug use, but did admit to a previous incarceration. He had multiple professionally-applied tattoos.

Vital signs at presentation included a temperature of 39.6°C, a pulse of 129 beats per minute, a respiratory rate of 25/minute, a blood pressure of 104/65 mmHg, and a blood oxygen saturation of 97% on 2 liters of oxygen by nasal cannula. The patient was alert, and oriented, but appeared to be ill and in significant pain. He had dry lips, oral candidiasis, anicteric sclerae, and reactive pupils. A nasogastric tube and nasal cannulae were in place. The neck was supple and without masses or lymphadenopathy. The cardiovascular exam was significant for tachycardia, and the patient’s lungs were clear to auscultation bilaterally. The abdomen was distended, demonstrated hyperactive bowel sounds, and was exquisitely tender to minimal palpation. His stool was grossly bloody. The rest of the physical examination was unremarkable.

Serum chemistries on presentation revealed a sodium of 130 mmol/L (normal range, 135-146 mmol/L), potassium of 4.9 mmol/L (3.6-5.2), chloride of 94 mmol/L (96-110), bicarbonate of 21 mmol/L (24-32), blood urea nitrogen of 28 mg/dL (7-25), creatinine of 5 mg/dL (0.6-1.2), glucose of 125 mg/dL (65-99), calcium of 8.7 mg/dL (8.4-10.3), magnesium of 1.3 mg/dL (1.5-2.6), and a phosphorous of 5.4 mg/dL (2.5-4.7). A liver function panel revealed an albumin of 2.0 gm/dL (3.4-5.0), total protein of 5.4 gm/dL (6.0-8.0), total

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**Disclosure**
Dr. DiBuono has nothing to disclose.
Dr. Saavedra has nothing to disclose.
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**Target Audience**
The January/February Clinical Case of the Month is intended for general practitioners, medicine subspecialists including gastroenterologists and infectious disease specialists, emergency medicine physicians, and radiologists.

**Educational Objectives**
The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to better identify and understand the pathophysiology, clinical presentation, diagnosis, and treatment of *C. difficile*-associated colitis.

Estimated time to complete this activity is 1 hour.
bilirubin of 0.8 mg/dL (<1.3), AST of 48 U/L (<45), ALT of 16 U/L (<46), and an alkaline phosphatase of 63 U/L (20-120). The patient’s blood count revealed a white blood cell count of 46 x 10³/uL (4.5-11.0 x 10³) with a differential of 41% neutrophils, 26% bands, 12% lymphocytes, 11% monocytes, 6% metamyelocytes, 3% myelocytes, and 1% promyelocytes; hemoglobin of 13 gm/dL (12-16); hematocrit of 40% (35-46%); platelet count of 449 x 10³/uL (130-400 x 10³); mean corpuscular volume of 89 FL (80-100); and RDW of 16% (11.5-14.5%). Coagulation studies revealed a prothrombin time of 15.1 sec (10-13), an INR of 1.3 (0.9-1.1), and a partial thromboplastin time of 30.3 sec (24-35). Serum lipase was <10 U/L (<61); amylase was 307 U/L (25-115); LDH was 485 U/L (<201); cortisol was 57.8 mcg/dL (3-16); and lactic acid was 5.5 mmol/L (0.3-2.4).

Plain films of the abdomen revealed a minimal amount of small bowel-associated gas but the study was limited by motion artifact. A computed tomogram (CT) of the abdomen and pelvis was limited by inadequate oral contrast, but the presence of ascites and the lack of contrast extravasation were noted (Figure 1).

The patient was started on intravenous metronidazole for empiric treatment of _Clostridium difficile_ colitis and intravenous ceftriaxone for concern of possible bowel infection. Despite aggressive volume resuscitation, the patient required the addition of vasopressors to maintain stable hemodynamics. The abdominal exam became increasingly concerning, and the patient was subsequently taken to the operating room for an exploratory laparotomy.

Exploratory laparotomy revealed the presence of copious amounts of ascitic fluid and a thickened, edematous, and inflamed large bowel wall. The patient underwent a subtotal abdominal colectomy and ileostomy. The resected colon demonstrated extensive pseudomembrane formation (Figure 2). Pathologic analysis of colonic specimens revealed pseudomembranous colitis involving the entire segment of colon and extending to the distal surgical margin (Figure 3). The patient had an extended and complicated hospital course and ultimately died approximately six weeks after admission.

**DISCUSSION**

_Clostridium difficile_-associated colitis is a common nosocomial infection affecting the large bowel. It occurs in approximately 10% of patients who are hospitalized for more than two days, with a significantly smaller incidence in outpatients. This bacterium, an anaerobic Gram-positive rod, colonizes the gastrointestinal tract following alteration of the normal gut flora in patients treated with antibiotics. Typically, infection with _C. difficile_ occurs in close temporal proximity to antibiotic administration and is dose-related. In addition, symptoms usually resolve with withdrawal of the offending agent, presumably due to normalization of the gut flora. The clinical presentation of _C. difficile_ ranges from asymptomatic patients to those with fulminant colitis. The severity of disease usually corresponds to the degree of toxigenicity of the particular strain, with less toxigenic strains causing milder symptoms and more toxigenic strains causing pseudomembranous colitis. The incidence of _C.
*difficile* colitis may increase with the emergence of more highly toxigenic strains.4

**CLINICAL PRESENTATION**

Patients with *C. difficile*-associated infections are variable in their presentation(s) ranging from asymptomatic carriers to those with fulminant colitis and megacolon.5 Patients will typically present after treatment with antibiotics. While most infected individuals present between 5 and 10 days after initiation of antibiotic therapy, presentation may occur as early as one day after beginning treatment, or as late as 10 weeks after cessation. In fact, approximately 30% of patients become symptomatic after antibiotics have been discontinued.2 Factors influencing the type of presentation include presence of toxin receptors on enterocytes, the amount of toxin present, and the presence or absence of *C. difficile* antibodies in the blood.

Many patients may be asymptomatic carriers of *C. difficile*, exhibiting no diarrhea and no physical findings consistent with infection. These patients may, however, serve as reservoirs of *C. difficile* by constantly shedding the spores in their stool.1 This state may exist due to the presence of specific antibodies which target the *C. difficile* toxin. The most common presentation, however, is acute diarrhea. Patients may experience mild symptoms including loose watery stools, abdominal discomfort, fever, and mild leukocytosis. It is important to be certain that the diarrhea in these patients is secondary to infection and not osmotic in nature, as this will impact management. Bloody diarrhea is a less frequently observed finding in *C. difficile* infection which may be seen in patients with concomitant inflammatory bowel disease.

Other patients will have more severe presentations including colitis without pseudomembrane formation. These patients may exhibit frequent diarrhea, malaise, fever, anorexia, and nausea. In addition, they may have right lower quadrant abdominal pain which is relieved with bowel movements. Endoscopy performed in these patients may reveal patchy areas of inflammation. Pseudomembranous colitis is a more severe variant which includes all of the sequelae described above plus pseudomembrane formation on the gut wall and mural thickening on CT of the abdomen.

A less frequent presentation of *C. difficile* infection is fulminant colitis, occurring in approximately 2-3% of infected patients. This presentation may include severe pain and abdominal distention, as well as dehydration, decreased urine output, and systemic toxicity.6 Air fluid levels, thumbprinting (submucosal bowel wall edema), and a scalloped appearance of the bowel wall may be evident with radiographic imaging. Megacolon, defined as an observed lumen of 7 centimeters or greater in diameter, may develop as well. This can increase the risk of perforation, with point tenderness, decreased bowel sounds, and abdominal rigidity noted on physical exam.7 Other presentations include protein losing enteropathy with resultant hypoalbuminemia, ascites, and edema, relapsing infection in 10-20% of patients following treatment, and *C. difficile* infection complicating inflammatory bowel disease.5,8

**PATHOGENESIS**

*C. difficile* is an anaerobic Gram-positive rod which produces spores that can be found ubiquitously in places such as day care centers, nurseries, restrooms, and hospital wards. The spores are typically transmitted fecal-orally and can colonize the intestinal mucosa once ingested. Once mucosal invasion occurs, protein exotoxins (toxin A and/or toxin B, depending on the strain of *C. difficile* in question) produced by *C. difficile* bind to receptors on the surfaces of intestinal cells. The binding of these toxins to the cells initiates a cascade of cellular events which may eventually lead to colitis with pseudomembrane formation.

Initially, normal function of cells is disrupted by *C. difficile* as actin filaments break down. Cellular necrosis ensues, and shedding of brush border cells occurs. This results in the formation of shallow mucosal ulcers in the areas of highest toxin concentration, as well as fluid secretion which leads to diarrhea. Inflammatory cells infiltrate the area and the release of cellular mediators and cytokines occurs. This, in turn, leads to the outflow of proteinaceous mucoid material from the ulcers and...
formation of pseudomembranous summit lesions that appear as yellowish raised plaques resting atop edematous bowel wall. The depth of involvement of the bowel wall in pseudomembranous colitis may vary in severity, ranging from superficial mucosal involvement (Type 1), to destruction of glands and basal lamina (Type 2), and, most extensively, to full thickness involvement with severe necrosis and pseudomembrane formation (Type 3).

RISK FACTORS

While many different factors may predispose patients to colonization with C. difficile, the most important risk factor is recent antibiotic therapy. Although some antibiotics have been more closely linked to this infection than others, virtually any antibiotic may place the patient at risk, even metronidazole and vancomycin which are typically the mainstays of treatment for C. difficile. The antibiotics which have been most often associated with this infection are ampicillin, amoxicillin, various cephalosporins, and clindamycin. Of these, clindamycin appears to be the most predisposing, with as many as 2% of patients treated with clindamycin eventually developing infection. In addition to these antibiotics, fluoroquinolones are increasingly associated with the development of C. difficile infection.

Risk of colonization is also related to exposure to infected individuals, such as hospitalized patients. Healthcare personnel may decrease the incidence of transmission by observing proper infection control measures, the most important of which is handwashing. Infants have been shown to be frequent carriers as well, although they are usually asymptomatic, presumably because the immature brush border of the infant gut lacks the appropriate receptors for the toxin. Other factors that contribute to the risk of colonization include gastrointestinal surgery with alteration of gut flora, long term treatment with proton pump inhibitors which may increase the pH thereby creating a more hospitable environment for organisms, and NSAID use. Enteral tube feeding may also be associated with C. difficile transmission, presumably secondary to handling by hospital personnel, decreased fiber content of tube feeds, or contamination of the feeds themselves.

DIAGNOSIS

Lab tests available for diagnosing infection with C. difficile include ELISA-based immunoassays for the presence of the toxin in stool samples and cytotoxin-targeted bioassays which look for the effect of the cytotoxin on fibroblasts in culture.

The cytotoxic assay, which is widely regarded as the gold standard for diagnosis, carries a sensitivity of 94-100% and specificity of 99%. In this test, a diluted stool sample is applied to cultured fibroblasts. The presence of C. difficile cytotoxin will result in rounding of the cultured cells. Specificity is tested by the addition of C. difficile antibody to the culture. If the rounding effect is neutralized, then C. difficile cytotoxicity is confirmed. If not, the cytotoxicity is regarded as nonspecific. While very sensitive and specific, this assay has drawbacks including high cost and the 2 to 3 days required for test results to become available.

ELISA tests are more widely available and more frequently used. These tests are easier and cheaper to perform, and are usually based on the presence of toxin A. This test has a lower sensitivity (approximately 70-90%) than cytotoxic assays because strains producing toxin B or a mutated variant of toxin A will result in false negatives. The specificity for this test is 99%.

No specific recommendations exist for endoscopy in patients with positive stool tests and clinical signs and symptoms of C. difficile infection. Findings that may be observed with flexible sigmoidoscopy include edema, erythema, and presence of pseudomembranes; however, in patients with more severe presentations, the risk of perforation with minimal air insufflation is greatly increased. In addition, flexible sigmoidoscopy will miss more proximal lesions in the absence of proctosigmoiditis. For patients with a negative stool ELISA for C. difficile-associated toxin, it is recommended that ELISA be repeated or cytotoxin bioassay performed if available. If suspicion is still high despite negative results, empiric treatment is warranted.

TREATMENT AND PROGNOSIS

Treatment of C. difficile infection includes discontinuation of the offending agent when possible. The majority of patients recover with minimal recurrences with cessation of antibiotics alone as opposed to a 10-20% reported relapse rate in those treated with antibiotics. Supportive care with correction of fluid losses and electrolyte imbalances is important. Antiperistaltic agents generally should be avoided since they may delay the clearance of C. difficile toxin from the stool.

Indications for antibiotic treatment of C. difficile include evidence of colitis with systemic symptoms, persistence of diarrhea despite cessation of the presumed offending agent, and the necessity for continued antibiotic therapy to treat the underlying infection. Antibiotics are generally not considered in asymptomatic carriers unless the presence of an outbreak is observed. The typical antibiotic regimen consists of oral metronidazole 250 mg four times daily or 500 mg three times daily, or oral vancomycin 500 mg four times daily, with the duration of treatment usually lasting 10-14 days. In severe cases or in pregnant patients, vancomycin may be preferred over metronidazole. In the presence of an ileus, intravenous metronidazole may be used though intraluminal concentrations are variable. Vancomycin retention enemas may be used in addition to intravenous metronidazole. Importantly, intravenous vancomycin is not useful, as it is not excreted into the colon.

Surgical intervention may be indicated if peritoneal signs
are observed, or if the patient has progressive symptoms with worsening leukocytosis and persistent diarrhea despite medical therapy. The treatment of choice is a subtotal colectomy with ileostomy. In severe disease, the risk of medical therapy. The treatment of choice is a subtotal colectomy with ileostomy. In severe disease, the risk of medical therapy. The treatment of choice is a subtotal colectomy with ileostomy. In severe disease, the risk of medical therapy. The treatment of choice is a subtotal colectomy with ileostomy.

REFERENCES

CME QUESTIONS

Read the preceding CME article and complete the registration, evaluation, and answer form on page 55 to earn CME credit. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to January 31, 2008. Participants must attain a minimum score of 75% to receive credit.

Choose the one answer that is most correct for each question.

1. All of the following are true concerning *C. difficile*-associated infections except:
   a. Infection with *C. difficile* occurs in close temporal proximity to antibiotic administration and is dose-related.
   b. The clinical presentation of patients infected with *C. difficile* ranges in spectrum from asymptomatic patients to those with fulminant colitis.
   c. While most infected individuals present between 5 and 10 days after initiation of antibiotic therapy, presentation may occur as early as one day after beginning treatment, or as late as 10 weeks after cessation.
   d. *C. difficile*-colitis occurs in approximately 75% of patients who are hospitalized for more than two days.

2. True or false: Virtually any antibiotic may place the patient at risk for *C. difficile*-associated colitis, even metronidazole and vancomycin which are typically the mainstays of treatment for *C. difficile*.

3. All of the following are true concerning *C. difficile* infections, except:
   a. Fluoroquinolones are increasingly associated with the development of *C. difficile* infection.
   b. Lab tests available for diagnosing infection with *C. difficile* include ELISA-based immunoassays for the presence of the toxin in stool samples and cytotoxin-targeted bioassays which look for the affect of the cytotoxin on fibroblasts in culture.
   c. Antiperistaltic agents are routinely recommended for patients with *C. difficile*-colitis.
   d. Intravenous vancomycin is not useful in the management of *C. difficile*-colitis.

4. True or false: Because of the potential severity of disease and the high risk for recurrence, follow-up testing for *C. difficile* toxin is generally recommended.