Title

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CLINICAL VIGNETTE

Revisiting Clostridium Difficile Infection

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Clostridium difficile infection is commonly seen in patients in the healthcare setting. It is typically associated with prior or current broad-spectrum antibiotic use and can be successfully treated with oral antibiotics chosen based on the severity of the infection.

Case Report

A 92-year-old female with a history of hypertension and chronic stage three kidney disease, presented to the emergency department complaining of diarrhea, abdominal pain, and nausea. Approximately one month prior to admission, she was admitted at an outside hospital for similar symptoms and was found to have C. difficile infection. At that time, she was treated with oral metronidazole, 500 milligrams (mg) every eight hours, with subsequent resolution of her diarrhea and abdominal pain. She was then discharged to a skilled nursing facility where she completed a total course of fourteen days of metronidazole, after which she was discharged home. Two days later, she developed voluminous, foul-smelling diarrhea. It did not improve with over-the-counter antidiarrheals and continued to worsen with accompanying abdominal pain, nausea, and vomiting.

Physical examination was remarkable for tachycardia and severe abdominal pain, left greater than right. She did not have any rebound tenderness, guarding, or rigidity. Routine lab testing was remarkable for a white blood cell count of $25.1x10^3/\mu L$ with 80% neutrophils and bands, a normal lactate, and a normal creatinine. A stool sample sent for enzyme immunoassay (EIA) testing was positive for C. difficile toxin. CT scan of the abdomen and pelvis was remarkable for markedly edematous large bowel wall with mucosal enhancement indicating pancolitis. There was no free air or fluid collection (Figure 1).

She was admitted for intravenous hydration and oral vancomycin, 125mg four times a day. By the next hospital day, her white blood cell count increased to $41.7x10^3/\mu L$ (with bands), her abdominal tenderness increased, and her lactate increased to 27 mg/dL-milligrams per deciliter (normal 6-20 mg/dL). An abdominal series was remarkable for colonic wall "thumbprinting" consistent with colitis (Figure 2). Intravenous metronidazole, 500mg every eight hours, was added to her regimen. Over the next five days, the patient's symptoms improved with resolution of her diarrhea. The metronidazole was stopped, and she continued on oral vancomycin. Her white blood cell count decreased to $18.22x10^3/\mu L$, and she was discharged to a skilled nursing facility to finish a fourteen-day total course.

Discussion

Clostridium difficile infection (CDI) is defined by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) as (1) the presence of diarrhea (3 or more loose stools in 24 hours) and (2) a positive stool test for C. difficile toxin or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis.[1] However, patients with an ileus, either from the infection or from opioid use (i.e. postoperative patients), may not have diarrhea.[2] In mild to moderate CDI, patients have a white blood cell count of $15x10^3/\mu L$ or less and a serum creatinine of less than or equal to 1.5 times their baseline level.

Otherwise, they have severe CDI. Severe, complicated (or fulminant) CDI includes those patients with hypotension/shock, ileus, or toxic megacolon[1], and is reported to occur in 3-8% of patients with CDI.[3]

C. difficile is the causative pathogen for 20-30% of cases of antibiotic-associated diarrhea, resulting in 3.4-8.4 cases per 1,000 acute care admissions. More worrisome is the rate at which CDI is rising, doubling between the years 2000 and 2003. Mortality remains low, occurring in less than 2% of patients. However, morbidity and health care costs are substantial, with an estimated cost of $3.2 billion per year in the US.[1]

The strongest risk factor for the development of CDI is prior antibiotic use, with a relative risk increase of 5.9.[2] Antibiotics strongly associated with the development of CDI include fluoroquinolones, clindamycin, broad spectrum penicillins, and broad spectrum cephalosporins. Hospitalized patients and residents in a long-term care center have much higher rates of colonization of C. difficile (10-25% and 4-20%, respectively) versus the general population (2-3%), and thus are at higher risk of CDI. Patients 65 years and older are up to 20 times more likely to develop CDI versus younger patients.[1,2] In addition, patients on acid-suppressive therapy may be at increased risk.[4] Risk factors for the development of severe, complicated CDI include a white blood cell count greater than $16x10^3/\mu L$ at the start of therapy, inflammatory bowel disease, operative therapy within the last 30 days, and a history of intravenous immunoglobulin (IVIG) therapy.[5]

Diagnosis of CDI is made primarily by stool testing. It is important to note testing cannot distinguish colonization from infection, and thus the entire clinical picture must be taken into account before the diagnosis of CDI can be made. At UCLA, toxins A and B can be detected in stool samples by EIA, or toxin B can be detected in fresh stool samples via tissue culture toxin neutralization test. EIA testing is most commonly used. It has a turnaround time of 24 hours, a specificity of 99%, and a sensitivity of 60-95%.[6] Given the somewhat high false negative rate, serial testing may be performed with an approximate increase in sensitivity of 12%.[7] Tissue culture is considered the gold standard, with a specificity of 99% and a sensitivity of 94-100%.[8,9] However, it is less commonly used given it has a turnaround time of 48 hours and is more expensive. The detection of pseudomembranous colitis on colonoscopy is diagnostic of CDI, though has a sensitivity of only 51-55%. CT imaging can show colonic wall thickening, pericolonic stranding, and ascites, but is neither sensitive nor specific for CDI.[1,2]

Treatment guidelines for CDI have recently been updated to reflect the epidemic NAP1/BI strain of C. difficile, which is more virulent.[1,10] Metronidazole achieves relatively low fecal concentrations whereas oral vancomycin achieves high fecal concentrations, such that any decrease in organism susceptibility may make metronidazole less effective.[1] In addition, one randomized control trial and one abstract suggest benefit of vancomycin versus metronidazole in severe CDI.[11,12] Therefore, there has been a shift in treatment recommendations for CDI. Previously, the initial episode of CDI was treated with metronidazole as first-line therapy, regardless of severity.[13] Now, the SHEA/ISDA guidelines recommend treatment based on severity (Table 1).

Table 1: Treatment of *Clostridium difficile* Infection (CDI)	
Episode/Severity	Treatment
Initial episode Mild to moderate	Metronidazole 500mg PO TID x10-14 days
Initial episode Severe	Vancomycin 125mg PO QID x10-14 days
Initial episode Severe, complicated	Vancomycin 500mg PO QID + Metronidazole 500mg IV Q8H. If complete ileus, consider adding rectal instillation of vancomycin.
First recurrence	Treat as initial recurrence above based on severity.
Second recurrence	Vancomycin 125mg PO QID x14 days then 125mg PO BID x7 days then 125mg PO daily x7 days then 125mg PO QOD x8 days then 125mg PO every 3 days x15 days
Adapted from 1,14	

Of note, patients with mild CDI may not require treatment, resolving in up to 23% of patients simply by removing the offending antibiotic.[13,15] Severe, complicated cases may require colectomy and a surgical consultation is advised. Various new treatments are currently being studied: monoclonal antibodies directed against both the A and B toxins[16]; intravenous immunoglobulin therapy[17]; and probiotics.[1] These treatments are not recommended at this time, though monoclonal antibodies appear promising.

Prevention of transmission of the C. difficile spores in healthcare settings is of utmost importance. Handwashing with soap and water are effective in reducing transmission, while alcohol-based cleaning products are not.[18] Moreover, patients with suspected or confirmed CDI should be placed on contact isolation.

Conclusion

Infection from Clostridium difficile is an ever-increasing problem in healthcare. Patients at risk for CDI are patients on antibiotics, elderly patients 65 years and older, and patients who are hospitalized or reside at long-term care facilities. Diagnosis is made by testing the stool for the toxin produced by C. difficile and by clinical symptoms of frequent, foul-smelling loose stools. Treatment should be initiated based on both the severity of the infection and whether it is the initial episode or a recurrence. Vancomycin is now preferentially recommended over metronidazole in patients with severe infection.

FIGURES:

Figure 1: CT scan of the abdomen and pelvis showing an edematous large bowel wall with mucosal enhancement (arrows).

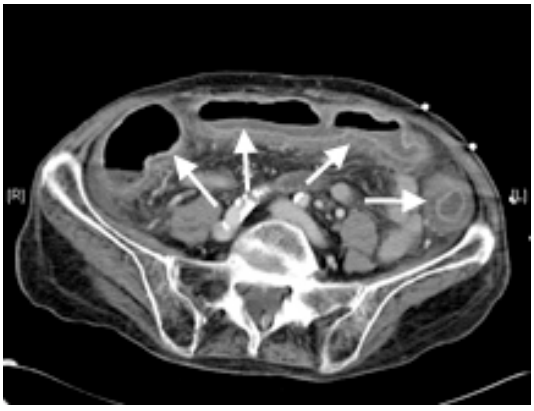
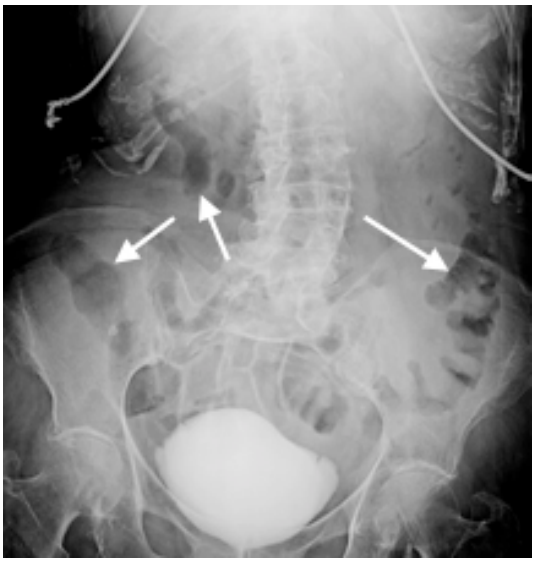


Figure 2: Abdominal x-ray showing "thumbprinting" (arrows) indicative of colonic wall edema.



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