**Clostridium difficile**: An uncommon presentation of an increasingly common infection

Kaila Pomeranz, OMSIII  
KPomeranz96@midwestern.edu

Charles Finch, D.O., FACOEP  
Clinical Professor of Emergency Medicine  
CFinch@midwestern.edu
Abstract

This clinical case describes a healthy 6 year old female presenting to the outpatient clinic with frequent, watery diarrhea after a course of antibiotics prescribed for acute sinusitis. She was subsequently diagnosed with *Clostridium difficile* Infection (CDI). *Clostridium difficile* Infection is a toxin mediated diarrheal illness typically presenting in adults during or within a few weeks of antibiotic use or a hospital stay. Antimicrobials perpetuating infection include Clindamycin, Cephalosporins, and other broad spectrum antibiotics. Primary treatment regimens includes oral Metronidazole for mild cases, or intravenous or oral Vancomycin for cases of increasing severity. Patients initially present with copious, frequent, watery diarrhea. The sequellae of the disease can range from resolution of mild diarrhea to pseudomembranous colitis, toxic mega colon, sepsis and death. *Clostridium difficile* Infection rarely affects the pediatric population. The incidence in the pediatric population is estimated at 24.2/100,000 cases per year. However, *Clostridium difficile* Infection has demonstrated an increasing incidence in this population over the past decade -- rising from 7.24 to 12.80 cases per 10,000 discharges. Antibiotic use within the past 12 weeks and the North American pulsed-field electrophoresis type 1 strain (NAP1), are associated with more severe outcomes in children. In the past decade, broad-spectrum antibiotic use has increased, with prescriptions increasing from 223 to 400 (per 1000 persons). This clinical presentation illustrates the importance of identification of increased antibiotic use, antibiotic resistance, as well as antibiotic associated illnesses in children. Programs that target decreasing antibiotic usage can make a significant impact on antibiotic resistance and antibiotic associated illness.
Introduction

*Clostridium difficile* is a toxin producing, gram positive (Figure 1), spore-forming bacteria. Asymptomatic colonization is frequent in infants. However, by the age of 12 months, colonization decreases to levels of non-hospitalized adults, less than 3%.\(^6\),\(^9\) Several risk factors are associated with CDI. Among them, immunodeficiency disorders, inflammatory bowel disease, cystic fibrosis, proton pump inhibitors, and frequent antibiotic usage.\(^9\) These risk factors are shared by both adult and pediatric populations. Several studies have demonstrated the course of infection in children. One particular study examined 944 cases across varying geographical areas of the United States. It was found that majority of the antibiotic associated cases were cephalosporins and penicillins and that 84% of the cases were being treated with antibiotics for ear, upper respiratory, and sinus infections.\(^6\)

CDI is a toxin-mediated infection. The typical route of infection is ingestion of spores through fecal-oral entrance. The spore form is ingested and germinates into the vegetative form, which colonizes the gastrointestinal tract. Once colonized, the toxins are released. The best understood toxins being toxins A, B, and cytolethal distending toxin (CDT).\(^9\) Toxins A and B cause the symptomatic effects of CDI. An interaction between toxins A and B results in buildup of neutrophils and monocytes leading to inflammation and degradation of epithelial cells in the colon.\(^4\) When a patient is taking antibiotics, the normal flora of the colon are removed, allowing *C. diff* to overgrow. Toxin A is an enterotoxin that interferes with the villi in the colon and the adherence of the mucosa to the basement membrane. Toxin B induces apoptosis by acting as a cytotoxin.\(^4\) In addition, toxins A and B cause disturbance of the tight junctions, allowing further inflammation. The emergence of a strengthened strain with altered binding sites, NAP 1, is a possible reason for the increase in incidence. This strain produces increased amounts of toxin A and toxin B and was the most common strain responsible in one study (23% of CDI).\(^10\)

A history of copious, frequent diarrhea following antibiotic use elevates the index of suspicion for CDI in children. Testing is not typically indicated in infants below 12 months secondary to the high rate of asymptomatic colonization.\(^5\),\(^9\) There are several tests available to diagnose CDI, each with limitations and differing sensitivities and specificities. The stool culture, or cytotoxigenic culture looks for the presence of organism, and is beneficial because it is able to distinguish toxigenicity, but it takes several days to complete. The cell cytotoxicity assay (CTTA) looks for the presence of toxin and is quicker to complete. Other methods such as polymerase chain reaction (PCR), laboratory findings such as increased ESR, CRP, low serum albumin, or leukocytosis can aid in diagnosis but are not specific for CDI. None of the tests are with 100% specificity, and because the prevalence is lower in the pediatric population, there is a low positive predictive value with false positives. The sensitivity and specificity values of these tests have not been extensively looked at in pediatric cases, but the CTTA results have shown similar sensitivity results to adults.\(^5\) When faced with a clinical picture and other causes of diarrhea has been ruled out, it is important to have a high index of suspicion for CDI. When considering *C diff*, the first course of action is to discontinue the offending antibiotic. Use of empiric antibiotics while awaiting laboratory results remains controversial and is recommended only for the gravely ill patient. The current primary regimen for mild to moderate infections is oral Metronidazole for 10-14 days.\(^7\) For severe or complicated infections or with multiple recurrences of infection, oral Vancomycin is the treatment of choice.\(^1\)
Case

The patient is a 6 year old caucasian female presenting with watery diarrhea after a course of antibiotics. She was initially placed on Cefdinir 250 Mg/5 mL (6 mL daily for 10 days) for an episode of acute sinusitis. After four days of treatment, she developed diarrhea and was switched to a Amoxicillin 250 Mg/5 mL (5 mL twice daily). Her mother noted that her stools were loose and continuing to increase in frequency, with up to 15-20 non-bloody, watery, bowel movements per day. The patient’s oral temperature never reached higher than 100.9 degrees. Her mother reported that she had decreasing oral intake, and within fifteen minutes of solids or liquids, she would experience diarrhea. She noted a change in odor of her stool, and described it as “mucousy and green.” The patient was having 15-20 non-bloody, watery, bowel movements per day.

Our patient has no significant past medical history. Birth history was uncomplicated. She was born full term by emergency caesarean section due to prolonged labor, weighing 9 lbs 1 oz. Vaccinations are up to date. She has no past surgical history, is not on any medication, and has no known medication or environmental allergies. Upon arrival to the clinic, patient appears weak and tired.

On exam, vitals signs revealed a height of 44 inches, weight 42 pounds. Her blood pressure is 90/62, heart rate 102 bpm, oral temperature of 98.9 degrees, respiratory rate 28 breaths per minute, and a room air saturation of 96%. Her general examination revealed a well-developed six year old female who appeared tired, weak, and clinically dehydrated. Mucus membranes were dry. TM’s clear bilaterally, nose and posterior pharynx clear. Neck exam revealed no evidence of meningismus. Cardiac exam noted a tachycardic, regular heart rhythm without any murmurs, rubs, or gallops. Lung sounds present bilaterally. Abdomen soft with diffuse abdominal cramping. No rebound or guarding. Bowel sounds present, and no abdominal masses palpated. Extremities had full range of motion. Pulses intact. Skin without rashes, although tenting present in the extremities. Neurologic exam is without any focal findings.

At the time of the office visit, the patient had already stopped the inciting antibiotic (stopped day 9 of 10) and was sent home with instructions to begin a probiotic, obtain a stool culture, to include ova and parasite, over the next three days, giardia, and C. diff toxin assay.

Over the next two days, the patient continued to have frequent, loose watery stools, and presented to the Emergency Department, as mother concerned about dehydration. A CT Scan of the abdomen revealed diffuse colitis. She was discharged with a course of oral Ciprofloxacin for 10 days, Metronidazole for 10 days, Dicyclomine, and Ondansetron, with diagnosis of presumed CDI. With positive CDI test results, she stopped Ciprofloxacin and continued a 10 day course of oral Metronidazole (250 mg every 8 hours). She returned to normal health with follow up stool testing negative for CDI. Within one week, symptoms returned and the patient was admitted to the pediatric intensive care, secondary to sepsis secondary to diffuse CDI colitis, complicated by hypovolemic shock. She was treated with a second course of Metronidazole, had one more recurrence, which was treated with a Vancomycin taper over 45 days. After completion of treatment with each episode of infection, the patient tested negative for CDI.
Discussion

Initially and with mild CDI, oral Metronidazole or Vancomycin is used for 10-14 days. If the initial episode is categorized as severe with signs of systemic toxicity, oral Vancomycin is the preferred treatment and can be used for 10-14 days.\textsuperscript{4} Recurrence of symptoms within the first few weeks after terminating antibiotic treatment can be seen in up to 20-30\% of patients after first infection\textsuperscript{14}, and is more often seen from Metronidazole use in the first event of CDI.\textsuperscript{7} Mild recurrence can be treated conservatively with symptomatic therapy. With a more severe or second recurrence, Vancomycin is often used in a tapered fashion, to target the bacteria when it is in the vegetative state.\textsuperscript{4} Oral medication is preferred to intravenous administration, but intravenous or intracolonic antibiotics can also be used. Therapies such as fecal microbiota transplants (FMT) are increasing in use for these patient populations. Antibiotic use severely depletes the natural gut microbiota that acts as protection for the patient. The theory is to replace the gut microbiota with healthy bacteria, which is found to be beneficial in patients who have recurrent infection.\textsuperscript{14} In small pediatric studies, it has been demonstrated that prior to FMT, the bacterial diversity of patients with recurrent CDI is decreased. After FMT, it is shown that several colonic bacteria, including, \textit{Firmicutes} and \textit{Bacteroides}, increase to levels that approach those of the donor.\textsuperscript{14} Several studies have demonstrated that through thorough testing of donors, it is a seemingly safe, relatively quick, and effective alternative to traditional treatment.

Additionally, osteopathic manipulative treatment (OMT) has shown to be a beneficial adjunct for treatment of infectious diarrhea. Diarrhea can present with overactivation of the parasympathetic activity in the pelvic splanchnic and vagus nerves.\textsuperscript{8} Utilizing OMT techniques to balance the parasympathetics and treating the affected Chapman’s reflexes can improve symptoms. Visceral treatments or deep inhibitory pressure to T10 can decrease tenesmus and pain associated with bowel movements.\textsuperscript{8}

Over the past decade, the incidence of CDI in children and adults has increased. With difficult to treat infections and increasing antibiotic resistance, it is important to prevent and control the infection rates. Control takes place by decreasing susceptibility of patients and by preventing transmission of the organism. The spore form of \textit{C. diff} is difficult to control because of its resistance to commonly used alcohol gels and typical cleaning agents. In addition, the resistance to antibiotics is growing.\textsuperscript{4} When a hospital patient acquires CDI, contact precautions need to be initiated to avoid spread of the organism. Washing hands with soap and water has demonstrated to be more effective than alcohol based rubs.\textsuperscript{4} With pediatric cases, it is important to keep the child home from school or daycare while symptomatic.

An additional method to minimizing infection rates is through antibiotic stewardship and decreasing the frequency of antibiotic use. Several studies demonstrate the benefit of proper antibiotic use and the benefits of initiating programs to decrease unnecessary use. Thorough examination of ensuring the diagnosis is established, the antibiotic is narrow spectrum, prescribed for the correct duration, and monitored for follow up to ensure it is stopped appropriately at the end of the course of treatment.\textsuperscript{13} UC Davis Children’s Hospital\textsuperscript{2} initiated an antibiotic stewardship program in which antibiotic use was monitored three times a week. Antibiotics were stopped if no longer needed and children were switched to narrow-spectrum antibiotics as allowed. Additionally, less expensive antibiotics were used and dosages were adjusted based off of several factors of organ function or weight. The hospital saw CDI rates
decrease from 9.2/10,000 to 2.8/10,000 infections. As we look at the increasing rates of not only CDI but other potentially deadly infections that are often acquired after medical treatment or hospital stays in the adult and pediatric populations it is imperative to look at what we can do to reverse this trend.

**Abbreviations**

CDI: Clostridium difficile infection; NAP1: North American pulsed-field electrophoresis type 1 strain; CDT: cytolethal distending toxin; CTTA: cell cytotoxicity assay; PCR: Polymerase chain reaction; FMT: Fecal microbiota transplant; OMT: Osteopathic manipulative treatment

**Acknowledgements**

I would like to thank Charles Finch, DO, for his mentorship and assistance with writing this case. I would also like to thank Dr. Farah Lokey, MD, for her preceptorship and guidance.

**References**


Figure 1. Gram stain of *Clostridium difficile.*

*Cited from:* http://www.asmusa.org/division/c/photo/cdiff1.JPG