REVIEW ARTICLE

Clostridium Difficile Colitis: Epidemiology, Diagnosis, Treatment and Modalities

Vincenzo A. Barbato, DO[1]; Robert Hasty, DO, FACOI[2]; Ilya Fonarov, DO[3]; Pedro Valdes, DO[4]; Qassam Jabbar, DO[5]; Jeff Klein, MD, FACEP[6]; John Reed, MD[7]

[1]Fellow in the Palmetto General Hospital Cardiology Fellowship
[2]Associate Dean for Postgraduate Affairs at Campbell University Jerry M. Wallace School of Osteopathic Medicine
[3]Program Director of the Internal Medicine Residency Program at Palmetto General Hospital/Nova Southeastern University School of Osteopathic Medicine and Hospitalist within Jackson Memorial Hospital System
[4]Fellow in the Palmetto General Hospital Cardiology Fellowship
[5]Internal Medicine Resident at Palmetto General Hospital/Nova Southeastern University School of Osteopathic Medicine
[6]Associate Director, Emergency Department, Southeastern Regional Medical Center
[7]Medical Director, Emergency Department, Southeastern Regional Medical Center

KEYWORDS:
C Diff
Clostridium difficile
Toxic megacolon
Unexplained leukocytosis

Clostridium difficile infection (CDI) or Clostridium difficile colitis is an infection that causes significant morbidity and mortality. It accounts for 20-30% of antibiotic associated diarrhea and is occurring more often in the absence of antibiotics. It is the leading cause of hospital associated diarrhea. The organism has a remarkable ability to thrive outside of the colon, making hand washing and other preventative measures particularly important.

The diagnosis of CDI involves obtaining a stool specimen positive for toxigenic Clostridium difficile or Clostridium difficile toxins. Pseudomembranous colitis findings during colonoscopy may also be utilized to make the diagnosis. Polymerase chain reaction (PCR) test is the ideal testing method because it is highly sensitive and specific and results may be obtained in approximately one hour.

The treatment of CDI involves terminating the offending agent followed by antimicrobial therapy dictated by these classifications:

1. Mild, moderate or severe
2. Complicated vs. non-complicated
3. First episode, first recurrence or second recurrence

Metronidazole and vancomycin remain the initial treatment of choice, but other considerations such as possible offending agents, severity of disease and number of previous episodes are also of great importance. There are several other treatments available including fecal microbiota transplant although this is reserved for severe cases or third recurrences. However the best way to combat the disease remains through preventative measures such as proper hand sanitation.

INTRODUCTION

Clostridium difficile infection (CDI) is a disease process that causes significant morbidity and mortality. It is caused by a gram-positive bacterium and classically causes colitis when fecal microflora are altered by antibiotics, causing an environment where this bacterium can flourish. This review will discuss epidemiological, diagnostic, and treatment considerations of this important clinical entity.

Address correspondence to: Robert Hasty, DO, FACOI, Campbell University School of Osteopathic Medicine; and Southeastern Health, Lumberton, NC; Email: hasty02@srmc.org

EPIDEMIOLOGY OF CLOSTRIDIUM DIFFICILE

CDI accounts for 20-30% of cases antibiotic-associated diarrhea and is the most common cause of healthcare-associated diarrhea, including long term nursing facilities.[24] Clostridium difficile is a gram-positive, spore-forming, anaerobic bacterium which is usually spread by the fecal-oral route. This bacterium possesses the ability to exist in both spore forming and vegetative forms. Vegetative cells have the ability to form spores under adverse conditions. The spore form preserves the bacteria from heat, dessication, and starvation. When conditions become more favorable for survival the spore form becomes the vegetative cell. Outside of the colon, Clostridium difficile has the durability to survive in the spore form, being resistant to acids, antibiotics, and heat. In the colon the spores convert to the toxin producing vegetative form, which is prone to death by certain antimicrobial agents.[12, 17]

The two toxins that are produced by Clostridium difficile have the ability to bind to the receptors of endothelial cells. These are known as toxins A and B. Toxin A is an enterotoxin and toxin B is a cytotoxin. Once bound to receptors on endothelial cells, mucosal injury, inflammation, and diarrhea may result. Toxin B is approximately ten times more potent than toxin A in regards to causing colonic mucosal damage.[17]

CDI is defined as the acute onset of diarrhea, (the passage of three or more unformed stools within 24 hours or less), and either a stool test result positive for toxigenic Clostridium difficile or Clostridium difficile toxins. Histologic findings on colonoscopy that exhibit pseudomembranous colitis can also be utilized to make the diagnosis. The earliest cases of CDI were identified soon after the widespread use of antimicrobial agents. Colonization by the organism was facilitated by altering the normal intestinal flora by use of antibiotics. One of the earliest culprits for causing infection was the antibiotic clindamycin, which continues to be a threat today. In the early 1990s there were large outbreaks of infection in four different hospitals within the United States due to a strain of Clostridium difficile in individuals who used clindamycin. This resistant strain is known as the J strain.[17] Since the early 2000s, a new highly-virulent strain has arisen. This new strain is known by various names (based upon clinical isolation techniques), such as NAP1, B1, and 027. It produces an additional toxin that is not present in other strains of Clostridium difficile. In vitro studies have shown this new strain to produce 16-23 times more toxins A and B than do other strains. It is also fluoroquinolone resistant.[12, 17]

There has been an increased appreciation of the importance of community associated CDI, occurring in the setting of no antibiotic exposure since 2005.[4] Although, antibiotic use is the most frequent risk factor for CDI, there are several other risk factors that have shown to increase incidence of infection. Some of these risk factors are hospitalization, gastric acid suppression, chemotherapeutic agents, and gastrointestinal surgery.

Since the year 2000, the rate of CDI has been increasing worldwide. A larger increase has been appreciated in people over the age of 65 with an increase from 22.4/10,000 to 49/10,000 between the years 2000 to 2005. Additionally, there has been an increase in the morbidity associated with CDI, resulting in a greater relative percentage of major complications, such as toxic megacolon and infections that require colectomy.[22]

DIAGNOSING CLOSTRIDIUM DIFFICILE INFECTION

Historically, CDI was primarily found in individuals with recent antibiotic use, the elderly, and those with prior hospitalizations. However, CDI infection is becoming more prevalent among young healthy individuals in the community setting.[4]

Clostridium difficile toxin may cause shallow ulcerations on the colonic mucosal surface. The pseudomembranes exhibit yellow or whitish plaques that can be as large as two centimeters in diameter.[16] Other findings that may be observed on colonoscopic examination are colonic wall erythema, inflammation, and edema. In rare cases, a symptomatic patient may present with colonic distention and ileus with little or no diarrhea.[5] According to the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA), it is recommended to only test for Clostridium difficile in patients with diarrhea, unless ileus is present.[5,12,22] The clinical spectrum by which CDI may present is wide. It ranges from an asymptomatic carrier state to toxic megacolon. Toxic megacolon is a medical emergency with the potential for emergent surgery. It is defined as radiographic evidence of colonic distension plus at least three of the following:

1. Fever greater than 38 degrees Celsius
2. Heart rate greater than 120 beats/minute
3. Anemia
4. Leukocytosis greater than 10,500/microL

There must also be at least one of the following:

1. Evidence of dehydration
2. Altered mental status
3. Electrolyte imbalances
4. Hypotension[23]

For approximately three decades, the two primary reference tests for diagnosing CDI were the Clostridium difficile cytotoxin neutralization assay (CCNA) and the toxigenic culture (TC).[22] Although the toxigenic culture has a high sensitivity, it is not widely used because of the amount of time it takes to grow the culture.[12, 22] It may take approximately two days for the culture to grow and there is a fair amount of labor required when compared to other methods of diagnosis that are available. Nucleic acid amplification testing (NAAT) for Clostridium difficile toxin genes, implementing Polymerase Chain Reaction (PCR), is superior to the enzyme immunoassay (EIA) for toxins A and B.[22] A great benefit of using real time PCR is that results may be available in approximately one hour. It is a highly sensitive and specific test. However, due to its potential for false positive results, some sources favor using PCR in combination with either EIA for toxins A and B or an EIA for glutamate dehydrogenase (GDH). GDH is an enzyme that is produced by all isolates of Clostridium difficile. The detection of GDH antigen does not distinguish between toxigenic and nontoxigenic strains, making this test useful only when combined with PCR. The turn-around time for this test is less than an hour.[16,22]

CLOSTRIDIUM DIFFICILE INFECTION TREATMENT

An important first consideration in treating CDI is to discontinue any antimicrobial agent that might be implicated in the infection whenever possible. The patient's disease severity must then be stratified into mild, moderate, or severe. Further categorization as complicated or non-complicated, first episode, first recurrence, or second recurrence all play into the decision-making process when choosing the proper antibiotic regimen as well as the duration of treatment for patients with Clostridium difficile colitis.[5,12,22] See Table 1 summarizing the key features of treating Clostridium difficile infection.

Table 1: Clostridium difficile Treatment Reference Guide

Clinical Category	Clinical Data	Treatment
Mild-Moderate Colitis (Initial Episode)	- WBC <15,000 - Creatinine <1.5 baseline	Metronidazole 500mg PO three times per day for 10-14 days.
Severe Colitis (Initial Episode)	- WBC >15,000 - Abdominal tenderness - Albumin < 3g/dl - Creatinine >1.5 baseline	Vancomycin 125mg PO four times per day for 10-14 days.
Severe, Complicated (Initial Episode)	- Hypotension/ Shock - Ileus - Toxic Mega Colon - Lactate levels >2.2mmol/L - End organ failure	Vancomycin 500mg PO four times per day and Metronidazole 500mg IV three times per day for 10 to 14 days with Surgical Consultation
First recurrence		Same as initial episode
Second recurrence		Vancomycin Taper
Third recurrence		Fecal Microbiota Transfer

Mild-moderate infection is described as three or more poorly formed stools per day with associated leukocytosis less than 15,000 cells/micro liter and a serum creatinine level within 1.5 times the normal baseline for the patient. For a first suspected episode, involving a mild-moderate infection, the consensus recommendation for treatment is metronidazole 500mg by mouth, three times per day for 10-14 days. If a patient has an allergy or intolerance to metronidazole, vancomycin 125mg orally four times per day may be substituted.[5,22]

Severe infection is classified as three or more poorly formed stools per day with associated leukocytosis greater than 15,000 cells/micro liter and an increase in baseline creatinine level of 1.5 times the normal baseline for the patient. In this case, the suggested treatment, as agreed upon by the Infectious Disease Society of America, is oral vancomycin 125 mg by mouth four times per day for 10-14 days. It is important to note that intravenous vancomycin has very poor gut mucosa penetrance and will therefore not be effective in fighting a colonic infection. However, via oral ingestion peak levels of vancomycin reach very high concentrations within the colon leading to excellent treatment results. Complications of severe infections can consist of toxic megacolon, ileus, hypotension, lactic acidosis, respiratory failure, renal failure, and septic shock. In these cases the dose of vancomycin administered is 500 mg oral or via rectal retention enema four times per day with added metronidazole 500 mg IV three times per day. In the case of patients suffering from an ileus, enema treatments are recommended. Also when encountering a patient with severe CDI, a surgical consultation is recommended. Early surgical intervention in cases of toxic megacolon have shown to decrease the mortality from 22 to 1.2%.[12]

For first recurrence of infection the treatment regimen is considered the same as initial therapy. For a second recurrence, a vancomycin taper or pulsed regimen should be administered. This consists of standard dosing therapy with vancomycin 125 mg oral four times per day for 10-14 days then a reduction to 125 mg twice daily for one week followed by 125 mg daily for one week and lastly 125 mg every two to three days for two to eight weeks is recommended.[5,12,22]

Newer agents recently added to the armamentarium to treat Clostridium difficile colitis include fidaxomicin, tygecycline, and fecal microbiota transfer. Fidaxomicin has been proven to be non-inferior to vancomycin for recurrent Clostridium difficile infection, however, this was not evaluated in severe or complicated cases of colitis and cost concerns have been reported.[6,7,20,22] In regards to tygecycline, there have been several anecdotal case reports of its use against Clostridium difficile after other alternative treatments have failed.[9,15,18,19] Additionally, the American Gastroenterological Association suggests individuals with a third recurrence of CDI should be considered for a fecal microbiota transplant.[2,14,22]

PREVENTION OF CLOSTRIDIUM DIFFICILE INFECTIONS

Patients with CDI can excrete large numbers of spores that contaminate hospital surfaces and the hands of healthcare workers. The spores can also contaminate healthcare devices and environmental surfaces and can persist on fomites for months. The cleaning products usually used to clean hospital surfaces do not contain sporicidal agents effective against Clostridium difficile.

CDI is linked to exposure via patient-to-patient transmission, healthcare worker to patient transmission, or coming into contact with contaminated surfaces. The prevention of CDI

includes strategies that include basic infection control and proper use of antibiotics. The following are some methods of prevention used by healthcare facilities:

1. Proper hand sanitation
2. Improving antibiotic use (stewardship)
3. Early and reliable detection of Clostridium difficile
4. Early contact isolation of symptomatic patients
5. Reducing Clostridium difficile contamination of health-care environmental services
6. Probiotics

Healthcare workers are the primary mode of transmission of Clostridium difficile spores. These spores can contaminate the hands of healthcare workers when they come into contact with infected patients and the surrounding environment. It is possible to have your hands contaminated even if you do not come into contact with the patient directly. Hand washing and the use of barrier methods such as gloves and gowns can help reduce this type of contamination. Glove use with strict adherence to changing gloves between each patient contact is the best proven method for prevention of becoming contaminated with the spores from symptomatic patients.[3] The combination of appropriate contact precautions and strict hand hygiene has been reported to reduce the incidence of Clostridium difficile infection by as much as 80%.[8] Studies show that alcohol-based sanitizers do not reduce the amount of Clostridium difficile spores on hands. Multiple studies show a preference for use of soap and water after caring for patients who are contaminated.[8] Neither alcohol nor soap will kill the spores, but when healthcare workers wash their hands properly with soap, most spores are removed because of friction and the detergent action of the soap.[10]

Antibiotic stewardship refers to the appropriate prescribing of antibiotics in order to reduce their unnecessary use. Antibiotics disrupt the normal protective bacterial flora of the lower intestine in a manner that increases the risk for developing Clostridium difficile colitis for three or more months.[3] Antibiotic use increases the risk of developing infections by seven to ten-fold while the patient is taking the antibioticand continues for one month after discontinuation.[3] Good antibiotic stewardship helps reduce the risk of developing the infection.

Patients who test positive for Clostridium difficile can be isolated early, which will prevent the transmission of the infection and lead to earlier treatment. Patients suspected or proven to be infected should be isolated with strict contact precautions in a private room. To prevent outbreaks of infection, contact precautions need to be maintained while awaiting the results of fecal tests. The Center for Disease Control (CDC) recommends contact precautions for the duration of illness when caring for patients with Clostridium difficile colitis.[8]

Rooms occupied by infected patients need to be cleaned with disinfectants that have a Clostridium difficile sporicidal label. Bleach solution should be used routinely for the terminal cleaning of the room during Clostridium difficile outbreaks as recommended by theSHEA/IDSA.[8] It is also important to educate environmental service personnel on how to properly decontaminate hospital surfaces, while not having them become contaminated in the process.

Although probiotics do not prevent acquiring the infection they reduce the diarrhea associated with it which may help decrease environmental contamination. In a meta-analysis of probiotic use for the prevention of Clostridium difficile associated diarrhea (CDAD) there was shown to be a protective effect. It demonstrated that out of 1000 persons treated with probiotics, 33 cases of CDAD were prevented in those patients receiving antibiotics.[13]

Based on the studies, they concluded that probiotics effectively reduce Clostridium difficile associated diarrhea.

CLOSTRIDIUM DIFFICILE INFECTION IN CHILDREN

Establishing a diagnosis of clostridium difficile infection in the pediatric population can present several challenges. Children below two years of age can have a high incidence of asymptomatic intestinal colonization with the bacteria, thus positive stool testing can represent an incidental finding. Testing for CD (clostridium difficile) in children younger than two years of age should be avoided in the absence of a strong suspicion of clinical infection due to the high rate of asymptomatic colonization and low probability of severe CD associated disease in this age group.

Historical findings of CD infection in children include the presence of 3 or more liquid or loose stools per day, symptoms that have been present for 5 or more days, and age greater than 24 months. Children at greater risk for CDI include those who have had antibiotic therapy within the last 6 to 10 weeks, hospitilization for greater than 72 hours, proton pump inhibitor therapy, presence of a feeding tube, immunocompromised state, inflammatory bowel disease, cystic fibrosis, Henoch-Schonlein purpura and hemolytic-uremic syndrome.[26]

Physical findings in the child with CD infection classically include a toxic appearance, fever of 102 degrees Fahrenheit or higher, abdominal tenderness and abdominal distension. It should be noted that children with severe CD infections may manifest with little or no diarrhea. In these cases, one must be alert for the presence of ileus or toxic megacolon. Severe CD

infections may also be present in an occult fashion manifested only by increased inflammatory markers, fever of unknown origin in the absence of abdominal symptoms or neutrophilia in the absence of abdominal symptoms.[26]

Definitive diagnosis of CD disease in children requires the presence of moderate to severe diarrhea (or ileus), and either a positive stool test for CD toxins or endoscopic findings of pseudomembranous colitis. It is important that when one is considering the diagnosis of CD infection in children, the differential diagnosis is lengthy and all alternative diagnoses must be considered. These alternative diagnoses include diarrhea of viral or parasitic origin, and bacterial infection due to Salmonella, Shigella, Yersinia, Campylobacter and toxigenic E-Coli. Finally, inflammatory bowel disease and neonatal necrotizing enterocolitis should also be considered as diagnostic possibilities.

The treatment of CD infections in the pediatric population includes those actions appropriate for adults, including culprit antibiotic and PPI discontinuation, supportive care and anti-CD antibiotic therapy. The antibiotic agents that are successful in treating CD infection in adults appear to be similarly effective in children.

FUTURE CONSIDERATIONS

Like any other disease process, the best way to combat Clostridium difficile associated colitis is through preventative measures. Immunological treatments are under development, which utilize the toxins A and B as targets. Lowy et al. reported a phase II double blinded placebo controlled trial on the efficacy of monoclonal antibodies against toxins A and B. With a 7% recurrence rate in the monoclonal antibody group versus a 25% recurrence rate in the placebo group (p-value<0.001,number needed to treat (NNT) for the recurrence rate: 25%-7% = 18% NNT = 100/18 or 5.6) this treatment modality is demonstrating promise.[21,23]

Foglia reported a vaccine which targets toxins A and B. Data exists that shows an initial intramuscular delivered vaccine was well tolerated in six phase I studies which incorporated a total of 200 subjects. This vaccine was able to induce an Immunoglobulin-G (IgG) response against toxins A and B in the majority of subjects.[11,24]

The most recent development is utilizing biotherapeutics, in other words, a non-toxigenic Clostridium difficile organism (NTCD). This NTCD can be given to patients with active infection and it will attach itself to bowel receptors, ultimately acting as a competitive antagonist to the pathogenic strain of Clostridium difficile, and blocking its ability to produce toxins. Phase I data demonstrated that the NTCD colonized stools of normal subjects following vancomycin treatment. Phase II studies were begun in 2011, and will test its ability to be used as a treatment modality to fight infection recurrence.[24,25]

The novel treatment modality for refractory Clostridium difficile colitis is the use of fecal transplantation. The concept is that people who have recurrent CDI have their normal intestinal flora imbalanced. One way to restore intestinal flora balance is to transplant the stool from a healthy donor into the diseased patient via colonoscope, enema, nasoduodenal or jejunal tube.[12] This notion has gained such popularity that the United States Food and Drug Administration (FDA) announced a public workshop, held in May 2013, entitled "Fecal Microbiota for Transplantation." The goal of the workshop was to provide a venue for the exchange of ideas and experiences with fecal microbiota transplantation. Fecal microbiota transplant is still in an investigational phase and is being regulated by the FDA. This modality should only be used as a last resort option and only performed in medical centers with experience in this procedure.[30]

SUMMARY AND FINAL THOUGHTS

Clostridium difficile is an anaerobic spore forming bacillus that is spread by spores and is acquired by patients via the fecal oral route. Patients with Clostridium difficile colitis can excrete large numbers of spores that contaminate hospital surfaces and the hands of healthcare workers and these can be transmissible to other patients potentially causing infection in them. It is an organism that causes substantial morbidity and mortality. We have effective treatments against the organism; however, it is becoming increasingly more common to see people relapse after completing an antibiotic course for Clostridium difficile colitis. Due to this observation, newer treatment modalities are being sought after which may come into play in the coming years. It is important to keep in mind, however, that all these treatment modalities are no substitute for the preventative strategies that can be utilized in the fight against this potent infectious process.

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