

PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 6 Number 6

June 2000

Clostridium difficile Lori Hamm, Pharm.D.

Clostridium difficile, a common gram-positive, spore-forming, anaerobic bacillus, is the leading cause of nosocomial diarrhea associated with antibiotic therapy. Clostridium difficile causes a variety of diarrheal syndromes, including C. difficile diarrhea, C. difficile colitis, antibiotic-associated C. difficile colitis, and pseudomembranous colitis, all of which vary widely in severity. Pseudomembranous colitis is an inflammation of the colon characterized by the presence of elevated lesions, or pseudomembranes, on the mucosal surface. Clostridium difficile is responsible for virtually all cases of pseudomembranous colitis.¹⁻⁵ This brief review will focus on the pathophysiology, diagnosis, treatment, and prevention of C. difficile infections.

Pathogenesis

Clostridium difficile colitis results from a disruption of the normal bacterial flora of the colon, colonization with C. difficile, and the release of toxins that lead to mucosal damage and inflammation. Antibiotic therapy is the key factor that is responsible for altering the colonic flora and allowing C. difficile to flourish. Colonization of C. difficile occurs through the oral-fecal route after antibiotic therapy has made the bowel susceptible to infection.¹

After colonization, the organism releases two protein exotoxins into the colonic lumen. Approximately 75% of C. difficile strains produce two toxins, A and B, that are responsible for causing diarrhea and colitis. Toxin A is an enterotoxin responsible for the colitis that allows Toxin B, a potent cytotoxin, to enter the cell. The binding of the toxins to membrane receptors produce toxic effects; both Toxin A and B produce inflammation of the mucosa and secrete a protein-rich exudate that contains neutrophils, monocytes, and sloughed enterocytes. Both

toxins are also responsible for activating cytokine release from monocytes.^{1,4,8} Diarrhea is caused by those toxins which are produced within the intestinal lumen and adhere to the mucosal surface.³

Epidemiology

Toxin-producing strains of C. difficile are carried in the normal colonic microflora of only about 5% of healthy adults.¹⁻³ However, 15% to 70% of neonates are carriers of C. difficile. This percentage varies as a result of the degree of hospital exposure, birth in an environment where C. difficile is abundant, or if the neonate obtained maternal antibodies through breast milk. Although neonates are more frequent carriers of C. difficile, they do not often develop pseudomembranous colitis unless gastrointestinal motility disorders or other conditions (eg, severe neutropenia with leukemia) are present to increase the risk. Neonatal resistance to C. difficile colitis is believed to be due to the inability of the toxins to attach to the mucosa of newborns, because of immature membrane toxin receptors, or the protection from the toxins by maternally-acquired antibodies. After the first year of life, the carrier rate gradually, reaching adult levels by three years of age.^{1,2}

Hospitalized patients, especially those receiving antibiotic therapy, are primary targets for C. difficile. Five to thirty-eight percent of patients receiving antibiotics experience antibiotic-associated diarrhea; C. difficile causes 15 to 20% of the cases. Several antibiotic agents have been associated with C. difficile. Broad-spectrum agents, such as clindamycin, ampicillin, amoxicillin, and cephalosporins, are the most frequent sources of C. difficile. Also, C. difficile infection has been caused by the administration of agents containing beta-lactamase inhibitors (ie, clavulanic acid, sulbactam, tazobactam) and intravenous agents that achieve substantial

colonic intraluminal concentrations (ie, ceftriaxone, nafcillin, oxacillin).^{3,6-9} Fluoroquinolones, aminoglycosides, vancomycin, and trimethoprim are seldom associated with *C. difficile* infection.⁸

Diagnosis

C. difficile infection can range from an asymptomatic carriage to pseudomembranous colitis with toxic megacolon.¹⁰ Symptoms usually appear during antibiotic therapy or up to 8 weeks after completing a course of antibiotics.³ An extensive range of symptoms are associated with *C. difficile* infection; the most common include watery diarrhea, abdominal cramping, fever $\geq 38^{\circ}$ C, leukocytosis $\geq 15,000$ cells/mm³, abdominal tenderness, and bloody diarrhea. Severe *C. difficile* colitis can lead to eight or more profuse watery, green, foul-smelling stools per day, along with nausea, vomiting, and anorexia.^{6,10,11}

The diagnosis of *C. difficile* infection should be considered in patients with diarrhea who have received antibiotic therapy within the previous two months and/or whose diarrhea began within 72 hours or more after hospitalization. A single stool specimen should then be sent for the presence of *C. difficile* and/or its toxins. With negative results and persistent diarrhea, one or two additional stools may be sent for the same test or additional tests.³ The cytotoxin assay is the "gold standard" laboratory test for detecting toxin B. This assay is highly sensitive (94-100%) and specific (99%) and takes 24 to 48 hours for results. Enzyme immunoassays (ELISA) detect toxin A or B and are more rapid (ie, 2 to 6 hours) than cytotoxin assays. These immunoassays are easier to perform and demonstrate excellent specificity (99%) but are less sensitive (70-90%) than cytotoxin assays. Several limitations have been recognized with ELISA toxin tests; these include false positive results with grossly bloody stool samples, false negative results if the toxin was not being shed by the isolate at the time the sample was obtained, lack of correlation with severity of the disease, and the inability to perform repetitive analyses because toxins degrade over time.^{6,11,12}

Other diagnostic tests include the latex agglutination test and stool culture. The latex agglutination test is convenient and inexpensive but not reliable. A stool culture is not specific for toxin-producing bacteria; thus, asymptomatic patients may have positive stool cultures because of colonization of nontoxigenic strains. Also,

stool culture results are unavailable for 2 to 5 days.^{2-3,6}

Endoscopy should only be pursued in special cases where rapid diagnosis is necessary, when no stool is available because the patient has an ileus, or when the differential diagnosis includes other colonic diseases.³ Procedures such as endoscopy, sigmoidoscopy and colonoscopy, have excellent specificities and sensitivities and provide immediate results. However, these procedures are expensive to perform, require trained personnel, and are contraindicated in patients with toxic megacolon due to the risk of bowel perforation.^{2-3,6}

Treatment

The first treatment of *C. difficile* infection should be to discontinue the causative antibiotic and allow the normal colonic flora to recover and the diarrhea to resolve. This approach alone has proven successful in approximately 15-25% of patients. In some patients, fluid and electrolyte replacement may also be necessary. With mild cases of *C. difficile* infection (ie, diarrhea with minimal symptoms), patients should be monitored for 48 hours for symptomatic improvement before treatment with an antibiotic is instituted. However, patients with more serious infections suggested by symptoms of high fever, pronounced leukocytosis, severe abdominal pain, and absence of diarrhea, may require antibiotic therapy immediately.^{2,9,13-14}

Vancomycin and metronidazole are the two primary antibiotics used in the treatment of *C. difficile* infection.^{1-3,6-7,9-14} A 7 to 10-day course of therapy is necessary with either agent in the treatment of *C. difficile* infections.^{3,14}

Oral metronidazole is the preferred oral agent of therapy.^{3,6,13-14} Metronidazole is readily absorbed in the upper gastrointestinal tract, and although usually well tolerated, systemic side effects can occur.^{1-3,6} Dosing recommendations for metronidazole are oral doses of 250-500 mg administered four times daily or 500-750 mg three times a day. If metronidazole is not tolerated orally, metronidazole can be given intravenously at a dose of 500-750 mg three or four times a day.^{3,14} Possible side effects of metronidazole include an unpleasant metallic taste, nausea, vomiting, diarrhea, abdominal pain, headache, pruritus, erythematous rashes, dizziness, and reversible neutropenia.^{1-3,6}

Vancomycin should be reserved for severe, life-threatening cases of *C. difficile* infection, for patients unable to tolerate metronidazole, or for patients without symptom resolution after completing a course of metronidazole. Vancomycin is more expensive than metronidazole and the emergence of vancomycin-resistant enterococci is also a concern.^{3,6,13-14} Oral vancomycin is not appreciably absorbed or metabolized, but is excreted in the stool unchanged, which is ideal for the treatment of *C. difficile* infection. Intravenous vancomycin should not be used, however, since bactericidal concentrations are not achieved in the colon.^{1-3,6} For vancomycin, oral doses of either 125 mg four times daily or 500 mg four times daily in adults are recommended. Both regimens have provided the same clinical outcome.¹⁴⁻¹⁵ The use of a rectal vancomycin enema (500 mg diluted in 1000 mL of 0.9% sodium chloride injection) is an alternative as described in several anecdotal reports.¹⁶

In 1983, Teasley et al performed a small, prospective, randomized trial which showed oral metronidazole 250 mg administered every 6 hours to be equivalent to oral vancomycin 500 mg administered every 6 hours in the treatment of *C. difficile* infection in adults. Response rates within six days of therapy were 98% with vancomycin and 93% with metronidazole, and eradication of *C. difficile* after 21 days of completing therapy was 26% versus 40%, respectively.¹⁵ Since then, other prospective, randomized comparisons have not shown significant differences between these two agents in the treatment of *C. difficile*.¹⁷⁻¹⁹

In the pediatric population, oral metronidazole has not been compared to oral vancomycin in the treatment of *C. difficile* infection. Recommended doses are 30-50 mg/kg/day divided every six hours for metronidazole and 40 mg/kg/day divided every six to eight hours for vancomycin. The oral vancomycin solution that is commercially available may prove to be more palatable than the extemporaneously prepared metronidazole suspension for children who are unable to swallow tablets.^{4,14} In severe cases, a combination of intravenous metronidazole and oral vancomycin has been used.²⁰ Alternative therapies for cases of mild *C. difficile* infection include bacitracin, teicoplanin, or a binding resin such as cholestyramine or colestipol. However, these agents are not as

reliable or as effective as vancomycin or metronidazole.^{3,14}

Approximately 10 to 20% of patients have a relapse of diarrhea from *C. difficile* infection after an initial course of antibiotic therapy. Failure to eradicate the organism or reinfection is a possible reason for these recurrences. Recurrent episodes traditionally respond to the same ten-day course of antibiotic therapy used with the first episode. Management of repeated relapses is more difficult; suggested options include a slow tapering of vancomycin or metronidazole, the use of rifampin or cholestyramine, bacteriotherapy with oral administration of nontoxicogenic *C. difficile*, or treatment with the yeast *Saccharomyces boulardii*. Due to the lack of data, no formal therapeutic recommendation for multiple relapses can be made at this time.^{1-3,10-11,14}

Prevention and Control

The first step in prevention of *C. difficile* infection is to limit the use of broad spectrum antibiotics.³ A substantial decrease in the prevalence of *C. difficile* infection after hospital formulary restriction of clindamycin has been successful.²¹ Another important intervention is handwashing before and after contact with all patients; *C. difficile* transmission from one person to another via the hands of hospital personnel is more prevalent than contact with environmental spores. Also, enteric (stool) isolation precautions should be instituted for patients with *C. difficile* infection. Gloves should be worn by all hospital personnel involved in the care of *C. difficile* patients, and contaminated objects should be properly disinfected. Most importantly, all hospital personnel involved in patient care should be educated about *C. difficile*, its epidemiology, treatment, and proper prevention and control.^{3,22}

Summary

Clostridium difficile is a common nosocomial pathogen that causes infectious diarrhea after toxin-producing strains invade and alter the normal bacterial flora of the colon. Neonates are the most frequent carriers of *C. difficile*, but rarely develop pseudomembranous colitis. The presence of this organism can be diagnosed by stool assays. Treatment begins with the discontinuation of the causative antibiotic and initiation of metronidazole. Vancomycin should be reserved for those patients who do not tolerate metronidazole or fail therapy with metronidazole.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 5/26/00:

1. Pneumococcal 7-valent conjugate vaccine (Prevnar[®]) was added to the Formulary. The recommended schedule is 0.5 ml given IM at 2, 4, 6, and 12-15 months. This vaccine has recently been added to the recommendations for routine childhood immunization by the American Academy of Pediatrics (see www.aap.org/advocacy/releases/junpcv7.htm).
2. Tizanidine (Zanaflex[®]) was also added to Formulary. This alpha-2 agonist used for muscle spasticity is restricted to those patients who cannot tolerate or fail to respond to baclofen.
3. Linezolid (Zyvox[®]) was added as a category A antibiotic (requiring ID approval). This agent is indicated for resistant bacterial infections, including vancomycin-resistant Enterococcus.
4. Ticarcillin/clavulanate (Timentin[®]) was also added as a category A antibiotic for use with trimethoprim/sulfamethoxazole in treating *Stenotrophomonas maltophilia* infections in adults.
5. Verteporfin (Visudyne[®]) was added for the treatment of age-related macular degeneration of the eyes.
6. Tobramycin solution for inhalation (TOBI[®]) was rejected based on lack of evidence demonstrating superiority to injectable tobramycin given by nebulization.

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