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Clostridium difficile–Associated Diarrhea and Colitis in the Hospitalized Patient

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A 55-year-old man with a 2-week history of cough, low-grade fever, and foul-smelling sputum was admitted to the hospital due to an acute change in mental status after a bout of vomiting. His past medical history was significant for alcohol abuse and chronic obstructive pulmonary disease. Physical examination showed poor oral hygiene, and clinical findings suggested right lower lobe pneumonia. Chest radiograph revealed a right lower lobe infiltrate. Aspiration pneumonia was suspected, and the patient was started on intravenous clindamycin. Five days into his hospital stay, the patient developed crampy abdominal pain, nausea, anorexia, and a profuse, watery diarrhea, averaging 15 bowel movements per day. On physical examination, the patient was febrile (38.8°C) and had right lower abdominal tenderness. Relevant laboratory studies included a white blood cell (WBC) count of 28,000/μL with left shift, and a stool Gram's stain showed many WBCs and fecal flora. Rapid enzyme immunoassay for *Clostridium difficile* toxin A was positive. The patient was treated with metronidazole 500 mg orally 3 times daily. He continued to spike a fever and developed an ileus with lower abdominal distension. Sigmoidoscopic examination revealed raised yellow plaques ranging up to 1 cm in diameter scattered over the colorectal mucosa interspersed with areas of hyperemia. Biopsy revealed epithelial ulceration with a volcano exudate of fibrin and neutrophils, characteristic of pseudomembranous colitis. After more than a week of severe illness, the patient began to improve and was discharged to a skilled nursing facility for rehabilitation.

Diarrhea and colitis caused by *Clostridium difficile* infection is a significant clinical problem in hospitalized patients. There are an estimated 3 million new cases of *C. difficile*–associated diarrhea and colitis in US hospitals each year, affecting as many as 10% of patients hospitalized for more than 2 days.[1] The incidence of *C. difficile*–associated diarrhea is increasing.[2] Data from the US Centers for Disease Control and Prevention (CDC) reveal that hospitalizations with a discharge diagnosis of *C. difficile*–associated disease have increased from 31 per 100,000 persons in 1996 to 61 per 100,000 persons in 2003.[3] The severity of observed disease also may be increasing, with an attributable 1-year mortality rate approaching 17% in 1 study.[4] It is not surprising that several studies have reported substantial increases in length of hospital stay associated with this disease.[5,6] The increased frequency of *C. difficile*–associated disease as well as the increasingly severe clinical presentations and poorer outcomes have been attributed to a recently recognized strain of *C. difficile* that was responsible for outbreaks of disease in North America. This article discusses the evolving virulence of *C. difficile* and reviews the current approach to recognition and management of diarrhea and colitis associated with this infection.

PATHOGENESIS AND EMERGING VIRULENCE

Although all antimicrobials have been associated with *C. difficile*–associated disease, some are more commonly associated with it, including cephalosporins, clindamycin, ampicillin, and fluoroquinolones.[7,8] Other organisms such as *C. perfringens* and *Staphylococcus aureus* rarely have been associated with pseudomembranous colitis.[9] Factors that predispose patients to the development of antibiotic-associated colitis include administration of gastric acid suppressants,[10] gastrointestinal surgery, advanced age, use of reusable rectal thermometers, prolonged hospital course, malnourishment, and chemotherapy.[11,12]

Ingested spores of toxigenic *C. difficile* survive the acidity and other upper gastrointestinal defense mechanisms, germinate, and colonize the lower intestinal

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TAKE HOME POINTS

- Judicious use of antibiotics is extremely important in reducing the incidence of *Clostridium difficile*–associated disease.
- *C. difficile* colitis should be considered in all hospitalized patients with unexplained leukocytosis.
- Strictly following infection control guidelines is vital to prevent spread of the disease.
- When *C. difficile*–associated disease is suspected, the implicated antimicrobial agent should be discontinued or substituted, if possible.
- Antimotility agents should be avoided.
- Symptom-free carriers should not be treated.
- Health care workers should wash their hands with soap and water rather than with alcohol-based hand sanitizing agents when dealing with outbreaks because alcohol is ineffective in killing *C. difficile* spores.
- Reusable rectal thermometers can spread the infection and should be replaced by disposable ones.

tract where they elaborate toxins. Toxin A and toxin B have enterotoxic and cytotoxic effects, and toxin A is a potent chemoattractant for neutrophils *in vivo*. Both toxins also induce cytokine release from monocytes. It is important to note that only a fraction of those colonized with the organism develop *C. difficile*–associated disease. One study suggests that serum IgG antibody to toxin A may be an important contributory factor in predisposing the host to colitis from *C. difficile*.[13]

A formerly rarely isolated strain of *C. difficile* known as BI/NAP1 has recently caused geographically diverse outbreaks of *C. difficile*–associated disease in a short time period. The BI/NAP1 strain has been associated with a higher frequency of disease, more serious disease that is refractory to therapy as indicated by higher rates of toxic megacolon and death, and higher rates of relapse in hospitalized patients.[8,14,15] Otherwise healthy persons residing in the community (some without antimicrobial exposure) also have been found to develop severe disease.[15] Evidence suggests that certain virulence characteristics of the BI/NAP1 strain may be responsible for more severe clinical presentations and poorer patient outcomes.[8] These characteristics include substantially increased toxin production (toxin A and toxin B),[14] the presence of a binary toxin,[15] altered antimicrobial resistance patterns (fluoroquinolone resistance),[15] and increased sporulation capacity.[16] These factors in combination with host and environmental factors may have precipitated the widespread establishment of this strain of *C. difficile*. The BI/NAP1 strain is distinguishable from previously identified outbreak (J-type) strains.[17]

CLINICAL FEATURES

Patients with *C. difficile*–associated disease have profuse watery diarrhea, with 5 to 20 watery bowel movements per day, malaise, anorexia and nausea. Other features that may be seen include dehydration, fever (30%–50% of patients), leukocytosis (50%–60%), and abdominal pain or cramping (20%–33%).[18,19] The pain and cramps are relieved by the passage of stools. The mean peripheral white blood cell count of patients with *C. difficile*–associated diarrhea is typically 15,000 to 16,000/μL.[20] *C. difficile* colitis should be considered in all hospitalized patients with unexplained leukocytosis.

An agent or clear mechanism is not identified in most cases of antibiotic-associated diarrhea without *C. difficile* infection. Certain antibiotics such as macrolides and ketolides have prokinetic effects on the gastrointestinal tract and increase the risk for developing antibiotic-associated diarrhea.[21,22] There is often a history of diarrhea associated with use of the same antibiotic or others on previous occasions. With non–*C. difficile* disease, the diarrhea is mild, systemic signs of infection are usually absent, and the diarrhea usually resolves when the dose is reduced or the specific drug is discontinued. *C. difficile*–associated diarrhea often persists or begins after the antibiotic has been discontinued, and it is usually more severe than antibiotic-associated diarrhea in the absence of *C. difficile*.[23]

Toxic megacolon is a serious complication of *C. difficile*–associated disease. It is characterized by the development of an enlarged dilated colon (> 7 cm in its greatest diameter) and may be accompanied by severe systemic toxicity. Radiographic evaluation may reveal "thumb printing" due to the presence of submucosal edema (**Figure 1**) and air-fluid levels resembling intestinal obstruction or ischemia.[24] Pseudomembranous colitis is characterized by the presence of an inflammatory pseudomembrane overlying the intestinal mucosa. The pseudomembrane is made of cellular and inflammatory debris and forms visible patches of yellow or gray exudate.

Unusual manifestations of *C. difficile*–associated disease include protein-losing enteropathy with ascites, ileus with minimal or no diarrhea, and extraintestinal manifestations such as bacteremia, splenic abscess, cellulitis, and osteomyelitis. Recurrent *C. difficile*–associated diarrhea complicates the course in approximately 20% of patients.[25–27]

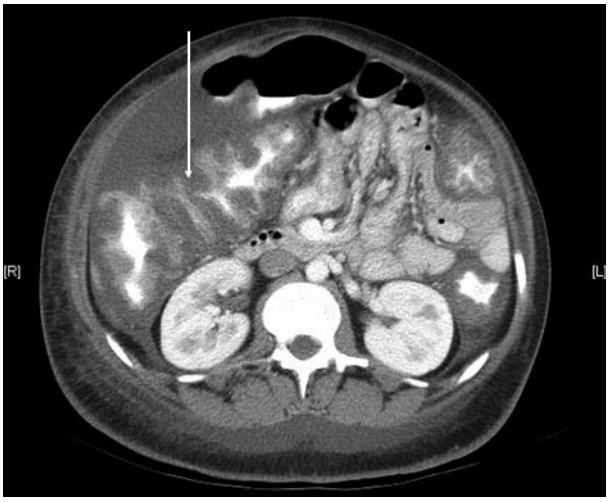

Figure 1. Diffuse severe colonic mural thickening with thumb print morphology in a patient with pseudomembranous colitis. (Image courtesy of Dr. Harold Katner, Mercer University School of Medicine, Macon, GA.)

Table 1. Danger Signs in Fulminant Colitis

Marked leukocytosis (white blood cell count > 30,000–40,000/μL)
Dehydration
Metabolic acidosis
Hypotension
Ascites
Thickened colon wall

Data from Fekety[28] and Finegold and George.[29]

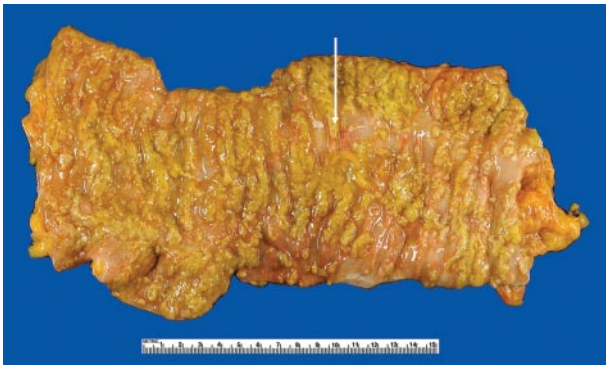

Figure 2. Gross appearance of the colon in a patient with pseudomembranous colitis. (Image courtesy of Dr. Harold Katner, Mercer University School of Medicine, Macon, GA.)

DIAGNOSIS

The diagnosis of *C. difficile*–associated disease is based on a combination of clinical and laboratory criteria. The diarrhea is defined as a minimum of 3 unformed stools per 24 hours for a minimum of 2 days with no other recognized cause for diarrhea.[11] The diagnosis of *C. difficile*–associated disease can be made when this clinical definition is combined with either visualization of colonic pseudomembranes or detection of toxin A or B in the stool. A stool culture capable of detecting *C. difficile* toxigenicity, if positive for a toxin-producing *C. difficile* organism, also confirms the diagnosis.[28] *C. difficile* should be suspected as the causative agent in any patient with acute diarrhea who has received antibiotics within the previous 3 months, and especially in patients whose diarrhea began 72 hours or more after admission to the hospital. Even with a negative enzyme immunoassay (EIA) for *C. difficile* toxin, strong clinical suspicion for *C. difficile* with a history of prior antibiotic therapy is often used as an indication for empiric antibiotic therapy. However, evidence suggests that 60% of community-acquired *C. difficile*–associated disease cases (as opposed to hospital acquired) have no history of prior antibiotic use.[10] Findings that suggest worsening of the disease are summarized in **Table 1**.[28,29]

Visualization of exudative plaques (pseudomembranes) on colonic mucosa establishes the diagnosis of pseudomembranous colitis. The characteristic lesion is raised, yellowish, and usually 2 to 10 mm in diameter with skip areas of normal mucosa (**Figure 2**); in severe disease, lesions may coalesce to form plaques.[27] Flexible sigmoidoscopy alone fails to detect up to 10% of cases without colonoscopy. The utility of these procedures is limited not only by the cost, but also by the risk for perforation due to the presence of friable colon tissue in severe disease. The American College of Gastroenterology recommends performing an endoscopic examination for the evaluation of suspected *C. difficile*–associated disease in the following situations: when rapid diagnosis is needed and test results are delayed or insensitive tests are used; the patient has an ileus and stool is not available; or other colonic diseases that can be diagnosed with endoscopy are being considered.[28]

The laboratory diagnosis of *C. difficile* infection depends on the demonstration of *C. difficile* toxins in stool. *C. difficile* testing is not recommended for patients with nondiarrheal stool specimens (unless ileus due to *C. difficile* is suspected); for infants younger than 1 year of age (in whom clinical illness does not correlate with presence of toxin in stools); or for "test of cure."[11] A test of cure culture or toxin assay means checking whether the organism has been eliminated following treatment. This testing is not recommended, as it is an imperfect predictor of subsequent relapse.[29]

Table 2. Treatment of *C. difficile*–Associated Disease

Discontinue the offending antibiotic
Replenish fluid and electrolytes
If specific treatment is required, use metronidazole 500 mg orally every 8 hr for 10 days; vancomycin at a dose of 125–250 mg orally every 6 hr is the second-line agent
Vancomycin is the agent of choice for patients with severe disease and disease associated with metronidazole-resistant strains
Treat recurrent episodes of disease with the agent that was used to treat the initial episode
Intravenous vancomycin has no effect on *C. difficile* colitis because the antibiotic is not excreted into the colon

Data from Cohen H, Brocavich JM. Managing Clostridium difficile colitis in patients who lack oral access. Infect Med 1996;13:101–9.

Stool Tests for Detecting *C. difficile*

Many tests are available for detection of *C. difficile* and its toxins, but no single test is ideal. The stool cytotoxin assay is a tissue culture assay that detects toxin B, and it is the gold standard for diagnosis because of its high sensitivity and specificity. Its main disadvantages are that it takes 24 to 48 hours to complete and requires a tissue culture facility. The most commonly used laboratory test for diagnosing *C. difficile*–associated disease is an EIA. EIA has the advantages of being fast (2–6 hr) and easy to perform, but it is neither as sensitive nor as specific as the cytotoxin assay. Some EIA kits detect only toxin A, so diarrhea due to a toxin A^-/toxin B^+ strain of *C. difficile* will be falsely negative. Therefore, commercial kits that detect both toxins A and B have a slight advantage over those that detect toxin A alone.[30] The typical clinical approach is to first use the EIA and then perform further testing in situations where the EIA is negative but strong clinical suspicion for *C. difficile* exists.

Stool culture for *C. difficile* is the most sensitive test available, but it has the highest rate of false-positive results because most clinical laboratories are not equipped to distinguish between toxigenic and nonpathogenic, nontoxigenic strains. Stool culture that is capable of determining the toxigenicity of the organism is potentially a more useful diagnostic test, but it is not available routinely at most hospitals. Stool culture is especially useful in the setting of an epidemic as it permits strain typing of individual isolates, allowing hospital outbreaks to be tracked for epidemiologic studies. Other limitations of stool culture include a longer length of time for testing (2–5 days), lack of standardization of methods and culture media in different laboratories, and the need for anaerobic culture.[31,32] Other infectious causes are less common in hospitalized patients who develop diarrhea more than 72 hours after admission. It is less effective to obtain routine stool cultures in this scenario unless tests such as the EIA for *C. difficile* are negative.

The latex agglutination test detects the bacterial enzyme glutamate dehydrogenase. It has the advantages of being fast, inexpensive, and easy to perform, but it is limited by poor sensitivity and specificity. Polymerase chain reaction assay to detect toxin A or B in isolates or from a direct stool specimen is a highly sensitive and specific test; however, it requires expertise in molecular diagnostic techniques.[33]

TREATMENT

The first and most important step in treating *C. difficile*–associated disease is to discontinue the implicated antibiotic agent or agents (**Table 2**).[34] Specific antimicrobial therapy to treat the infection should be administered orally for 10 days. The drug of choice is metronidazole 500 mg orally 3 times daily for 10 days.[11] Vancomycin at a dose of 125 to 250 mg orally every 6 hours for 10 days is as effective as metronidazole, but it is more expensive. The potential emergence of vancomycin-resistant staphylococci and enterococci is concerning but does not obviate the need to use vancomycin for severely ill or rapidly deteriorating patients at high risk for *C. difficile*–associated disease in the hospital setting.[28] Vancomycin is also used in patients who are intolerant of metronidazole, pregnant women, and children. Metronidazole crosses the placenta and should be avoided during the first trimester since there are no adequate studies demonstrating safety in pregnant women.[35] For patients with severe disease who do not respond rapidly to metronidazole, therapy should be switched to vancomycin.[11,34,36]

For patients who lack oral access, intravenous metronidazole (500 mg every 6–8 hr), vancomycin retention enemas (500 mg every 4–8 hr), or vancomycin via colonic catheter should be considered.[37] Intravenous vancomycin should not be used to treat *C. difficile* colitis because the antibiotic is not excreted into the colon. Colonoscopic decompression with vancomycin instillation has been used successfully in toxic megacolon.[38,39] For patients who have a first recurrence of diarrhea following treatment of *C. difficile*–associated disease, treatment in the same manner as the initial episode (metronidazole or vancomycin) is recommended.[40] Indications for surgery include severe peritoneal disease, bacteremia, unresponsiveness to antibiotics, unremitting fever, and computed tomography evidence of significant pericolonic inflammation with increasing bowel wall edema.[41]

Evidence to support the efficacy of probiotic agents in *C. difficile*–associated disease is lacking,[42] and in fact,

numerous reports show that they may be harmful. Fungemia due to *Saccharomyces boulardii* and bacteremia due to *Lactobacillus* species after administration to both immunocompetent and immunocompromised hosts have been reported.[43–45] The anion-binding resin colestipol has been shown to be clinically no better than placebo in its ability to affect the fecal excretion of toxins.[46] Antimotility agents such as diphenoxylate[47] and loperamide[48] should be avoided in *C. difficile*–associated disease. Several case reports have linked the use of antimotility agents in patients with *C. difficile*–associated disease with the development of toxic megacolon because they probably delay excretion of the toxin.[49]

PREVENTION AND CONTROL

Important preventive measures include hand washing, glove use, isolation of patients in a single room, barrier precautions, and cleaning of the physical environment throughout the duration of symptomatic disease.[50,51] Hand washing with soap and water after glove removal is recommended during outbreaks.[52] Because alcohol is ineffective in killing *C. difficile* spores, health care workers should wash their hands with soap and water rather than with alcohol-based waterless hand sanitizers when dealing with outbreaks. Implementation of contact precautions combined with the use of private rooms has been successful in limiting transmission of *C. difficile* in hospital and long-term care settings.[53,54] Thorough cleaning of surfaces and disinfection with agents that eradicate *C. difficile* and its spores (eg, 10% sodium hypochlorite solution) are also recommended.[28,55] Reusable rectal thermometers can spread the infection and should be replaced by disposable ones.[56]

CONCLUSION

C. difficile infection is recognized as the most frequent cause of antibiotic-associated diarrhea and colitis, and the incidence of *C. difficile*–associated disease appears to be increasing.[2] Virulence characteristics associated with the BI/NAP1 strain may be responsible for increasingly severe clinical presentations and poor outcomes. Apart from the judicious use of antimicrobials, incorporating stringent infection control guidelines and environmental interventions is likely to be necessary to control this new threat. Appropriate management of *C. difficile*–associated disease requires prompt recognition and proper monitoring and treatment as well as implementation of effective preventive measures to reduce nosocomial acquisition of this organism. **HP**

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