Clostridium Difficile Infection in The Elderly

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ABSTRACT

The aging society and the advanced of supportive treatment means that large numbers of elderly patients with risk factors for C difficile enterocolitis will continue to receive care in intensive care unit. Antibiotic resistance and older, sicker patients means that combination antibiotic therapy will become a trend in clinical setting. Age, several co-morbidities, and gastrointestinal surgery appear to be specific risk factors for C difficile infection. Diarrhea which is the only symptom in hospitalized patient should drive us to rethink about the possibility of C difficile infection especially in the elderly patient. Prudent use of antibiotic, infection control are strategies to prevent C difficile infection in clinical setting.

Elderly patients who undergo gastrointestinal surgery have an increased rate of C difficile infection because of commonly used nasogastric tube. Gastrointestinal surgical patients typically have preoperative bowel preparation, receive oral preoperative antibiotics that are poorly absorbed, impaired bowel motility secondary to ileus, receive systemic preoperative antibiotics prophylaxis, and have variable lengths of no oral caloric intake during the preoperative period. The continued imprudent use of prolonged postoperative systemic antibiotics for presumed preventive purposes, particularly among the elderly and patients who have nasogastric tubes or other enteric tubes, appears to be a recipe for preventable infections with C difficile.

Key words: *clostridium difficile, elderly patient, enterocolitis.*

INTRODUCTION

Clostridium difficile (C difficile) enterocolitis is a disease that occurs primarily in hospitalized patients, particularly among those older than 60 years of age. In the United States it is estimated that three million cases per year are interpreted to indicate C difficile is a major nosocomial pathogen in inpatients.[1] In outpatient setting it is estimated only about 20.000 cases per year.[2]

Clinical pseudomembranous enterocolitis and antibiotic-associated diarrhea secondary to C difficile are most common in the older population. Of interest, healthy neonates and infants may have very high rates of asymptomatic stool colonization but very low rates of clinical disease.[3] Up to 3% of asymptomatic adults can be found to have colonization of the stool with C difficile.[1] Hospitalized adult patients have rates of colonization of 20% or more,[4] and virtually 100% of adult patients with pseudomembranous enterocolitis will have positive stool cultures.[5] Clearly, the presence of the C difficile spore in the stool is not necessarily associated with clinical disease; certain host factors promote the transition to the vegetative form of the organism.

Age appears to be a specific risk factor for C difficile enterocolitis. One report noted that 80% of positive studies for the enterotoxin of C difficile occurred in patients older than age 65 years.[6] Colonization resistance may diminish with the aging process such that lesser antibiotic exposures result in a microenvironment in the colon conducive to enterocolitis. High rates of colonization in patients from extended care facilities and rehabilitation institutions, the disproportionate number of elderly people who have severe illnesses in the intensive care unit, more frequent extended courses of antibiotics, and more common underlying illnesses and immunosuppression offer more opportunities for colonization with C difficile among the elderly. The apparent increase of C difficile infection in the elderly may be viewed more appropriately as a consequence of

underlying disease and higher rates of colonization than as an independent predilection for this infection based solely on age. Underlying illnesses that compromises host defenses should be viewed in the patient receiving antibiotics as a clinical situation that favors C difficile infection, regardless of the patient's age.

There is quite a number of elderly patients underwent chemotherapeutic treatment. Antineoplastic chemotherapy agents have been implicated with C difficile infection. Because the patient undergoing aggressive treatment for cancer may be receiving concurrent or recent systemic antibiotic therapy, it has been difficult to establish a clear association. C difficile infections have been well documented when no antibiotics were being given to patients receiving anticancer chemotherapy. Most of these patients have been hospitalized for a period of time, so colonization from the hospital environment with C difficile and other hospital-acquired organisms is likely. Certain regime of anticancer chemotherapy may implicate the infection. 5-fluorouracil may affect gut mucosa and enhance the patient's susceptibility to infection with C difficile. Radiation therapy without antineoplastic chemotherapy or antibiotics also has been associated with C difficile infection. Long term usage of certain medication such as immunosuppression, antacid therapy may contribute to the disruption of colonization resistance and increased risk of C difficile infection.

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SIGNS AND SYMPTOMS

Classic signs and symptoms of C difficile infection may present in any of five different patterns: 1). Asymptomatic carriage; 2).Colitis syndrome without pseudomembranes; 3). Colitis with pseudomembranes; 4). Toxic megacolon; 5).Fulminant colitis.

The severity of the disease usually depends on the duration of infection, quantity of inoculum of colonization and host risk factors.

Diarrhea is the cardinal symptom that signals the diagnosis of C difficile enterocolitis. It should be emphasized that hospitalized patients, especially elderly, have several reasons to develop a diarrhea syndrome, and about 30% of hospital-associated diarrhea syndromes will be positive for C difficile infection.[7] Bloody diarrhea is uncommon with C difficile enterocolitis, and gross blood that is identified in the bowel movement favors other diagnostic possibilities. In addition to diarrhea, other clinical symptoms suggestive of C difficile enterocolitis include crampy abdominal pain, anorexia, and perhaps mild fever and leukocytosis. In elderly patients with pseudomembranes and those with unusually severe cases of enterocolitis, severe consequences of diarrhea include dehydration, hypoalbuminemia, and other electrolyte abnormalities.

In diagnosing C difficile infection, proctosigmoidoscopy is commonly undertaken at the onset of the diarrhea syndrome, but the presence of pseudomembranes over the colonic surface is not a requirement for the diagnosis of enterocolitis,[8] but it does confirm the diagnosis. Pseudomembrane formation is uncommon with other causes of hospital-associated diarrhea. The pseudomembranous exudate is visual testimony to the severity of the infection or to the duration of the enterocolitis. Promptly recognized and diagnosed enterocolitis will not have pseudomembranous changes and likely will respond more promptly to treatment. In a small percentage of patients, the pseudomembranous changes may be in the more proximal segments of the colon and outside the length of the proctosigmoidoscope.[9]

LABORATORY EXAMINATION

The diagnosis of C difficile enterocolitis is best made by detection of the toxin within a specimen of diarrheal stool. A host of different enzyme-linked immunosorbent assays (ELISAs) are used that employ either monoclonal or polyclonal antibodies.[10,11] Most commonly, the antibodies are directed toward the detection of toxin A. ELISA studies for toxin should be performed only on diarrheal stools; false positive findings can occur in up to 10% of formed stool specimen.[12] Other method of examination includes Latex Agglutination which detects glutamate dehydrogenase in stool.[13] It has been specificity and sensitivity than does ELISA for establishing the diagnosis, and colonization of the colon with nontoxigenic species of C difficile will result in false-positive findings.

Culture isolation for Clostridium difficile is used mostly in epidemiologic study. However, culturing of anaerobic species has proven difficult for many

laboratories and because sensitivities play no practical role in the selection of antibiotic therapy, only toxin detection is considered a clinically necessary diagnostic study. Some believe that recovery of the pathogen by culture identification is the most accurate method for establishing the diagnosis,[14,15] but the complexity of the culturing process has limited its use in most clinical laboratories. Further, recovery of C difficile in the stool does not identify whether the isolate is a toxin-producing species.

Direct identification of the gene from either toxin A or toxin B in the stool specimen is the best way for diagnosing C difficile enterocolitis.[16-18] The polymerase chain reaction (PCR) is used to amplify the toxin-producing genes.

RADIOGRAPHIC EVALUATION

Radiographic studies offer little diagnostic value for routine C difficile enterocolitis; abdominal roentgeno-grams will provide only nonspecific findings. However, radiographic studies assume greater value when enterocolitis evolves into toxic megacolon.

Abdominal computes tomography (CT Scan), which is essentially of no value for the typical case of C difficile enterocolitis, will demonstrate the thickening of the colonic wall, and mucosal abnormalities if gastrointesti-nal contrast is used with the study.[19,20]

Proctosigmoidoscopy or flexible colonoscopy must be approached with caution to avoid perforation. Pseudomembranes can be visualized and colonic contents sampled for toxin assays via endoscopy.[21] It is most important to remember that the elderly surgical patient receiving systemic antibiotic therapy is at high risk for C difficile enterocolitis even when the number of unformed stools is small or when the patient has acute onset of abdominal distention, pain, or tenderness without diarrhea.

TREATMENT

There are three basic strategies to treat C difficile enterocolitis:

1. Discontinuation of the antibiotic that has mediated the change in patient's colonic microflora. Or the antibiotic should be changed to drugs that have less of an association with enterocolitis. C difficile clinical isolates are resistant to cephalosporins, and these antibiotics have strong association with the development of enterocolitis. Clindamycin, ampicillin, and amoxicillin therapy should be discontinued or changed to an alternative without strong associations with enterocolitis.

2. Avoidance of antiperistaltic medication.[22] Diarrhea is the body physiological response to expel pathogens responsible for enterocolitis. Use of antiperistaltic medications results in retention of the pathogen, probably worsens enterocolitis-associated necrosis of the colonic mucosa, and increases the risk of colonic dysmotility and toxic megacolon.[23]

3. Specific treatment for offending C difficile pathogen should be initiated. Vancomycin or metronidazole is recommended, although some other type of drugs have been used, but the results in several randomized control trial are still controversial and have not been confirmed yet. Increased use of systemic vancomycin for the treatment of infections caused by methicillin-resistant staphylococci and for empirical therapy in the intensive care unit has been directly associated with the emergence of the vancomycin-resistant enterococci. Metronidazole is the preferred treatment of choice for C difficile enterocolitis in institutions where the emergence of vancomycin-resistant enterococci is an established problem.

Oral rifaximin, a nonabsorbable antibiotic with good in-vitro activity against Clostridium species is currently under investigation for the treatment of C difficile colitis.[24] Other oral drugs that have been used are teicoplanin and bacitrasin. Teicoplanin has considerable in vitro activity against C difficile, it has been shown to be clinically as effective as or slightly more superior to vancomycin in several Cochrane review.

Drugs which are still in development include nitazoxanide (nitrothiazole benzamide), PAR-101 (a macrocyclic antibiotic), and ramoplanin (a lipoglycodepsipeptide).

In refractory cases of C difficile enterocolitis, it is believed that hosts may have impaired ability to mount antibody to C difficile toxin A. Based on this finding some clinicians start to use intravenous immunoglobulin to treat severe C difficile colitis.[25]

Recurrent infection with C difficile is a big problem in clinical setting. Recurrent infection is associated with a history of previous episodes of enterocolitis, continued or interval antibiotic therapy for another infection with drugs that have a strong association with Clostridium species infection, and with specific strains of C difficile.[26] Treatment of recurrent infection requires resumption of therapy. Oral metronidazole 250-500 mg four times per day is recommended. If patient does not respond within 48 hours, vancomycin therapy should be started.[27]

PREVENTION

Prevention and control of C difficile infection requires strict-regulated use of antimicrobial agents, reducing patient-to-patient spread of infection, hand washing procedures, and on going surveillance. Reduced use of drugs that are strongly associated with enterocolitis when alternative choices are available is desirable. A shorter duration of antibiotic administration and less use of combination antibiotics will help to prevent enterocolitis.[28]

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