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Original article

Evaluation of advanced age as a risk factor for severe *Clostridium difficile* infection

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ABSTRACT

Background/purpose: Although advanced age has been associated with the incidence of *Clostridium difficile* infection (CDI), its relationship with disease severity remains inconclusive. The objective of this study was to evaluate risk factors, specifically advanced age, which may be associated with the acquisition of severe CDI.

Methods: A retrospective chart review at a Veterans Affairs Hospital was conducted on hospitalized veterans aged ≥ 18 years with a positive stool toxin assay for *Clostridium difficile* between May 2008 and September 2012 (n = 224). One hundred and sixty-one (72%) patients were in the mild–moderate infection group and 63 (28%) patients in the severe infection group. The primary outcome was to determine the effect of advanced age (≥70 years old) on the acquisition of severe CDI. The secondary outcome was to identify other potential risk factors for severe CDI. Disease severity was classified according to the criteria established in the 2010 Society for Healthcare Epidemiology of America/Infectious Disease Society of America practice guidelines for CDI. Demographic and disease-specific data were collected. A logistic regression model was used to identify characteristics predictive of disease severity.

Results: Our regression model found advanced age to be significantly associated with severe CDI (odds ratio 2.43, $p \leq 0.005$, 95% confidence interval 1.31–4.50). A larger proportion of veterans were diagnosed with severe CDI in the intensive care unit (p = 0.004). In addition, multiple antibiotic use (≥3) and association with severe CDI was statistically significant (34% mild–moderate vs. 48% severe, p = 0.041). The univariate analyses did not reveal any other characteristics predictive of disease severity.

Conclusion: Advanced age was associated with severe CDI. A prospective evaluation is warranted to validate this finding. Efforts to identify patients at risk for severe CDI will be important as it may direct treatment and positively affect outcomes.

1. Introduction

Clostridium difficile, a Gram-positive, spore-forming, toxin-producing anaerobic *bacillus* remains the leading cause of health care associated infectious diarrhea accounting for 15–25% of antibiotic associated diarrhea cases and its incidence is dramatically increasing.[1,2] *C. difficile* infection (CDI) is associated with a wide spectrum of clinical disease presentation from mild diarrhea to fulminant and fatal toxic colitis. The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) have developed guidelines to direct treatment based on severity of disease. The guidelines utilize laboratory parameters including white blood cell count (WBC) and serum creatinine (SCr), as well as potential complications from CDI (hypotension, shock, ileus or toxic megacolon) to distinguish mild to moderate disease from severe disease.[1] The guidelines also identify risk factors for CDI including advanced age (>64 years of age), duration of hospitalization, previous exposure to antimicrobial agents, exposure to chemotherapy, immunosuppression,

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gastrointestinal (GI) surgery or manipulation of the GI tract (i.e., tube feedings), and acid suppressive therapy.[1] Specific risk factors for severe CDI as opposed to CDI in general are not differentiated in the guidelines, however, studies that have evaluated possible risk factors associated with severe CDI have been conducted.[3,4] A few retrospective studies have identified age >70 years old as an independent risk factor for severe disease.[5–10] Of note, the SHEA/IDSA guidelines have highlighted advanced age (>64 years of age) being positively associated with incidence of CDI, however, its relationship with severity remains undefined as current literature is conflicting. The primary objective of our study is to evaluate advanced age (≥70 years of age) as a possible risk factor that may predispose patients to severe CDI, as defined by the SHEA/IDSA guidelines, in a veteran population.

2. Methods

2.1. Study design and setting

This was a retrospective, cohort chart review at the Edward Hines Jr. Veterans Affairs (VA) Hospital. This VA hospital is a tertiary care, teaching hospital located in the Chicago, Illinois metropolitan area, with approximately 500 beds for acute and long-term care, serving >56,000 veterans. Eligible patients for screening were identified via microbiology reports identifying patients with a positive stool toxin assay for *C. difficile* between January 2008 and September 2012. Patients were then evaluated by review of their electronic medical records in the VA Computerized Patient Record System. Patients were eligible for inclusion in the study if they were aged ≥ 18 years, and had acute CDI symptoms including episodes of diarrhea. Patients were excluded from the study if they had CDI within the 3 months prior to the study period, were asymptomatic, or had any other identified causes of diarrhea at the time of inclusion. Included patients were stratified into two groups—nonsevere CDI and severe CDI based on the SHEA/IDSA criteria. At the time of symptom onset, patients with a SCr < 1.5 times the baseline and WBC < 15,000 cells/uL were classified as a nonsevere case, whereas those with SCr ≥ 1.5 times the baseline or WBC ≥ 15,000 cells/uL were considered as having a severe case.

2.2. Measures

Data collection included demographic information (age, gender, race), comorbid conditions, location within the hospital at the time of diagnosis of CDI, previous (within the past 90 days) or concurrent medications shown to be related to increased risk for CDI (antibiotics, acid suppressive therapy, steroids, antiperistaltic agents, immunosuppressive agents, and enteral/parenteral nutrition), classification of CDI, complications of CDI, prior surgical or endoscopic procedures in the past 90 days, prior hospital admission in the past 90 days, long-term care or nursing home stay during the past 90 days, and laboratory parameters (SCr, WBC, albumin). This study was approved by the Hines VA Institutional Review Board and Research and Development Committee prior to the commencement of data collection.

2.3. Outcomes

The primary outcome of the study was to determine risk factors, specifically advanced age (≥70 years old), which may be associated with severe CDI within a hospital veteran population. The secondary outcomes of the study were to identify other potential risk factors for severe CDI, as well as compare outcomes between the severe and nonsevere groups: specifically, the number of relapsed CDI episodes within 60 days, treatment failures, defined as signs and symptoms of CDI not resolving by the end of a 10–14-day course of standard therapy, and mortality at 30 days and 90 days were all evaluated. These outcomes were compared between the severe and nonsevere groups.

2.4. Statistical analysis

The baseline characteristics of the study population were described using counts and percentages for categorical variables and means and standard deviations for continuous variables. Differences in demographics, clinical background, and laboratory data between patients with and without severe CDI were analyzed using *t*-test, chi-square tests, or Fisher's exact test. A logistic regression model was created to evaluate independent associations between disease severity and significant clinical variables identified in our univariate analyses.

3. Results

A total of 283 patient charts were reviewed with 59 patients being excluded (recent CDI or other causes of diarrhea identified; Table 1) and 224 patients meeting the inclusion criteria. There was a statistically significant difference found in the primary outcome of advanced age as a risk factor for the acquisition of severe CDI. Patients aged ≥ 70 years comprised 43% of the total severe CDI population and 23% of the nonsevere CDI population (Table 2, $p = 0.004$). Table 2 highlights the secondary endpoints of patient demographics including ethnicity and gender, laboratory parameters, previous healthcare exposure including prior hospitalization or long-term care exposure, and hospital unit at the time of diagnosis. There were no statistically significant differences found when comparing patient demographics. Laboratory parameters including WBC ≥ 15,000 cells/uL, SCr ≥ 1.5 times the baseline, and albumin < 2.5 mg/dL were found to be statistically significant for severe CDI ($p < 0.001$). In terms of location at the time of diagnosis, there was a higher proportion of patients with severe CDI in the intensive care unit (ICU; $p = 0.004$). There were no statistically significant differences when comparing medication use in the preceding 90 days, including antibiotics and acid suppressives between the two groups (Table 2). A statistical significant difference in patients receiving three or more antibiotics was identified with 48% having severe CDI and 34% with nonsevere CDI ($p = 0.041$). Comorbidities did not play a factor in the severity of CDI. The following clinically significant variables were included in our logistic regression model: age ≥ 70 years, proton-pump inhibitor use, and use of three or more antibiotic (Table 3). This model controlled for antibiotic and proton-pump inhibitor use and demonstrated

Table 1
Excluded patients (other causes for diarrhea).

	Total patients, $n = 59$
No labs	8 (14)
Hyperthyroidism	2 (3)
Ulcerative colitis	6 (10)
Cytomegalovirus colitis	1 (2)
Colon cancer	11 (19)
Gastric cancer	2 (3)
Pancreatic cancer	3 (5)
IBD-D [a]	2 (3)
Diverticulitis	20 (34)
Malabsorption	2 (3)
Appendectomy	1 (2)
Olgilvie Syndrome	1 (2)

Data are presented as *n* (%).
[a] Irritable bowel disease-diarrhea.