

Original Articles

Co-morbidity, not age predicts adverse outcome in *Clostridium difficile* colitis

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Abstract

AIM To examine whether age alone or co-morbidity is a risk factor for death in older adults who developed *Clostridium difficile* (Cd) colitis during hospitalization.

METHODS A retrospective, observational study design was performed in our Lady of Mercy Medical Center, a 650-bed, urban, community-based, university-affiliated teaching hospital. 121 patients with a positive diagnosis of Cd colitis (aged 23-97 years) were studied, and data pertinent to demographic variables, medical history, co-morbidity, physical examination, and laboratory results were collected. Age was examined as a continuous variable and stratified into Age1 (<80 vs 80+); Age2 (<60, 60-69, 70-79 and 80+); or Age3 (<60, 60-69, 70-79, 80-89, 90+).

RESULTS Cd colitis occurs more frequently with advancing age (55% of cases >80 years). However, age, *per se*, had no effect on mortality. A history of cardiac disease ($P=0.036$), recurrent or refractory infection >4 weeks ($P=0.007$), low serum total protein ($P=0.034$), low serum albumin ($P=0.001$), antibiotic use >4 weeks ($P<0.01$), use of over

4 antibiotics ($P=0.026$), and use of certain classes of antibiotics ($P=0.035-0.004$) were predictive of death. Death was strongly predicted by the use of penicillin-like antibiotics plus clindamycin, in the presence of hypoalbuminemia, refractory sepsis, and cardiac disease ($P=0.00005$).

CONCLUSION Cd colitis is common in the very old. However, unlike co-morbidity, age alone does not affect the clinical outcome (survival vs death).

INTRODUCTION

Infection with the *Clostridium difficile* (Cd) bacterium is associated with a wide spectrum of gastrointestinal disorders that range from asymptomatic, to mild and sporadic diarrhea, to life threatening colitis^[1]. In older people, Cd colitis occurs frequently and is associated with high morbidity and mortality^[2]. In addition, epidemiological studies of Cd-induced diarrhea have identified an almost exclusive relationship to both antibiotic use and advancing age^[3]. Those most commonly affected are older people, the immunocompromised, and patients who undergo gastrointestinal surgery^[4]. In this report, we examined whether age alone or co-morbid conditions are risk factors for an adverse clinical outcome (death) in a sample of 121 patients who developed Cd colitis during hospitalization.

MATERIALS AND METHODS

This study was conducted at a 650-bed community teaching hospital in the Bronx, New York. We performed a retrospective review of the medical records of all patients who were admitted from the community or nursing homes during 2a (1995-02/1997-02). 121 patients with a positive diagnosis of Cd colitis were identified. Most Cd patients were older adults from the inner city. Demographic variables were collected, as were all data pertinent to their past and present medical history and their recent physical examinations. A positive diagnosis of Cd colitis was based on medical history,

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gastrointestinal symptoms or signs plus a positive enzyme-link fluorescent immunoassay of *Cd* cytotoxin in A, and/or endoscopic biopsy-proven pseudomembranous colitis. Patient ages ranged from 23 to 97 years (78 ± 14). Included were 13 patients below 60 years (10 females and 3 males), 16 patients from 60-69 years (7 females and 9 males), 25 patients from 70-79 years (14 females and 11 males), 52 patients from 80-89 years (35 females and 17 males), and 15 patients from 90-97 years (9 females and 6 males). Study variables included patient's age, sex, and length of hospital stay. Data referring to pre-existing medical conditions (diabetes, dementia, tube feeding, COPD, hypertension, cardiac disease), gastrointestinal symptoms, fever, and the number, class, and duration of all antibiotics used were collected. Sepsis or infection were defined as the presence of a body temperature $>38^{\circ}\text{C}$, heart rate >90 beats/min, respiratory rate >20 /min, and WBC count $>12 \times 10^9/\text{L}$. Sepsis not responsive to therapy after four weeks was defined as refractory. Laboratory results (total protein, albumin, BUN, creatinine, creatinine clearance, CBC) were noted.

The effect of age was examined using age both as a continuous variable and stratified into integer variables as follows: Age1 (2 groups; 23-79 years and over 80), Age2 (4 groups; 23-59, 60-69, 70-79, and over 80 years), Age3 (5 groups; 23-59, 60-69, 70-79, 80-89, and over 90 years). Study variables [low total protein ($<70\text{g/L}$), low albumin ($<35\text{g/L}$), elevated BUN (7.15mmol/L), high creatinine ($132.6\mu\text{mol/L}$), low creatinine clearance ($<50\text{mL/min}$)] were examined using Fisher's exact test, Student *t* test for unpaired data, and (simple, multiple, and logistic) regression analysis to determine whether age, co-morbidity, antibiotic use, or specific laboratory chemistries were associated with an adverse clinical outcome (death). Statistical analyses were performed on an IBM-compatible PC using STATA-TM (version 5.0, Stata Corp., College Station, TX, <http://www.stata.com>) and a two-tailed significance level of $P < 0.05$ was considered to be significant.

RESULTS

In this sample of 121 *Cd* colitis patients ranging in age from 23-97 years, we observed that *Cd* colitis occurred more frequently in those with advanced age, (55% of our subjects were >80 years). Nevertheless, when age was examined as a continuous variable (23-97 years) or stratified into different integer variables (Age 1, Age 2, and Age 3) it was not associated with increased mortality (Table 1). We also found that a number of co-morbidity related variables were predictive of an adverse outcome (Table 2). For example, the

presence of cardiac disease ($P=0.036$), an elevated serum BUN ($P=0.039$), low serum total protein ($P=0.034$), and low serum albumin ($P=0.001$) predicted death. In addition, recurrent or refractory infection over 4 weeks ($P=0.007$), prolonged antibiotic use ($P=0.010$), use of 4 or more antibiotics ($P=0.026$), and use of different classes of antibiotics ($P=0.035-0.004$) were found to predict death. The strongest predictor of death was the combined use of penicillin-like-antibiotics plus clindamycin, in the presence of hypoalbuminemia and refractory sepsis >4 weeks, in a patient with a history of cardiac disease ($P=0.00005$).

Table 1 Patient age and sex vs outcome at discharge
(n,%, $\bar{x} \pm s$)

Variable	Alive	Dead	P value
Patient age (yrs)	76.1 ± 15.0	78.9 ± 13.5	0.383(1,a)
Patient sex (M/F)	36/58	10/17	0.546(2)
Age 1 (yrs)			
23-79	45(83%)	9(17%)	0.192(2)
80-97	48(73%)	18(27%)	
Age 2 (yrs)			
23-59	12(92%)	1(8%)	0.428(2)
60-69	12(75%)	4(25%)	
70-79	21(84%)	4(16%)	
80-97	49(73%)	18(27%)	
Age 3 (yrs)			
23-59	12(92%)	1(8%)	0.577(2)
60-69	12(75%)	4(25%)	
70-79	21(84%)	4(16%)	
80-89	37(71%)	15(29%)	
90-97	12(80%)	3(20%)	

(1):Student *t* test; (2):Fisher's exact test; (a):Additional log istic regression analysis.

Age (as continuous variable) did not predict adverse outcome or death ($P=0.382$).

Table 2 Co-morbidity vs adverse outcome at discharge

Variable	Not predictive	Predictive	P value
Co-morbidity			
Cardiac disease (1)	—	×	0.036
COPD	×	—	0.200
Dementia	×	—	0.075
Diabetes	×	—	0.622
Hypertension	×	—	0.387
Elevated BUN	—	×	0.039
High creatinine	×	—	0.106
Low creatinine clearance	×	—	0.928
Nutrition related			
Tube-fed	×	—	0.241
Low serum total protein	—	×	0.034
Low serum albumin	—	×	0.001
Sepsis related			
Aminoglycosides	×	—	0.034
Clindamycin	—	×	0.004
Penicillin-like (2)	—	×	0.035
Antibiotic use $>4\text{wk}$	—	×	0.010
Use of >4 antibiotics	—	×	0.026
Fever ($>38.3^{\circ}\text{C}$)	×	—	0.181
Infection $>4\text{wk}$	—	×	0.007

Results are given as predictive or not predictive of death as the adverse outcome and were determined using logistic regression analysis.

(1): 64 cardiac patients were identified with 19 deaths during hospitalization.(2): Excluding cephalosporins.

DISCUSSION

Our study revealed that the use of broad spectrum penicillins (ampicillin, amoxi cillin clavulanic acid, nafcillin, piperacillin, ticarcilin-clavulanate, ampicillin-sulbactam), cephalosporins (cefazolin, cefuroxime, cefoxitin, ceftaz idime, ceftriaxone), macrolides (erythromycin, clarithromycin, azithromycin), aminoglycosides (gentamicin, amikacin), vancomycin, clindamycin, ciprofloxacin, trimetoprim-sulfamethoxazole, and doxycycline was associated with an increased risk of *Cd* colitis. In particular, we found that clindamycin, aminoglycosides and penicillin-like antibiotics were positively related to an adverse outcome (death). Interestingly, although cephalosporins are among the most common agents associated with the development of *Cd* colitis, reflecting their widespread use, our study did not identify their use to correlate with increased mortality^[5].

Our patients ranged in age from 23 to 97 years with the majority (108/121) over the age of 60 years and advancing age is often referred to as a risk factor for developing *Cd* colitis^[2-4]. Other factors reported to be associated with an increased risk of *Cd* colitis are immunosuppression, hospitalization, surgical procedures involving the gastrointestinal tract and medications that alter intestinal motility or intestinal flora^[3-8]. Among medications, the key factor appears to be antibiotic therapy that can alter the normal equilibrium of colonic flora and create an environment that permits *Clostridium difficile* to flourish^[7]. Many antibiotics have been linked to *Cd* infection, but broad spectrum antibiotics with activity against enteric bacteria are the most frequently implicated agents^[7]. Clindamycin is notorious for its association with *Cd* colitis^[8]. The literature further suggests that the most common antibiotics associated with *Cd* colitis are the broad spectrum penicillins and cephalosporins which may simply reflect their widespread use^[5]. *Cd* colitis infection may be induced by oral, parenteral, or topical antibiotic therapy^[9].

Antibiotic associated *Cd* colitis has been linked to *Clostridium difficile* bacterium and to the cytotoxin produced by the organism^[9-11]. Antibiotic-associated diarrhea and colitis are important and increasingly frequent complications of antibiotic therapy that occur often in hospitals, nursing homes, and in the community^[12]. Population based studies in Sweden showed that the incidence of *Cd* toxin positive stools increases 20-100 fold when persons aged 10-20 yr are compared with those over 60^[13]. Multivariate analysis of hospitalized patients, colonized with the *Cd* bacterium, also show that increasing age correlates

positively with the clinical expression of the disease^[14]. This finding suggests that aging promotes susceptibility to *Cd* colonization, *Cd* toxin production, and the onset of *Cd* colitis^[15].

While most studies demonstrate that *Cd* colitis occurs commonly in the geriatric population, few comment on patient age as a variable that could affect an adverse outcome. We analyzed age as a continuous variable and as different integer variables and our analyses did not reveal that age was directly associated with an adverse outcome (death). As presented in this report, we believe that other factors associated with the aging process such as cardiac disease, refractory sepsis and/or low serum albumin were the more likely contributory factors linked to an increased risk of death. Among comorbid factors, coronary artery disease and congestive heart failure appeared to be the strongest predictor of death. Of our 64 cardiac patients, 19 died during hospitalization.

Other co-morbid factors studied such as diabetes mellitus, hypertension, COPD, and dementia did not affect mortality. In addition, the use of tube feeding, the presence of gastrointestinal symptoms, fever, and laboratory abnormalities such as high serum creatinine or low creatinine clearance were not predictive of increased mortality. On the other hand, we observed that an elevated BUN alone was predictive of increased mortality ($P=0.039$). Elevated BUN may have resulted (in these patients) from one or more of several pre-renal factors such as cardiac failure, volume depletion, catabolic states, and gastrointestinal bleeding as the basis. Also, factors predictive of death were refractory or recurrent infection lasting longer than 4 weeks ($P=0.007$), the use of penicillin-like antibiotics, ($P=0.035$), clindamycin ($P=0.004$) or aminoglycosides ($P=0.034$), and antibiotic use over 4 weeks ($P=0.01$). Obviously, the presence of recurrent or refractory infection usually requires prolonged use of antibiotics. Thus, it is conceivable that long-standing infection alone led to the increased mortality, while prolonged use of antibiotics was merely an association or a contributing factor to the adverse outcome. While we did not study treatment failure or relapse, previous work from our institution examined the factors influencing treatment failure and relapse, age, sex, co-morbid illnesses, and found that the type(s) of antibiotics that precipitate colitis were not associated with either the response to therapy or relapse^[16,17].

Nutritional status also appears to influence outcome in *Cd* colitis patients. In our study, hypoalbuminemia was strongly predictive of an adverse outcome ($P=0.001$). The literature states that serum albumin (<25 g/L) is a risk factor for

increased mortality, more significantly, a fall in serum albumin of greater than 11g/L at the onset of symptoms of *Cd* infection is positively associated with poor outcome^[17].

Hypoalbuminemia probably results from a loss of body protein in the stool caused by the inflammatory exudate, or by depressed hepatic protein synthesis in response to sepsis or malnutrition which is common among hospitalized elderly^[18]. Low serum albumin is a well-recognized marker for malnutrition^[19] and is strongly associated with poor clinical outcome in *Cd* colitis^[17].

While *Cd* colitis is more common in older individuals, our study suggests that age, per se, does not influence clinical outcome (survival/death). We observed that refractory sepsis, requiring use of antibiotics (in particular, certain classes of antibiotics) for over four weeks in the presence of hypoalbuminemia and coexisting cardiac disease were strongly predictive of adverse outcome (death) in *Cd* colitis in our hospitalized patients ($P < 0.00005$). Other factors such as COPD, dementia, hypertension, elevated creatinine or low creatinine clearance, and tube feeding were found not to affect the outcome in *Cd* colitis.

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