

ORIGINAL ARTICLE

연령군에 따른 *Clostridium difficile* 감염 입원환자의 임상경과

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Clinical Outcomes in Hospitalized Patients with *Clostridium difficile* Infection by Age Group

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Background/Aims: Advanced age is a known risk factor of poor outcomes for colitis, including *Clostridium difficile* infection (CDI). The present study compares the clinical outcomes of young and old patients hospitalized for CDI.

Methods: The clinical records of patients admitted from January 2007 to December 2013 with a diagnosis of CDI were analyzed. Patient baseline characteristics, clinical courses, and outcomes were compared with respect to age using a cut-off 65 years.

Results: Of the 241,391 inpatients registered during the study period, 225 (0.1%) with a diagnosis of CDI were included in the study. The mean patient age was 67.7 years. Seventy-two patients (32.0%) were younger than 65 years and 153 patients (68.0%) were 65 years old or more. The male to female ratio in the younger group was 0.8, and 0.58 in the older group. All 225 study subjects had watery diarrhea; six patients (8.3%) complained of bloody diarrhea in the young group and 21 patients (13.7%) in the old group ($p=0.246$). Right colon involvement was more common in the old group (23.5% vs. 42.7%, $p=0.033$). Furthermore, leukocytosis (41.7% vs. 67.3%, $p=0.000$), a CDI score of ≥ 3 points (77.8% vs. 89.5%, $p=0.018$), and hypoalbuminemia (58.3% vs. 76.5%, $p=0.005$) were more common in the old group. Failure to first line treatment was more common in the old group (17 [23.6%] vs. 58 [37.9%], $p=0.034$).

Conclusions: Severe colitis and failure to first line treatment were significantly more common in patients age 65 years or more. More aggressive initial treatment should be considered for older CDI patients. (Korean J Gastroenterol 2016;67:81-86)

Key Words: *Clostridium difficile* infection; Elderly; Severity; Treatment

INTRODUCTION

The rise in incidence and severity of *Clostridium difficile* infection (CDI) is of concern.¹⁻⁵ According to a study conducted in the United States, from 1997 to 2007 the prevalence and mortality, case-fatality, and colectomy rates of patients with CDI increased markedly.⁶ These increases are attributed to increases in older patients with underlying diseases and the use of antibiotics, including newly developed cephalosporin and quinolone.^{6,7} In addition, the emergence of the highly

toxigenic strain, BI/NAP1, has resulted in CDI becoming a cause of increased health care costs and mortality, especially in older patients.^{2,3,8} In BI/NAP1 outbreaks, age over 65 years was an important risk factor of CDI, of higher mortality and greater disease severity.^{1,9,10} CDI in older patients was identified as a major contributor to the increased cost of healthcare.¹¹⁻¹⁴

Although advanced age has been identified as a risk factor of CDI, few comparative studies have been conducted on the clinical outcomes of CDI in young and old patients.

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Accordingly, the aims of the present study were to evaluate and compare clinical features, severities of symptoms, treatment, and clinical outcomes of young vs. old (less than 65 years vs. 65 years and up) CDI hospitalized patients.

SUBJECTS AND METHODS

The medical records of hospitalized patients with a diagnosis of CDI treated from January 2007 to December 2013 were reviewed. We included only patients who were diagnosed more than 72 hours after admission. Individuals with a history of inflammatory bowel disease, toxic megacolon, exposure to vancomycin or metronidazole, or more than one occurrence of CDI within a period of three months prior to admission were excluded.

Patient baseline characteristics, clinical features of CDI, including symptoms, disease severity, laboratory findings, treatment, and outcomes were assessed. To compare clinical outcomes in the young and old study groups, patients were divided into two groups using a cutoff of 65 years.

CDI was diagnosed based on the presence of symptoms (usually diarrhea), and either a stool test result positive for *C. difficile* toxins or toxigenic *C. difficile*, or colonoscopic findings typical of pseudomembranous colitis.⁷

Disease severity was classified as follows: mild disease (severity 1), CDI with only diarrhea; moderate disease (severity 2), CDI with diarrhea but without additional symptoms and signs meeting the definition of severe or complicated CDI detailed below; severe disease (severity 3), CDI presenting with or developing hypoalbuminemia (serum albumin < 3 g/dL) and either of the following: (a) a white blood cell (WBC) count of $\geq 15,000$ cells/mm³, or (b) abdominal tenderness without the criteria of complicated disease. Complicated CDI (severity 4) is defined as CDI presenting with or developing at least one of the following signs or symptoms: admission to an intensive care unit, hypotension with or without the required use of vasopressors, fever ($\geq 38.5^{\circ}\text{C}$), ileus, or significant abdominal distention, mental status changes, WBC $\geq 35,000$ cells/mm³ or $< 2,000$ cells/mm³, serum lactate levels > 2.2 mmol/L, or any evidence of organ failure. Symptoms of ileus include acute nausea, emesis, sudden cessation of diarrhea, abdominal distention, or radiological signs consistent with disturbed intestinal transit.¹⁵

Treatment failure was defined as the absence of clinical

improvement after five days of treatment or the need to change treatment regimen because of poor clinical response. Recurrence was defined as any recurrence of CDI within 90 days after initial presentation.

All deaths that occurred after diagnosis of CDI were reviewed by medical chart. We determined whether the death was (1) directly related to CDI (the patient had no other underlying condition that would have caused death during admission); (2) indirectly related to CDI (the CDI contributed to the patient's death but was not the primary cause). We included only mortality directly related to CDI.

Statistical analysis was performed using PASW Statistics ver. 18.0 software for Windows (IBM Co., Armonk, NY, USA). Values are presented as means \pm SDs. The independent t-test was used to compare continuous variables and the chi-square test to compare categorical variables. Binary logistic regression analysis was used to identify risks for first line treatment failure. Null hypotheses of no difference were rejected if p-values were less than 0.05 or equivalently, if the 95% CIs of risk point estimates excluded 1.

RESULTS

Of the 241,391 patients hospitalized during the study period, 225 (0.1%) received a diagnosis of CDI. The mean patient age was 67.7 ± 15.3 years, 72 (32.0%) were younger than 65 years (the young group) and 153 (68.0%) were 65 years or more (the old group). The mean ages in the young and old groups were 49.5 and 76.3 years, respectively, corresponding male/female ratios were 1:0.8 and 1:0.58, and the mean times between admission and diagnosis of CDI were 11.1 and 8.7 days, respectively. Regarding the admission departments involved, 143 patients (63.6%) were admitted to internal medicine, 18 (8.0%) to neuromedicine, 16 (7.1%) to general surgery, 13 (5.8%) to orthopedic surgery, and 13 (5.8%) to neurosurgery. Patients with hypertension were more common in the old group (26.4% vs. 53.6%; $p < 0.05$). However, malignancy and diabetes mellitus rates were not significantly different in the two groups.

The mean durations of antibiotic exposures (7.6 ± 5.5 and 7.1 ± 5.0 days, respectively; $p=0.593$), H₂-blocker (66.7%), and proton pump inhibitor use (77.8%) before diagnosis did not differ significantly between the young and old groups. Types of antibiotic used before diagnosis included cepha-

Table 1. Patient Baseline Characteristics

Characteristic	Young group (n=72)	Old group (n=153)	p-value
Mean age (yr)	49.5±12.3	76.3±6.5	
Gender (male:female)	32:40 (0.8:1)	54:93 (0.58:1)	0.215
Underlying diseases			
Hypertension	19 (26.4)	82 (53.6)	0.000
Diabetes mellitus	15 (20.8)	38 (24.8)	0.509
Cancer	8 (11.1)	13 (8.5)	0.529
Ambulation	50 (69.4)	83 (54.2)	0.031
Duration from admission to diagnosis (day)	11.1±16.7	8.7±14.8	0.294
Antibiotics before diagnosed as CDI			
Cephalosporins	39 (54.2)	74 (48.4)	
Quinolones	18 (25.0)	39 (25.5)	
Penicillins	6 (8.3)	16 (10.5)	
Anti-tuberculous drug	5 (6.9)	6 (3.9)	
Others ^a	4 (5.6)	18 (11.7)	
Duration of antibiotics exposure	7.6±5.5	7.1±5.0	0.593
H ₂ -blocker or PPI ^b usage	48 (66.7)	119 (77.8)	0.076
Diagnostic modality			
<i>C. difficile</i> -toxin assay	68 (94.4)	144 (94.1)	0.922
Endoscopy	28 (38.9)	62 (40.5)	0.815

Values are presented as mean±SD, n only, or n (%).

Young group, less than 65 years; old group, 65 years and up.

CDI, *Clostridium difficile* infection; PPI: proton pump inhibitor.

^aCarbapenem, aminoglycosides; ^bwithin 30 days before presentation.

losporins (54.2% vs. 48.4%), quinolone (25.0% vs. 25.5%), and penicillin (8.3% vs. 10.5%) in young vs. old group. Anti-tuberculosis drugs caused CDI in five members of the young group (5/72, 6.9%) and in six members of the old group (6/153, 3.9%).

A greater percentage of young patients were able to ambulate (69.4% vs. 54.2%, $p < 0.05$). Modalities used for diagnosing CDI were the *C. difficile* toxin assay and endoscopy. The diagnostic modalities used in the two groups were similar. Typical endoscopic findings were obtained in 67.9% of the young group and in 70.9% of the old group (Table 1).

The right colon involvement was more common in the old group (8/34 [23.5%] vs. 35/82, [42.7%], $p=0.033$). All 225 study subjects complained of watery diarrhea. Fifty-four (75.0%) patients had fever in the young group and 124 (81.0%) in the old group ($p=0.298$). Twenty-six young patients (36.1%) and 63 (41.2%) old patients had abdominal pain ($p=0.469$). Six (8.3%) young patients and 21 old patients (13.7%) had bloody diarrhea ($p=0.246$). Leukocytosis (41.7% vs. 67.3%, $p=0.000$) and hypoalbuminemia (58.3% vs. 76.5%, $p=0.005$) were more common in old patients. However, hypotension (30.6% vs. 29.4%, $p=0.861$), hypokalemia (32.4% vs. 31.4%, $p=0.878$), and renal dysfunction

Table 2. Clinical Characteristics of the Two Study Groups

Characteristic	Young group (n=72)	Old group (n=153)	p-value
Right colon involvement	8/34 (23.5)	35/82 (42.7)	0.033
Symptoms			
Watery diarrhea	72 (100)	153 (100)	
Blood in stool	6 (8.3)	21 (13.7)	0.246
Abdominal pain	26 (36.1)	63 (41.2)	0.469
Fever	54 (75.0)	124 (81.0)	0.298
Hypotension	22 (30.6)	45 (29.4)	0.861
Leukocytosis	30 (41.7)	103 (67.3)	0.000
Hypokalemia	23 (32.4)	48 (31.4)	0.878
Kidney failure	18 (25.0)	40 (26.1)	0.855
Hypoalbuminemia	42 (58.3)	117 (76.5)	0.005
Severity			
1	4 (5.6)	3 (2.0)	
2	12 (16.7)	13 (8.5)	
3	54 (75.0)	134 (87.6)	
4	2 (2.8)	3 (2.0)	

Values are presented as n (%).

Young group, less than 65 years; old group, 65 years and up.

(25.0% vs. 26.1%, $p=0.855$) did not differ significantly between groups (Table 2).

Old patients had a higher mean severity score (2.7 vs. 2.9, $p=0.036$), and a greater percentage in the old group had a severity score of ≥ 3 points (77.8% vs. 89.5%, $p=0.018$).

Table 3. Clinical Outcomes in the Young and Old Study Groups

Variable	Young group (n=72)	Old group (n=153)	p-value
Failure of 1st line treatment	17 (23.6)	58 (37.9)	0.034
Recurrence	6 (8.3)	23 (15.0)	0.162
Time to recurrence (day)	33.6±8.2	25.1±11.0	0.479
Associated mortality	1 (1.4)	9 (5.9)	0.127

Values are presented as n (%) or mean±SD.

Young group, less than 65 years; old group, 65 years and up.

Metronidazole was used most commonly as an initial treatment (70 [97.2%] vs. 135 [88.2%]) in both groups. However, the rate of vancomycin use as an initial treatment was greater in the old group (2 [2.8%] vs. 18 [11.8%], $p=0.027$), and failure of first line treatment was more common in the old group (17 [23.6%] vs. 58 [37.9%]; $p=0.034$). Recurrence rates were 8.3% (6/72) and 15.0% (23/153) in the young and old groups, respectively, which was not a significant difference ($p=0.162$). From initial infection to recurrence, the period was not significantly different (33.6±8.2 in young group vs. 25.1±11.0 in old group, $p=0.479$). Mortality rates attributed to CDI were not significantly different (1 [1.4%] vs. 9 [5.9%]; $p=0.127$) (Table 3). During the study period, a 35-year-old female patient underwent surgery due to severe refractory CDI, and achieved a good condition without evidence of recurrence.

An age of ≥ 65 years, leukocytosis, hypoalbuminemia were found to be associated with first line treatment failure (Table 4). However, multivariate analysis failed to identify a risk factor significantly associated with treatment failure (Table 5).

DISCUSSION

CDI is a serious disease that is associated with significant morbidity and mortality, with incidence that has increased over last years.⁹ Advanced age, usually described as above 65 years, is associated with greater risk of CDI, with more severe disease, and a more frequent recurrence, resulting in higher morbidity and mortality.^{9,10,16,17} The present study shows that advanced age is associated with more severe disease and failure to respond to first line treatment. However, no significant intergroup difference was found for recurrence or mortality rates.

In a previous study, advanced age was observed to be as-

Table 4. Clinical Comparisons of Patients by Response to First Line Treatment

	Failure (n=75)	Success (n=150)	p-value
Age ≥ 65 years	58 (77.3)	95 (63.3)	0.035
Right colon involvement	19/41	24/71	0.228
Bloody diarrhea	9 (12.0)	18 (12.0)	1.000
Hypotension	21 (28.0)	46 (30.7)	0.758
Leukocytosis	52 (69.3)	81 (54.0)	0.031
Hypoalbuminemia	59 (78.7)	100 (66.7)	0.042

Values are presented as n (%) or n only.

Table 5. Risk Factors for First Line Treatment Failure

Parameter	OR	95% CI	p-value
Age ≥ 65 years	0.157	0.300-1.105	0.097
Leukocytosis	1.716	0.939-3.316	0.079
Hypoalbuminemia	1.498	0.761-2.951	0.242

sociated with CDI severity. The other variables associated with complicated disease were leukocytosis, renal failure, hypoalbuminemia, the presence of small bowel obstruction or ileus, and an imaging study showing colorectal inflammation.¹⁸ The relationship between leukocytosis and greater disease severity¹⁹ was described in initial reports of B1/NAP1 strain outbreaks.^{8,10} In the present study, leukocytosis and hypoalbuminemia were more common in the old group, which supports the findings that advanced age is a major risk factor of an unfavorable outcome in CDI.^{9,10,16,17}

There was no previous studies about right side colon involvement in patients with CDI. However, according to the study of ischemic colitis and ulcerative colitis, right colon involvement was associated with severe colitis and poor prognosis.²⁰ We thought that it could be similar in CDI because right colon involvement means more extensive disease. For this reason, the severity of disease in the patients in the old age group was higher in this study.

We found the use of vancomycin as an initial treatment was more frequent in the old group. The best treatment for CDI has not been determined. Many experts suggest vancomycin as first-line therapy in older patients, especially for patients with leukocytosis, severe abdominal pain, or an elevated creatinine level,²¹⁻²⁴ and several studies have confirmed that oral vancomycin provides higher rates of resolution than metronidazole in patients with severe CDI.²¹

In the present study, the rate of treatment failure was

greater in the old group. In a previous study, in elderly CDI patients, treatment failure on metronidazole occurred frequently and appeared to be related to a higher peak WBC count,¹⁹ concurrent with our results.

The limitations of the present study include a retrospective design and a small sample size. However, the study is unique as it is the first to compare clinical outcomes of CDI in young and old patients in Korea.

Greater efforts toward prevention would be more effective, especially as this is a nosocomial problem. Previous studies indicate the importance of the protective role played by immune response after colonization.²⁵⁻²⁹ Thus, the decreased immune responsiveness commonly observed in the elderly maybe an important component of CDI development in patients older than 65 years.

A state of immune deficiency contributes to the risk of adverse outcomes in elderly patients. The leukocytosis observed in such patients at presentation could be indicative of disease severity. Furthermore, thymic involution, an increase in natural killer cell numbers, and a decrease in B cell and immune responsive T-cell number are characteristic of the aging process.³⁰⁻³³ Although T cell numbers in peripheral blood remain stable with age, the number of immunoresponsive virgin CD 95 T cells falls markedly, while the majority of T cells are committed to the containment of endogenous viruses. These age-related changes result in a chronic proinflammatory state that leaves the host hyporesponsive to neoantigens^{30,34,35} and diminishes immunologic responses to infectious challenges.

In conclusion, right side colon involvement, leukocytosis, hypoalbuminemia, severe CDI, initial usage of vancomycin, and failure of first line treatment were more common in CDI patients at least 65 years old than in patients less than 65 years old. Furthermore, old age, leukocytosis, and hypoalbuminemia were found to be associated with first line treatment failure. We recommend intensive therapy be considered at time of diagnosis in CDI patients of 65 years or older exhibiting leukocytosis and hypoalbuminemia.

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