

Hematologic diseases: High risk of *Clostridium difficile* associated diarrhea

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METHODS: We retrospectively reviewed the medical records of patients who underwent *C. difficile* testing in a tertiary hospital in 2011. The incidence and risk factors for CDAD and its clinical course including recurrence and mortality were assessed in patients with hematologic disease and compared with those in patients with nonhematologic disease.

RESULTS: About 320 patients were diagnosed with CDAD (144 patients with hematologic disease; 176 with nonhematologic disease). The incidence of CDAD in patients with hematologic disease was estimated to be 36.7 cases/10000 patient hospital days, which was higher than the 5.4 cases/10000 patient hospital days in patients with nonhematologic disease. Recurrence of CDAD was more frequent in patients with hematologic disease compared to those with nonhematologic disease (18.8% vs 8.5%, $P < 0.01$), which was associated with higher re-use of causative antibiotics for CDAD. Mortality due to CDAD did not differ between the two groups. Multivariate analysis showed that intravenous immunoglobulin was the only significant factor associated with a lower rate of recurrence of CDAD in patients with hematologic disease.

CONCLUSION: The incidence and recurrence of CDAD was higher in patients with hematologic disease than in those with nonhematologic disease.

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Key words: *Clostridium difficile* associated diarrhea; Incidence; Clinical outcome; Patients with hematologic disease; Intravenous immunoglobulin

Abstract

AIM: To investigate the incidence and clinical outcome of *Clostridium difficile* (*C. difficile*) associated diarrhea (CDAD) in patients with hematologic disease.

Core tip: Our study included a large number of *Clostridium difficile* associated diarrhea (CDAD) patients at a dedicated hematopoietic stem cell transplantation center, which is one of the most renowned centers for

the treatment of hematologic diseases. The incidence and recurrence of CDAD was higher in patients with hematologic disease than in those with nonhematologic disease. This might be related to higher use of antibiotics. Use of intravenous immunoglobulin was associated with a lower CDAD recurrence rate. Based on our data, we suggest that physicians should be more aware of the higher incidence and rate of recurrence of CDAD in patients with hematologic disease.

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INTRODUCTION

Diarrhea is a common problem in patients with hematologic disease. Major causes of diarrhea include graft-versus-host disease, anticancer chemotherapy, and infections such as *Clostridium difficile* (*C. difficile*), *Escherichia coli* and cytomegalovirus^[1,2]. Patients with hematologic disease are susceptible to *C. difficile* associated diarrhea (CDAD) because of their frequent antibiotic use, prolonged duration of hospital stay, and chemotherapy-induced disruption of the intestinal mucosa^[3-7]. Prophylactic and empirical use of broad spectrum antibiotics is the common treatment for neutropenic fever patients with hematologic disease^[8,9]. It is difficult for most patients with hematologic disease and CDAD to discontinue treatment with broad spectrum antibiotics. From this perspective, the incidence and the clinical outcome of CDAD in hematologic disease might be different from that in nonhematologic disease. The incidence of CDAD in patients with hematologic disease has been reported to be 7.0%-14%^[4,6,7,10]. However, most studies have dealt with a small number of patients and some studies only included patients receiving hematopoietic stem cell transplantation^[4,6,7]. The aims of this study were to evaluate the incidence of CDAD in patients with hematologic disease and to assess factors associated with its clinical outcome.

MATERIALS AND METHODS

Study population

Between January 2011 and December 2011, 53334 patients (hematologic disease patients 2061; nonhematologic disease patients 51273) were admitted to Seoul St. Mary's Hospital, a tertiary university-affiliated hospital in South Korea. Among them, we retrospectively reviewed the medical records of patients who underwent *C. difficile* testing during the same period. Our hospital is one of the most renowned centers for the treatment of hematologic diseases with 360 cases of hematopoietic stem cell

transplantation carried out in 2011, which was the highest number in Asia. CDAD was defined as a combination of toxigenic stool culture (chromID *C. difficile*; bioMérieux, Marcy l'Etoile, France) and the presence of diarrhea of 3 unformed stools in 24 h^[11]. The toxin assay was conducted by either enzyme immunoassay (Wampole Tox A/B Quik Chek; Alere, Orlando, FL, United States) or polymerase chain reaction to detect toxin genes (*tcdA*, *tcdB*, *cdtA*, *cdtB*).

Exclusion criteria were as follows: (1) community-acquired CDAD, defined as onset of diarrhea within 48 h of hospital admission^[11]; (2) patients with loose stools or diarrhea fewer than 3 times a day; and (3) patients with inadequate medical records. The incidence and risk factors for CDAD and its clinical course including recurrence and mortality were assessed in patients with hematologic disease and compared with those in patients with nonhematologic disease. Risk factors for recurrence of CDAD were investigated in patients with hematologic disease. This study protocol was approved by the Institute Review Board of Seoul St. Mary's Hospital.

Methods

Demographic information, risk factors for CDAD, medications, and hospitalization information during the previous 60 d were investigated in patients with CDAD. Blood samples taken within 2 d of testing for *C. difficile* were used in the analysis. Admission days and antibiotic duration were calculated from the sum of hospital days during the 60 d prior to the index *C. difficile* test. Recurrence was defined as presence of diarrhea and positive toxigenic stool culture at least 2 wk after resolution of CDAD. Severe CDAD was defined as the presence of any of the following: (1) leukocytosis with white blood cell (WBC) count $\geq 15000/\text{mm}^3$; (2) acute kidney injury (AKI), serum creatinine $\geq 1.5 \times$ baseline creatinine; and (3) hypoalbuminemia with serum albumin < 2.5 g/dL^[11,12]. Antibiotic use was defined as the use of any antimicrobial agents once or more during the 60 d prior to the index *C. difficile* test. Concomitant medication was defined as the use of such agents for more than 5 d during the 60 d prior to the index *C. difficile* test.

Statistical analysis

The incidence, risk factors, and clinical course of CDAD were compared between the two groups. For this analysis, we used a *t* test for continuous variables and a χ^2 test or *F* test for categorical variables. The incidence of hospital-acquired CDAD was calculated as the total number of CDAD cases per 10000 patient hospital days. In patients with hematologic disease, factors possibly related to recurrence of CDAD were investigated in univariate and multivariate logistic regression models. Odds ratio and 95% confidence intervals were calculated for each risk factor. A *P* value < 0.05 was considered significant. All statistical analyses were conducted using SAS software (SAS Institute, Cary, NC, United States).

Table 1 Demographic characteristics and risk factors for *Clostridium difficile* associated diarrhea of the study subjects *n* (%)

Characteristics	HD (<i>n</i> = 144)	NHD (<i>n</i> = 176)	<i>P</i> value
Male	84 (58.3)	102 (58.0)	0.90
Age (mean ± SD)	47.4 ± 17.2	65.2 ± 16.0	< 0.01
Body mass index (mean ± SD), kg/m ²	22.4 ± 3.4	20.4 ± 7.1	< 0.01
Charlson score	2.3 ± 1.0	4.0 ± 2.5	< 0.01
WBC (mean ± SD)/mm ³	3093.6 ± 3879.1	9160.0 ± 6252.1	< 0.01
ANC (mean ± SD)/mm ³	2014.7 ± 3052.4	6843.2 ± 5473.9	< 0.01
Neutropenia	67 (46.5)	4 (2.3)	< 0.01
Total hospital days within 60 d	22.2 ± 13.9	23.1 ± 17.0	0.62
Previous anti-cancer chemotherapy	139 (96.5)	60 (34.1)	< 0.01
Antibiotics			
Use of antibiotics	142 (98.6)	166 (94.3)	0.07
Number of antibiotics	4.0 ± 1.6	2.6 ± 1.6	< 0.01
Days of antibiotics	27.8 ± 15.7	17.3 ± 13.9	< 0.01
Concomitant medications			
Anti-fungal agents	111 (77.1)	21 (11.9)	< 0.01
Acyclovir, ganciclovir	44 (31.7)	7 (4.0)	< 0.01
Proton pump inhibitor	62 (43.1)	56 (31.8)	0.04
H2 antagonist	71 (51.1)	91 (45.3)	0.67
Toxin assay			0.30
Toxin A + B	111 (77.1)	132 (75.0)	
Toxin B	26 (18.1)	40 (22.7)	
Toxin A + B + binary toxin	7 (4.9)	4 (2.3)	
Pseudomembranous colitis	7/31 (22.6)	16/32 (50)	0.02

CDAD: *Clostridium difficile* associated diarrhea; HD: Hematologic disease; NHD: Nonhematologic disease.

RESULTS

Incidence of CDAD

In 2011, 2106 patients were tested for *C. difficile*, 408 of whom had toxigenic *C. difficile*. Eighty-eight patients were excluded for the following reasons: 14 with community acquired CDAD, 20 with inadequate medical records and 54 with diarrhea or loose stools fewer than 3 times per day. Three hundred and twenty patients were diagnosed with CDAD, of whom 144 had hematologic disease and 176 nonhematologic disease. Total episodes of CDAD was 174 in the hematologic disease group and 194 in the nonhematologic disease group. The overall incidence of CDAD in our hospital was 9.1 cases/10000 patient hospital days. The incidence of CDAD in patients with hematologic disease was 36.7 cases/10000 patient hospital days, which was higher than that in patients with nonhematologic disease (5.4 cases/10000 patient hospital days).

Demographic characteristics and risk factor for CDAD

Patients with hematologic disease group were comprised as follows: acute myeloid leukemia 62, acute lymphoid leukemia 32, lymphoma 14, multiple myeloma 14, myelodysplastic syndrome 11, others 11. Among them, 56 patients underwent hematopoietic stem cell transplantation. Comorbidities of patients with nonhematologic

Table 2 Antibiotic use of the study subjects *n* (%)

Antibiotics	HD (<i>n</i> = 144)	NHD (<i>n</i> = 176)	<i>P</i> value
Cephalosporin	128 (88.9)	119 (67.6)	< 0.01
Aminoglycoside	96 (66.7)	34 (19.3)	< 0.01
Quinolone	99 (68.9)	63 (35.8)	< 0.01
Carbapenem	58 (40.3)	39 (22.2)	< 0.01
Glycopeptide	43 (29.9)	47 (26.7)	0.53
β lactam/β lactamase inhibitor	40 (27.8)	82 (46.6)	< 0.01
TMP/SMX	30 (20.8)	9 (5.1)	< 0.01
Macrolide	16 (11.1)	19 (10.8)	0.93

HD: Hematologic disease; NHD: Nonhematologic disease; TMP/SMX, Trimethoprim/sulfamethoxazole.

disease were as follows: solid organ cancer 62, infection (pneumonia or acute pyelonephritis or cholecystitis) 42, cardiovascular disease 20, cerebrovascular disease 16, musculoskeletal disease 9, chronic kidney disease or liver cirrhosis 12, abdominal organ surgery 4, others 11. Patients with hematologic disease were younger and had a higher body mass index and lower Charlson comorbidity score than patients with nonhematologic disease (Table 1). WBC counts and absolute neutrophil counts were lower in patients with hematologic disease.

Almost all patients with hematologic disease had received previous anticancer chemotherapy. The percentage of the patients who received antibiotic therapy did not differ significantly between the two groups (98.6% *vs* 94.3%, *P* = 0.07). However, the total number of antibiotics administered and the duration of antibiotic treatment were higher in patients with hematologic disease than in patients with nonhematologic disease (*P* < 0.01). Cephalosporin, quinolone, and carbapenem were used in 88.9%, 68.9% and 40.3%, respectively, of patients with hematologic disease, which was significantly higher than the rate in patients with nonhematologic disease (Table 2). Concomitant use of an antifungal agent and antiviral agents (acyclovir, ganciclovir) was higher in patients with hematologic disease. Use of a proton pump inhibitor (PPI) was higher in patients with hematologic disease, but use of an H2 antagonist was not. The results of the toxin assay did not differ between the two groups.

Clinical course of CDAD

Treatment of CDAD included cessation of causative antibiotics, metronidazole and oral vancomycin. Initial treatments for CDAD did not differ between the two groups (Table 3). The rate of additional use of causative antibiotics was higher in patients with hematologic disease (*P* < 0.01), as was the rate of concomitant use of intravenous immunoglobulin (*P* < 0.01). Severe CDAD was less common in patients with hematologic disease. Overall mortality (16.0% *vs* 16.5%, *P* = 0.90) and mortality attributable to CDAD (0.7% *vs* 0.6%, *P* = 0.89) within 1 mo did not differ between the two groups. The rate of recurrence of CDAD in patients with hematologic disease was 18.8%, which was higher than that in patients with nonhematologic disease (8.5%).

Table 3 Treatment and clinical course of the study subjects *n* (%)

Characteristics	HD (<i>n</i> = 144)	NHD (<i>n</i> = 176)	<i>P</i> value
Treatment			0.82
Cessation of causative antibiotics for CDAD	42 (29.2)	57 (32.4)	
Metronidazole	95 (66.0)	111 (63.1)	
Oral vancomycin	7 (4.9)	8 (4.5)	
Additional use of causative antibiotics for CDAD	109 (75.7)	79 (44.9)	< 0.01
Continuous use	67 (46.5)	22 (12.5)	
Re-use	42 (29.2)	57 (32.4)	
Concomitant use of IVIG	80 (55.6)	11 (6.3)	< 0.01
Severe CDAD	11 (7.6)	43 (24.4)	< 0.01
Leukocytosis	3 (2.1)	18 (10.2)	< 0.01
Hypoalbuminemia	5 (3.5)	31 (17.6)	< 0.01
AKI	3 (2.1)	11 (6.3)	0.10
Clinical outcome			
Overall mortality within 1 mo	23 (16.0)	29 (16.5)	0.90
Mortality due to CDAD within 1 mo	1 (0.7)	1 (0.6)	0.89
Recurrence	27 (18.8)	15 (8.5)	< 0.01

HD: Hematologic disease; NHD: Nonhematologic disease; CDAD: CDAD: *Clostridium difficile* associated diarrhea; IVIG: Intravenous immunoglobulin; AKI: Acute kidney injury.

Factors projecting recurrence of CDAD in patients with hematologic disease

Univariate analysis showed that a low WBC count, neutropenia, toxin A + B, toxin B, and additional use of causative antibiotics were significantly associated with recurrence. Use of intravenous immunoglobulin was higher in patients with nonrecurrence. Multivariate analysis demonstrated that intravenous immunoglobulin was the only significant factor associated with reduced recurrence of CDAD (Table 4).

DISCUSSION

The annual incidence of CDAD at our hospital was 9.0 cases/10000 patient hospital days, which was comparable to a previous report from a single tertiary hospital in South Korea (7.2 cases/10000 patient hospital days)^[13]. The incidence of CDAD in Korea seems to be lower than in Western countries. One study from Canada reported the incidence of hospital-acquired CDAD as 28.1 cases/10000 patient hospital days^[14]. The higher incidence of CDAD in Western countries might be associated with a higher prevalence of the hypervirulent strain B1/NAP1/027^[3,15,16], which comprises up to 60% of hospital-acquired CDAD in Western countries^[14,16] compared with 2.1% of CDAD reported in South Korea^[13].

At a single tertiary center in Korea, the incidence of CDAD in patients with hematologic disease was estimated to be 36.7 cases/10000 patient hospital days, which was higher than the 5.4 cases/10000 patient hospital days in patients with nonhematologic disease. CDAD recurrence was more frequent in patients with hematologic disease than in patients with nonhematologic disease. Higher recurrence of CDAD in patients with hemato-

logic disease was associated with higher additional use of causative antibiotics for CDAD^[17]. Multivariate analysis revealed that intravenous immunoglobulin was the only significant preventative factor for recurrence of CDAD in patients with hematologic disease.

Well-known risk factors for CDAD are older age, use of PPI, prolonged duration of hospital stay, comorbidity, and antibiotics^[18]. Despite the younger age and lower Charlson comorbidity score of the patients with hematologic disease in our study, their incidence of CDAD was higher than that in patients with nonhematologic disease. This might be related to their previous anticancer chemotherapy and higher number of antibiotics with longer treatment duration. Febrile neutropenia is a common complication of chemotherapy and hematopoietic stem cell transplantation in patients with hematologic disease^[19]. Broad spectrum antibiotics are routinely prescribed to prevent and to treat neutropenic fever^[2,8,9]. In South Korea, fourth generation cephalosporin and aminoglycoside are also commonly used for empirical therapy in neutropenic fever^[20]. Cumulative exposure to antibiotics increases the risk of CDAD^[21]. Cephalosporin, quinolone, and carbapenem were the antibiotics most frequently associated with CDAD^[18,22,23], and were used in 88.9%, 68.9% and 40.3%, respectively, of the patients in this study with hematologic disease, a significantly higher rate than in patients with nonhematologic disease. Use of PPI was higher in patients with hematologic disease, which might increase the risk of CDAD^[24,25].

In our study, risk factors associated with the recurrence of CDAD in patients with hematologic disease were low WBC count, number of neutropenia, toxin A + B, continuous use of causative antibiotics for CDAD, and lower use of intravenous immunoglobulin in univariate analysis. Interestingly, use of intravenous immunoglobulin was the only factor associated with fewer recurrences of CDAD in multivariate analysis. Intravenous immunoglobulin had been used as adjuvant therapy for infection, and is routinely administered in hematopoietic stem cell transplantation^[2,26,27]. Several studies have reported that intravenous immunoglobulin is a promising adjuvant therapy for CDAD. However, its therapeutic efficacy against CDAD remains controversial, although monoclonal antibodies targeting *C. difficile* toxin were effective for prevention of CDAD recurrence^[28-31]. Given our data showing a favorable effect of intravenous immunoglobulin, further study is needed to investigate its use in treatment of CDAD in patients with hematologic disease. Mortality due to CDAD did not differ between the two groups. Mortality due to CDAD is less common in Korea than in Western countries, which might be explained by the fact that there has been no outbreak of the hypervirulent B1/NAP1/027 strain in South Korea^[13,32].

Due to the retrospective design, some patients might have been omitted from *C. difficile* testing which is a limitation of our study.

This study was a large-scale single-center study comparing CDAD in patients with hematologic disease with

Table 4 Comparison of recurrent *vs* non-recurrent *Clostridium difficile* associated diarrhea in the hematologic disease group *n* (%)

Characteristics	Recurrent <i>n</i> = 27	Single episode <i>n</i> = 117	Univariate analysis <i>P</i> value	Multivariate analysis <i>P</i> value Odds ratio (95%CI)	
Male	13 (48.1)	71 (60.7)	0.23		
Age (mean ± SD)	47.5 ± 16.0	47.3 ± 17.6	0.93		
Body mass index (mean ± SD), kg/m ²	22.3 ± 3.6	22.4 ± 3.4	0.87		
Total hospital days within 60 d	24.3 ± 12.9	21.8 ± 14.1	0.89		
Charlson score	2.5 ± 1.7	2.2 ± 0.8	0.13		
Antibiotics					
Use of antibiotics	27 (100)	115 (98.3)	0.49		
Number of antibiotics	4.2 ± 1.4	4.0 ± 1.7	0.57		
Duration of antibiotics	27.8 ± 13.3	27.8 ± 16.2	1.0		
WBC (mean ± SD)/mm ³	1326.7 ± 1813.7	3501.4 ± 4113.1	< 0.01	0.50	1.0 (0.998-1.003)
ANC (mean ± SD)/mm ³	751.1 ± 1224.5	2306.2 ± 3269.9	0.02	0.83	1.0 (0.997-1.002)
Neutropenia	17 (63.0)	50 (42.7)	0.04	0.87	1.13 (0.37-4.74)
Severe CDAD	2 (7.4)	9 (7.7)	1.0		
Toxin assay					
Toxin A + B	26 (96.2)	85 (72.6)	< 0.01	0.87	0.82 (0.8-8.8)
Toxin B	0 (0.0)	26 (22.2)	< 0.01	1.00	0
Toxin A + B + binary toxin	1 (3.7)	6 (5.1)	1.0		
Treatment for CDAD			0.68		
Metronidazole or vancomycin	20 (74.1)	82 (70.1)			
Discontinuation of causative antibiotics	7 (25.9)	35 (29.9)			
IVIG	8 (29.6)	72 (61.5)	< 0.01	< 0.01	0.24 (0.09-0.65)
Additional use of causative antibiotics for CDAD	27 (100.0)	82 (70.1)	< 0.01	1.00	0
Continuous use	20 (74.1)	47 (40.2)			
Re-use	7 (25.9)	35 (29.9)			

CDAD: *Clostridium difficile* associated diarrhea; WBC: White blood cell; ANC: Absolute neutrophil count; IVIG: Intravenous immunoglobulin.

that in patients with nonhematologic disease. Our study showed that the incidence of hospital-acquired CDAD in patients with hematologic disease was about six times higher than that in patients with nonhematologic disease, and that CDAD recurrence was more frequent in patients with hematologic disease. Use of intravenous immunoglobulin was associated with a lower CDAD recurrence rate. Based on our data, we suggest that physicians should be more aware of the higher incidence and rate of recurrence of CDAD in patients with hematologic disease.

COMMENTS

Background

Patients with hematologic disease are susceptible to *Clostridium difficile* associated diarrhea (CDAD) because of their frequent antibiotic use. The aims of this study were to evaluate the incidence of CDAD in patients with hematologic disease and to assess factors associated with its clinical outcome.

Research frontiers

Treatment failure and recurrence of CDAD is increasing, especially in Western countries. Some drugs for CDAD and fecal microbiota transplantation for refractory CDAD are hot research topics.

Innovations and breakthroughs

Patients with hematologic disease are susceptible to CDAD because of frequent antibiotic use and immunocompromised status. However comprehensive clinical studies regarding this issue are rare. A large number of patients was included in this study. The authors revealed higher incidence and recurrence rate of CDAD in patients with hematologic disease compared with those in patients with nonhematologic disease. However, mortality due to CDAD was not different between the two groups.

Applications

Physicians should be more aware of the higher incidence and rate of recurrence of CDAD in patients with hematologic disease. Metronidazole was a good treatment option for the treatment of CDAD in patients with hematologic

disease.

Peer review

The authors have retrospectively investigated the incidence and clinical outcome of CDAD in patients with hematologic disease and compared them with those in patients with nonhematologic disease in a large-scale single center setting. The data are interesting and provide some reference in clinical practice. The increased incidence of CDAD in hematologic diseases was shown and the multivariate analysis revealed that intravenous immunoglobulin-injected patients showed less frequent recurrence of CDAD in hematologic disease patients.

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