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Original Article

Bloodstream Infections in Patients with Hematologic Diseases: Causative Organisms and Factors Associated with Resistance

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ABSTRACT

Background: Patients with hematologic diseases are at high risk of bloodstream infections (BSIs). This study aimed to analyze clinical features and distributions of microorganisms in patients with hematologic diseases presenting at a tertiary care university-affiliated hospital in Korea.
Materials and Methods: We retrospectively reviewed all BSI episodes recorded in patient medical records at two hematologic wards of the Catholic Hematology Hospital from January to December 2020. Our aim was to analyze demographic and clinical characteristics relevant to BSIs. We also described the antimicrobial resistance patterns of the major pathogens identified in this study, and evaluated risk factors for extended-spectrum beta-lactamase (ESBL) production in *Enterobacteriaceae* isolates and for vancomycin resistance in enterococcal isolates.
Results: A total of 380 BSI episodes were identified in 334 patients over the course of 1 year (monomicrobial BSI episodes, 86.1%; polymicrobial BSI episodes, 13.9%). Gram-negative bacteria accounted for 242 isolates (54.8%). The most frequently isolated Gram-negative bacteria isolates were *Escherichia coli* (107 [24.2%]) followed by *Klebsiella* spp. (72 [16.3%]), *Pseudomonas* spp. (21 [4.8%]), and *Enterobacter* spp. (12 [2.7%]). The most commonly identified Gram-positive bacteria were *Enterococcus* spp. (72 [16.3%]) followed by viridans streptococci (54 [12.2%]), coagulase-negative staphylococci (CoNS) (24 [5.4%]), and *Corynebacterium* spp. (22 [5.0%]). ESBL-producing *Enterobacteriaceae* accounted for 25.1% of the total distribution. Among 54 *Enterococcus faecium* isolates, 100.0% were resistant to ampicillin and 55.6% showed resistance to vancomycin, while 100.0% (n = 12) of *Enterococcus faecalis* isolates were susceptible to ampicillin and vancomycin, respectively. Use of ciprofloxacin prophylaxis (odds ratio: 5.20; 95% confidence interval: 1.11 - 24.34; $P = 0.04$) was an independent risk factor for ESBL production in *Enterobacteriaceae* BSIs.
Conclusion: Compared with the results of a previous study conducted at the same institution, our findings demonstrated that Gram-negative bacteria remained dominant pathogens in BSIs occurring in patients with hematologic diseases. Our findings also demonstrated a comparatively decreased prevalence of ESBL-producing *Enterobacteriaceae* in the evaluated BSIs. However, the prevalence of enterococcal BSIs had not decreased, and the proportion of vancomycin-resistant *Enterococcus* isolates from *E. faecium* BSIs had increased. In addition, we found that ciprofloxacin prophylaxis was statistically significantly associated with ESBL production in *Enterobacteriaceae* BSIs. We conclude that, in order to avoid critical

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complications and to reduce the burden of antimicrobial-resistant organisms in patients with hematologic diseases, it is necessary to conduct periodic examinations evaluating changes in BSI epidemiology within a single medical center.

Keywords: Antimicrobial stewardship; Bacteremia; Drug resistance, Bacterial; Hematologic diseases

INTRODUCTION

Bloodstream infections (BSI) are critical complications that commonly occur in immunocompromised patients with hematologic diseases, especially in those undergoing intensive chemotherapy or hematopoietic stem cell transplantation. BSI leads to increased patient mortality, delays the timing of treatment, and prolongs hospitalization, thereby leading to a poor prognosis [1]. Among various causative organisms, Gram-negative bacteria and Gram-positive bacteria are common pathogens leading to BSI in patients with hematologic diseases [1-3]. As is well known, most patients are neutropenic at the onset of BSI, and neutropenia is a risk factor for BSI development in immunocompromised hosts [4-6].

Pathogens underlying bacteremia have been changing over time, as have antimicrobial resistance patterns. For example, several studies from Europe and the United States have demonstrated a gradual increase in the prevalence of Gram-positive bacteria isolated from BSIs [7]. This may be due to the increased use of indwelling catheters as well as to more frequent exposure to antimicrobials in the general population [8]. We note that mucosal barrier injury is another common complication occurring in patients with hematologic diseases that can lead to BSIs. In addition, the use of antimicrobial prophylaxis and the administration of empirical broad-spectrum antimicrobials each contribute to transitions in antimicrobial susceptibility trends [7, 9, 10]. However, many recent studies performed in Korea show that Gram-negative bacteria are still the dominant causative pathogens for BSIs [11, 12].

Emerging antimicrobial-resistant organisms adversely affect clinical outcomes in patients with hematologic diseases, due to unexpected delays in administering appropriate antimicrobials and prolonged hospitalizations [11, 13]. Given that the treatment of infections due to multidrug-resistant Gram-negative bacteria has presented a clinical challenge, the recently detected increase in antimicrobial-resistant Gram-negative bacterial infections is of great concern [14].

Hence, this study aimed to examine the clinical characteristics of recent BSI episodes at our medical center, to identify the causative microorganisms leading to these BSIs, and to identify antimicrobial resistance patterns in patients with hematologic diseases presenting at a single hematology hospital. We also aimed to evaluate risk factors for extended-spectrum beta-lactamase (ESBL) production in *Enterobacteriaceae* BSIs and for vancomycin resistance in enterococcal BSIs.

MATERIALS AND METHODS

1. Data collection

We retrospectively reviewed medical records for all BSI episodes in adult patients with hematologic diseases that occurred between January and December 2020 at the Catholic

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Hematology Hospital (Seoul, Korea). Patients older than 19 years of age with hematologic diseases were included in this study.

The clinical and demographic data collected for each patient included age, sex, underlying hematologic diseases, treatment for underlying diseases, disease status, absolute neutrophil counts (ANC) at the onset of BSI, C-reactive protein (CRP) levels, comorbidities, organisms isolated from blood samples, and the antimicrobial susceptibility of the detected organisms.

Two sets of blood samples were obtained from each patient. One set was obtained from a peripheral vein puncture and another set was simultaneously obtained from a central venous catheter. In patients in which central venous catheters were absent, two sets of blood samples were collected 30 minutes apart from two different peripheral venipuncture sites. Blood culture results were obtained using an automated blood culture system (BACTEC FX, Becton Dickinson, Sparks, MD, USA). The positive blood culture bottle was sent to Vitek MS (bioMérieux, Marcy L'Etoile, France) and Vitek 2 (bioMérieux, Hazelwood, MO, USA) for direct identification and antimicrobial susceptibility testing. The resulting minimum inhibitory concentration values were classified according to the guidelines set forth by the Clinical and Laboratory Standards Institute [15-17].

2. Ethics statement

The research protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC22RISI0001). The requirement for informed consent was waived due to the retrospective study design.

3. Definitions

Neutropenia was defined as an ANC of <500 cells/mm^3 or an ANC of <1,000 cells/mm^3 that was expected to fall to <500 cells/mm^3 within the next 48 hours [3, 18]. Bacteremia was defined according to the isolation of the same bacterial species or pathogen in at least one blood culture examination [19]. If the blood samples yielded potential skin contaminant isolates, these isolates were considered true pathogens only if antimicrobial treatment was initiated under the supervision of infectious disease specialists and if the patient presented with clinical signs and symptoms consistent with infection [20].

BSI was considered polymicrobial if two or more organisms were isolated from a single blood culture sample simultaneously or from separate blood cultures obtained within a span of <48 hours [1, 12]. Consecutive positive blood cultures detecting the same microorganism during the same antimicrobial treatment period were considered indicative of a single BSI episode. Different organisms isolated from a single patient ≥48 hours apart were considered separate bacteremia episodes.

In addition, patients' highest CRP level was obtained within five days from the culture-positive day, in accordance with previous methodologic study findings [21, 22]. Pathogens presenting with intermediate antimicrobial susceptibility were considered antimicrobial-resistant [11].

4. Prophylaxis, antimicrobial strategies, and antimicrobial stewardship interventions

At our institution, infectious disease specialists are responsible for administering strategies addressing prophylaxis, empirical antimicrobial therapy, and antimicrobial stewardship programs (ASPs). Before October 2016, oral ciprofloxacin (500 mg every 12 hours [q12h]) had

been used as routine antibacterial prophylaxis during any chemotherapy regimen as well as in the course hematopoietic stem cell transplantation until the recovery of the patient's ANC to >500/mm^3 or the first febrile episode. At this time, the initial empirical antimicrobials for neutropenic fever were anti-pseudomonal cephalosporins, cefepime, or ceftazidime (2 g q12h given intravenously [IV]) with aminoglycoside, isepamicin (400 mg q24h by IV), or amikacin (7 – 10 mg/kg q24h by IV). Carbapenems were selected as second-line antimicrobials.

After October 2016 (*i.e.*, following the modification of our ASP), the use of routine ciprofloxacin antibacterial prophylaxis was interrupted. Instead, we started selectively authorizing remission induction or re-induction chemotherapy for patients with acute leukemia as well as in those undergoing cord blood transplantation. Monotherapy with cefepime (2 g q8h by IV) was selected as the first-line empirical antimicrobial, piperacillin/tazobactam (4.5 g q8h by IV) was selected as the second-line antimicrobials, and carbapenems were chosen as the third-line treatment for use in empirical therapy. Empirical glycopeptides were allowed only with evidence of severe mucositis (grade ≥3), combined skin and soft tissue infections, catheter-related infections, Gram-positive bacteremia, or hemodynamically unstable states, with the consultation of infectious disease specialists. Infectious disease specialists changed empirical antimicrobials depending on the confirmed pathogens, findings of antimicrobial susceptibility, and recovery from neutropenia or a febrile state. Antimicrobials were discontinued if a sufficient duration of recovery had been achieved. Patients were followed up at our outpatient clinic if antimicrobial therapy had to be continued.

5. Statistical analyses

The clinical characteristics of the BSIs are presented using counts and percentages for categorical variables and using medians and ranges for continuous variables. Univariate and multivariate logistic regression models were implemented to analyze risk factors for ESBL-producing *Enterobacteriaceae* and vancomycin-resistant *Enterococcus* (VRE). A two-sided *P*-value of <0.05 was considered the threshold for statistical significance. All statistical analyses were performed using SPSS statistical software (version 25.0; SPSS Inc., Chicago, IL, USA).

RESULTS

1. Clinical characteristics of the BSI episodes

The clinical characteristics of the evaluated BSI episodes are described in **Table 1**. A total of 380 BSI episodes were identified, 48.4% of which occurred in men, and the median age of the presenting patients was 53 years. Patients with acute myeloid leukemia (AML) accounted for 62.6% of these cases, followed by patients with acute lymphoblastic leukemia (ALL; 25.5%), multiple myeloma (MM; 4.5%), and lymphoma (2.6%).

In sorting the BSI episodes into treatment groups, we found that BSIs occurring in patients who underwent consolidation chemotherapy prior to the BSI episode accounted for 50.8% of the evaluated episodes, BSIs associated with remission induction chemotherapy or re-induction chemotherapy accounted for 25.5% of the BSI episodes, and hematopoietic stem cell transplantation accounted for 23.4% of the episodes; there was only one BSI episode in the palliative care group (0.3%).

Regarding the disease status of patients experiencing BSI episodes, 64.2% of the episodes occurred in patients who were in complete remission (CR), 22.1% occurred in patients who

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Table 1. Clinical and demographic characteristics of bloodstream infection episodes

Characteristics	Total (n = 380)
	n (%)
Male sex	184 (48.4)
Age (years), median (range)	53 (18 – 78)
Underlying hematologic diseases	
AML	238 (62.6)
ALL	97 (25.5)
MM	17 (4.5)
Lymphoma	10 (2.6)
MDS	9 (2.4)
AA	4 (1.1)
Others[a]	5 (1.3)
Treatment for underlying diseases	
Chemotherapy	
Remission induction/re-induction	97 (25.5)
Consolidation	193 (50.8)
Stem cell transplantation	
Allogeneic stem cell transplantation	66 (17.4)
Autologous stem cell transplantation	23 (6.0)
Palliative care	1 (0.3)
Disease status	
Naïve	52 (13.7)
Complete remission	244 (64.2)
Incomplete remission	84 (22.1)
Neutropenia at the onset of BSI (ANC <500/mm^3)	367 (96.6)
CRP (mg/dL), median (range)	14.7 (0.83 – 45.17)
ICU admission	40 (10.5)
Septic shock	36 (9.5)
Use of prophylactic ciprofloxacin	71 (18.7)
Comorbidities	
None	304 (80.0)
Diabetes	72 (18.9)
Chronic liver disease	4 (1.1)
Type of BSI	
Monomicrobial	327 (86.1)
Polymicrobial	53 (13.9)

[a]This category includes chronic myelogenous leukemia (n = 2) and hemophagocytic lymphohistiocytosis (n = 3).
AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; MDS, myelodysplastic syndrome; AA, aplastic anemia; BSI, bloodstream infection; ANC, absolute neutrophil count; CRP, C-reactive protein; ICU, intensive care unit.

were in incomplete remission (IR), and 13.7% occurred in naïve cases. Moreover, 10.5% of the BSI episodes required intensive care unit (ICU) admission, and 9.5% required the use of vasopressors. A total of 18.7% of the BSI episodes had occurred following the use ciprofloxacin prophylaxis, and 20% were associated with comorbidities (diabetes, 18.9%; chronic liver disease, 1.1%). A total of 86.1% of the BSI episodes were monomicrobial episodes, while 13.9% were polymicrobial BSI cases.

2. Distribution of microorganisms

A total of 442 microorganisms were identified in the 380 BSI episodes analyzed in the present study. Gram-negative bacteria accounted for 242 (54.8%) of the microorganisms, while Gram-positive bacteria accounted for 196 (44.3%). The most frequently isolated Gram-negative bacteria were *Escherichia coli* (107, 24.2%), followed by *Klebsiella* species (72, 16.3%), *Pseudomonas* species (21, 4.8%), and *Enterobacter* species (12, 2.7%).

The most commonly identified Gram-positive bacteria were *Enterococcus* species (72, 16.3%), followed by viridans streptococci (54, 12.2%), coagulase-negative staphylococci (CoNS; 24,

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Table 2. Microorganisms isolated from bloodstream infections

Microorganisms (n = 442)	n (%)
Gram negatives (n = 242)	242 (54.8)
Escherichia coli	107 (24.2)
Klebsiella spp.	72 (16.3)
Pseudomonas spp.	21 (4.8)
Enterobacter spp.	12 (2.7)
Stenotrophomonas maltophilia	4 (0.9)
Acinetobacter baumannii	4 (0.9)
Bacteroides spp.	4 (0.9)
Citrobacter spp.	3 (0.7)
Fusobacterium spp.	3 (0.7)
Others[a]	12 (2.7)
Gram positives (n = 196)	196 (44.3)
Enterococcus spp.	72 (16.3)
Enterococcus faecium	54 (12.2)
Enterococcus faecalis	12 (2.7)
Other *Enterococcus* spp.[b]	6 (1.4)
Viridans streptococci	54 (12.2)
CoNS	24 (5.4)
Corynebacterium spp.	22 (5.0)
Staphylococcus aureus	11 (2.5)
Bacillus spp.	6 (1.4)
Streptococcus spp.[c]	4 (0.9)
Others[d]	3 (0.7)
Fungus (n = 4)	4 (0.9)
Candida spp.[e]	3 (0.7)
Fusarium spp.	1 (0.2)

[a]*Capnocytophaga sputigena* (n = 2), *Serratia marcescens* (n = 2), *Proteus mirabilis* (n = 1), *Haemophilus parainfluenza* (n = 2), *Campylobacter jejuni* (n = 2), *Raoultella planticola* (n = 1), *Pantoea* spp. (n = 1), *Leptotrichia trevisanii* (n = 1), and *Morganella morganii* (n = 1).
[b]*Enterococcus gallinarum* (n = 5) and *Enterococcus avium* (n = 1).
[c]All *Streptococcus* species other than viridans streptococci such as *Streptococcus agalactiae* (n = 2), *Streptococcus dysgalactiae* (n = 1), and *Streptococcus pneumoniae* (n = 1).
[d]*Clostridium tertium* (n = 1), *Rothia mucilaginosa* (n = 1), and *Granulicatella adiacens* (n = 1).
[e]*Candida glabrata* (n = 1), *Candida krusei* (n = 1), and *Candida parapsilosis* (n = 1).
spp., species; CoNS, coagulase-negative staphylococci.

5.4%), and *Corynebacterium* species (22, 5.0%). Of the 72 isolates of *Enterococcus* species detected in this study, 54 (12.2%) were *Enterococcus faecium*, 12 (2.7%) were *Enterococcus faecalis*, and other *Enterococcus* species such as *Enterococcus gallinarum* (n = 5) and *Enterococcus avium* (n = 1) accounted for six (1.4%) of the remaining isolates. Of the 22 *Corynebacterium* spp. isolates, most were *Corynebacterium striatum* (n = 21); there was one *Corynebacterium jeikeium* isolate (**Table 2**).

3. Pathogen antimicrobial resistance patterns

The antimicrobial resistance patterns of the identified Gram-negative and Gram-positive bacteria are described in **Tables 3** and **4**, respectively. Among the 107 *E. coli* isolates, 40 isolates (37.4%) were ESBL-producing *E. coli*, 67.3% were resistant to ciprofloxacin, and none showed resistance to carbapenems. Of the 72 *Klebsiella* spp. isolates, 6.9% were ESBL producers and 16.7% were resistant to ciprofloxacin, which added up to a total prevalence of 25.1% for ESBL-producing *Enterobacteriaceae.* Of the 21 *Pseudomonas* species isolates, 9.5% of were carbapenem-resistant, showing resistance to imipenem and meropenem. Among the four *Acinetobacter baumannii* isolates, 100.0% were multidrug-resistant organisms (MDROs). All *Stenotrophomonas maltophilia* isolates (n = 4) were found to be susceptible to trimethoprim-sulfamethoxazole (TMP/SMX).

Analyzing the antimicrobial resistance patterns of the detected Gram-positive bacteria, 100.0% (n = 54) of the *E. faecium* isolates showed resistance to ampicillin and 55.6% (n = 30)

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Table 3. Antimicrobial resistance patterns of the major Gram-negative organisms identified in this study

Pathogens (No. of isolates)	Antimicrobial resistance					
	ESBL	CIP	TMP/SMX	ETP	IPM	MEM
Escherichia coli (107)	40/107	72/107	51/107	0/107	0/107	0/107
Klebsiella spp. (72)	5/72	12/72	12/72	3/72	2/72	2/72
Pseudomonas spp. (21)	-	1/21	1/21	-	2/21	2/21
Acinetobacter baumannii (4)	-	4/4	4/4	-	4/4	4/4
Stenotrophomonas maltophilia (4)	-	-	0/4	-	-	-
Total no.	45/179	89/204	68/208	3/179	8/204	8/204
% resistance	25.1	43.6	32.7	1.7	3.9	3.9

ESBL, extended spectrum beta-lactamase; CIP, ciprofloxacin; TMP/SMX, trimethoprim-sulfamethoxazole; ETP, ertapenem; IPM, imipenem; MEM, meropenem; spp., species.

Table 4. Antimicrobial resistance patterns of the major Gram-positive organisms identified in this study

Pathogens (No. of isolates)	Antimicrobial resistance							
	OXA	TMP/SMX	AMP	CTX	CRO	VAN	TEC	LZD
Enterococcus faecium (54)	-	-	54/54	-	-	30/54	29/54	0/54
Enterococcus faecalis (12)	-	-	0/12	-	-	0/12	0/12	0/12
Other *Enterococcus* spp.[a] (6)	-	-	1/6	-	-	5/6	0/6	0/6
Viridans streptococci (54)	-	-	24/54	5/54	5/54	0/54	-	0/54
CoNS (24)	23/24	12/24	-	-	-	0/24	6/24	0/24
Staphylococcus aureus (11)	3/11	0/11	-	-	-	0/11	0/11	0/11
Total no.	26/35	12/35	79/126	5/54	5/54	35/161	35/107	0/161
% resistance	74.3	34.3	62.7	9.3	9.3	21.7	32.7	0

[a]*Enterococcus gallinarum* (n = 5) and *Enterococcus avium* (n = 1).
OXA, oxacillin; TMP/ SMX, trimethoprim-sulfamethoxazole; AMP, ampicillin; CTX, cefotaxime; CRO, ceftriaxone; VAN, vancomycin; TEC, teicoplanin; LZD, linezolid; spp., species; CoNS, coagulase-negative staphylococci.

showed resistance to vancomycin, while 100.0% (n = 12) of *E. faecalis* isolates were susceptible to both ampicillin and vancomycin. Among the other identified *Enterococcus* species, including *E. gallinarum* and *E. avium,* 83.3% of the isolates showed resistance to vancomycin, resulting in a prevalence of 48.6% of the VRE in total. Of the 54 viridans streptococci isolates, 9.3% were resistant to third-generation cephalosporins. Of the 24 CoNS isolates, 95.8% were methicillin-resistant CoNS (MRCNS). Finally, of the 11 *S. aureus* isolates, 27.3% were methicillin-resistant *S. aureus* (MRSA).

4. Risk factors of ESBL-producing *Enterobacteriaceae* and VRE

We performed univariate analyses for the 179 identified *Enterobacteriaceae* isolates. Five variables were identified as potential risk factors for ESBL production, including remission induction/re-induction chemotherapy (odds ratio [OR]: 4.10; 95% confidence interval [CI]: 1.80 - 9.34; P <0.01), IR disease status (OR: 3.48; 95% CI: 1.49 - 8.14; P <0.01), ICU admission (OR: 4.61; 95% CI: 1.51 - 14.14; P = 0.01), septic shock (OR: 3.34; 95% CI: 1.10 - 10.13; P = 0.03), and the use of prophylactic ciprofloxacin (OR: 5.64; 95% CI: 2.22 - 14.36; P <0.01). Consolidation chemotherapy (OR: 0.17; 95% CI: 0.08 – 0.36; P <0.01) and CR disease status (OR: 0.21; 95% CI: 0.10 – 0.44; P <0.01) each showed an inverse relationship with ESBL production (**Table 5**). These variables were additionally evaluated using multivariate analysis, which demonstrated that ciprofloxacin prophylaxis was statistically significantly associated with ESBL production (OR: 5.20; 95% CI: 1.11 – 24.34; P = 0.04).

On univariate analysis, ALL (*i.e.*, an underlying hematologic disease) was identified as a risk factor for vancomycin resistance in 72 enterococcal isolates (OR: 6.29; 95% CI: 1.58 –24.94; P = 0.01), and AML was inversely associated with vancomycin resistance (OR: 0.17, 95% CI: 0.05 – 0.59; P = 0.01). However, additional multivariate analysis showed no statistically significant associations with vancomycin resistance (**Table 6**).

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Table 5. Factors associated with extended spectrum beta-lactamase production in patients with *Enterobacteriaceae* bloodstream infections

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Underlying hematologic diseases				
AML	1.12 (0.55 - 2.29)	0.75	0.67 (0.16 - 2.86)	0.59
ALL	0.83 (0.39 - 1.77)	0.63	0.56 (0.12 - 2.57)	0.45
Lymphoma	0.62 (0.07 - 5.46)	0.67	0.40 (0.03 - 5.15)	0.48
MM	1.00		1.00	
Treatment for underlying diseases				
Chemotherapy (I/RI)	4.10 (1.80 - 9.34)	<0.01	1.50 (0.58 - 3.90)	0.41
Chemotherapy (consolidation)	0.17 (0.08 - 0.36)	<0.01	0.21 (0.09 - 0.48)	<0.01
Stem cell transplantation	1.00		1.00	
Disease status				
Naïve	1.00		1.00	
Complete remission	0.21 (0.10 - 0.44)	<0.01	0.16 (0.05 - 0.53)	<0.01
Incomplete remission	3.48 (1.49 - 8.14)	<0.01	0.66 (0.17 - 2.62)	0.56
Comorbidities	0.46 (0.19 - 1.13)	0.09	0.57 (0.20 - 1.63)	0.29
ICU admission	4.61 (1.51 - 14.14)	0.01	-	
Septic shock	3.34 (1.10 - 10.13)	0.03	-	
Polymicrobial	0.46 (0.20 - 1.07)	0.07	0.63 (0.23 - 1.70)	0.36
Use of prophylactic ciprofloxacin	5.64 (2.22 - 14.36)	<0.01	5.20 (1.11 - 24.34)	0.04

OR, odds ratio; CI, confidence interval; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; I/RI, remission induction/re-induction; ICU, intensive care unit.

Table 6. Factors associated with vancomycin resistance in patients with enterococcal bloodstream infections

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Underlying hematologic diseases				
AML	0.17 (0.05 - 0.59)	0.01	0.30 (0.03 - 3.50)	0.33
ALL	6.29 (1.58 - 24.94)	0.01	2.00 (0.13 - 30.16)	0.62
MM	1.00		1.00	
Treatment for underlying diseases				
Chemotherapy (I/RI)	0.79 (0.31 - 2.01)	0.62	0.71 (0.20 - 2.59)	0.61
Chemotherapy (consolidation)	1.09 (0.42 - 2.86)	0.86	0.86 (0.23 - 3.25)	0.82
Stem cell transplantation	1.00		1.00	
Disease status				
Naïve	1.00		1.00	
Complete remission	0.61 (0.24 - 1.59)	0.31	0.78 (0.25 - 2.41)	0.66
Incomplete remission	1.84 (0.66 - 5.08)	0.24	1.59 (0.48 - 5.31)	0.45
Comorbidities	2.44 (0.66 - 9.00)	0.18	4.24 (0.70 - 25.78)	0.12
ICU admission	1.90 (0.55 - 6.48)	0.31	-	
Septic shock	1.60 (0.46 - 5.61)	0.46	-	
Polymicrobial	0.64 (0.20 - 2.05)	0.46	0.99 (0.27 - 3.64)	0.99
Use of prophylactic ciprofloxacin	1.24 (0.45 - 3.42)	0.68	2.55 (0.47 - 13.91)	0.28

OR, odds ratio; CI, confidence interval; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; I/RI, remission induction/re-induction; ICU, intensive care unit.

DISCUSSION

This retrospective study examined the clinical characteristics and distributions of microorganisms within 380 BSI episodes occurring in patients with hematologic diseases who presented at our medical center in the year 2020. In addition, antimicrobial resistance patterns for major pathogens were described in this work, which likewise addressed the associated risk factors for ESBL production in *Enterobacteriaceae* BSIs and for vancomycin resistance in enterococcal BSIs.

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We found that the relative prevalence of underlying hematologic diseases in the patients enrolled in our study were somewhat similar to those of a study previously conducted at the same institution between June 2009 and May 2010 [12]. However, as the treatment paradigms for addressing the underlying hematologic diseases have since been revolutionized (for instance, with the use of venetoclax and hypomethylating agents in AML, as well as through the use of targeted immunotherapy agents such as blinatumomab and inotuzumab ozogamicin in ALL [23, 24]), the study populations are clearly distinguishable from each other. Therefore, periodic monitoring evaluating epidemiologic transitions in regard to BSI and changes in resistance patterns of the identified microorganisms at a single medical facility is critical with respect to effective infection prevention and control.

The distribution of the causative microorganisms underlying the BSIs evaluated in this study demonstrated the current persistent dominance of Gram-negative bacteria. *E. coli* was the most commonly identified pathogen, followed by *Klebsiella* spp., *Enterococcus* spp., viridans streptococci, CoNS, and *Corynebacterium* spp. (**Table 2**). We also found an unexpected result in that *Corynebacterium* spp. was the sixth most prevalent pathogen isolated from BSIs occurring in patients with hematologic diseases [11, 25]. We note that there was no *Corynebacterium* outbreak at our institution during the study period, and that none of the *Corynebacterium* BSI episodes were related to infective endocarditis.

Recently, the proportion of ESBL-producing *Enterobacteriaceae* BSIs in patients with hematologic diseases has increased, according to the results of several previous studies [13, 26, 27]; this trend was consistent within data from different countries [7, 28]. In addition, results from previous studies showed statistically significantly higher mortality due to BSIs caused by ESBL-producing pathogens compared with BSIs caused by non-ESBL-producing *Enterobacteriaceae*, implying an urgent need for an effort to reduce infections caused by MDROs [9, 13].

The most prominent finding in this study is the detected change in ESBL production in *Enterobacteriaceae* over time, compared with the data collected from our medical center from approximately 8 years ago. This previous study showed a prevalence of 43.7% for ESBL-producing *Enterobacteriaceae* BSIs, reflecting the 31.9% prevalence of ESBL-producing *E. coli* and the 71.0% prevalence of ESBL-producing *Klebsiella pneumoniae* [12]. In contrast, our data demonstrated a total prevalence of 25.1% for ESBL-producing *Enterobacteriaceae* within the evaluated BSI episodes, with a 37.4% prevalence of ESBL-producing *E. coli* and 6.9% prevalence of ESBL-producing *Klebsiella* spp.

Although this research did not aim to investigate the effects of the described ASP intervention, the ASP modification implemented during the intervening time period could comprise a possible explanation for the marked decrease in ESBL-producing *Enterobacteriaceae* BSI that was detected in this study. More specifically, we speculate that this finding could be due to an effort to reduce the use of quinolone prophylaxis at our hospital. In addition, multivariate analysis showed an association between ciprofloxacin prophylaxis and ESBL production in *Enterobacteriaceae* BSIs, corresponding to the findings of previous investigations [29, 30].

Our study findings demonstrated that the prevalence of ESBL-producing *E. coli* BSIs had declined, while quinolone-resistant *E. coli* continued to show a high prevalence. Moreover, although the number of identified cases was small, carbapenem-resistant *Enterobacteriaceae* were identified among the *Klebsiella* spp. BSIs detected in this study. In addition, even though

there were only a few confirmed *A. baumannii* isolates, all were carbapenem-resistant, which strongly suggests a research and clinical focus for future studies and intervention protocols.

We note that the prevalence of pseudomonal BSIs was not found to increase at our medical center compared with the evaluation conducted 8 years prior, even though the use of prophylactic ciprofloxacin was reduced. However, we stress that careful monitoring is required. Moreover, we found that quinolone-resistant and carbapenem-resistant *Pseudomonas* did not pose much of an issue at this time. Of the BSI episodes, only 11 (2.5%) were due to *S. aureus*, and the resistance rate to methicillin was less than that found in other studies conducted in Korea [31, 32]. The rate of enterococcal BSIs did not decrease even after implementing the ASP intervention, and no statistically significant independent risk factors for vancomycin resistance in enterococcal BSI were detected in the present study. However, the prevalence of VRE isolates from *E. faecium* BSIs increased compared with that in a previous study conducted at the same institution [33], and hence we conclude that a strenuous effort is required in order to effectively prevent VRE BSIs.

This study has several limitations. First, our findings are based on a single-center investigation with a retrospective study design, and possible missing data for some variables could have led to underestimation or overestimation of the detected associations. Second, some patient information could have overlapped due to the use of episode-based data. Third, a mortality analysis was omitted from this study. Lastly, a data gap exists between this research and the previous study conducted at the same institution, and as such, changes in BSI epidemiology could not be analyzed serially over time.

In addition to these potential limitations, we note several substantial strengths of our study. First, our presentation of subsequent findings from the same medical facility provides a better and more comprehensive understanding of recent trends, periodic transitions of BSI pathogens, and differences in resistance patterns that do standalone investigations conducted in different contexts. Also, the number of BSI episodes evaluated in this study was large compared with that of previous studies, even though the study period was short and the data were collected from a single medical center (likely because this research was conducted at a specialized center) [34, 35]. Future research endeavors as well as a systematic literature review are needed in order to build effective new ASP strategies with the goal of reducing BSIs caused by MDROs. Additional studies evaluating the clinical and molecular epidemiology of the detected increase in *Corynebacterium* BSIs are needed as well. In addition, the relationship between antimicrobial resistance and mortality needs to be addressed more comprehensively in future investigations.

In conclusion, the findings of this study demonstrated that Gram-negative bacteria remained the dominant pathogens detected in BSIs in patients with hematologic diseases, mirroring the results found in a previous study conducted at our medical institution. We also detected a decreased prevalence of ESBL-producing *Enterobacteriaceae* BSI. However, the prevalence of enterococcal BSIs had not decreased, and the prevalence of VRE isolates from *E. faecium* BSIs had increased. In addition, we found that the use of ciprofloxacin prophylaxis was statistically significantly associated with ESBL production in *Enterobacteriaceae* BSIs. We conclude that periodic examinations of changes in BSI epidemiology following alterations in prophylaxis and empirical antimicrobial strategies are needed in order to better avoid critical complications and to reduce the burden of antimicrobial-resistant organisms in patients with hematologic diseases. Moreover, we strongly recommend that future studies evaluate the

potential association between antimicrobial resistance and mortality in patients with BSIs and underling hematologic diseases. Our findings thereby inform future research directions and directly guide clinical practice and health management at our institution, as well as providing a model for other health care institutions.

REFERENCES

1. Mikulska M, Del Bono V, Raiola AM, Bruno B, Gualandi F, Occhini D, di Grazia C, Frassoni F, Bacigalupo A, Viscoli C. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant 2009;15:47-53.
PUBMED | CROSSREF
2. Scheich S, Weber S, Reinheimer C, Wichelhaus TA, Hogardt M, Kempf VAJ, Kessel J, Serve H, Steffen B. Bloodstream infections with gram-negative organisms and the impact of multidrug resistance in patients with hematological malignancies. Ann Hematol 2018;97:2225-34.
PUBMED | CROSSREF
3. Lee DG, Kim SH, Kim SY, Kim CJ, Park WB, Song YG, Choi JH. Evidence-based guidelines for empirical therapy of neutropenic fever in Korea. Korean J Intern Med 2011;26:220-52.
PUBMED | CROSSREF
4. Carvalho AS, Lagana D, Catford J, Shaw D, Bak N. Bloodstream infections in neutropenic patients with haematological malignancies. Infect Dis Health 2020;25:22-9.
PUBMED | CROSSREF
5. Jung SM, Kim YJ, Ryoo SM, Sohn CH, Seo DW, Lim KS, Kim WY. Cancer patients with neutropenic septic shock: etiology and antimicrobial resistance. Korean J Intern Med 2020;35:979-87.
PUBMED | CROSSREF
6. Finello M, Suasnabar DF, García MJ, Díaz MV, Richetta L, Toranzo A, Hernández D, Cometto MA, Vázquez SM, Caeiro JP, Sierra J, Saad EJ. [Clinical and microbiological characteristics of bloodstream infections in adult neutropenic patients]. Rev Argent Microbiol 2021;53:183-93. [Spanish].
PUBMED | CROSSREF
7. Haddad S, Jabbour JF, Hindy JR, Makki M, Sabbagh A, Nayfeh M, Boustany M, El-Zein S, Tamim H, Zakhem AE, El Cheikh J, Bazarbachi A, Kanj SS. Bacterial bloodstream infections and patterns of resistance in patients with haematological malignancies at a tertiary centre in Lebanon over 10 years. J Glob Antimicrob Resist 2021;27:228-35.
PUBMED | CROSSREF
8. Kern WV, Weber S, Dettenkofer M, Kaier K, Bertz H, Behnke M, Weisser M, Götting T, Widmer AF, Theilacker C; Hospital Infection Surveillance System for Patients with Haematologic/Oncologic Malignancies Study Group (ONKO-KISS). Impact of fluoroquinolone prophylaxis during neutropenia on bloodstream infection: Data from a surveillance program in 8755 patients receiving high-dose chemotherapy for haematologic malignancies between 2009 and 2014. J Infect 2018;77:68-74.
PUBMED | CROSSREF
9. Mert D, Ceken S, Iskender G, Iskender D, Merdin A, Duygu F, Ertek M, Altuntas F. Epidemiology and mortality in bacterial bloodstream infections in patients with hematologic malignancies. J Infect Dev Ctries 2019;13:727-35.
PUBMED | CROSSREF
10. Cattaneo C, Zappasodi P, Mancini V, Annaloro C, Pavesi F, Skert C, Ferrario A, Todisco E, Saccà V, Verga L, Passi A, Da Vià M, Ferrari S, Mometto G, Petullà M, Nosari A, Rossi G. Emerging resistant bacteria strains in bloodstream infections of acute leukaemia patients: results of a prospective study by the Rete Ematologica Lombarda (Rel). Ann Hematol 2016;95:1955-63.
PUBMED | CROSSREF
11. Kang CI, Chung DR, Ko KS, Peck KR, Song JH; Korean Network for Study of Infectious Diseases. Risk factors for infection and treatment outcome of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with hematologic malignancy. Ann Hematol 2012;91:115-21.
PUBMED | CROSSREF
12. Kwon JC, Kim SH, Choi JK, Cho SY, Park YJ, Park SH, Choi SM, Lee DG, Choi JH, Yoo JH. Epidemiology and clinical features of bloodstream infections in hematology wards: one year experience at the catholic blood and marrow transplantation center. Infect Chemother 2013;45:51-61.
PUBMED | CROSSREF

13. Liang T, Xu C, Cheng Q, Tang Y, Zeng H, Li X. Epidemiology, risk factors, and clinical outcomes of bloodstream infection due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in hematologic malignancy: A retrospective study from Central South China. Microb Drug Resist 2021;27:800-8.
PUBMED | CROSSREF

14. Trecarichi EM, Giuliano G, Cattaneo C, Ballanti S, Criscuolo M, Candoni A, Marchesi F, Laurino M, Dargenio M, Fanci R, Cefalo M, Delia M, Spolzino A, Maracci L, Nadali G, Busca A, Del Principe MI, Daffini R, Simonetti E, Dragonetti G, Zannier ME, Pagano L, Tumbarello M; Haematologic Malignancies Associated Bloodstream Infections Surveillance (HEMABIS) registry–Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne (SEIFEM) group, Italy. Bloodstream infections caused by Escherichia coli in onco-haematological patients: Risk factors and mortality in an Italian prospective survey. PLoS One 2019;14:e0224465.
PUBMED | CROSSREF

15. Jo SJ, Park KG, Han K, Park DJ, Park YJ. Direct identification and antimicrobial susceptibility testing of bacteria from positive blood culture bottles by matrix-assisted laser desorption/Ionization time-of-flight mass spectrometry and the vitek 2 system. Ann Lab Med 2016;36:117-23.
PUBMED | CROSSREF

16. Cho SY, Park YJ, Cho H, Park DJ, Yu JK, Oak HC, Lee DG. Comparison of *Enterococcus faecium* bacteremic isolates from hematologic and non-hematologic patients: Differences in antimicrobial resistance and molecular characteristics. Ann Lab Med 2018;38:226-34.
PUBMED | CROSSREF

17. Yang M, Choi SJ, Lee J, Lee DG, Kim YJ, Park YJ, Oh EJ. Serum procalcitonin as an independent diagnostic markers of bacteremia in febrile patients with hematologic malignancies. PLoS One 2019;14:e0225765.
PUBMED | CROSSREF

18. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of Americaa. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:427-31.
PUBMED | CROSSREF

19. Al-Otaibi FE, Bukhari EE, Badr M, Alrabiaa AA. Prevalence and risk factors of Gram-negative bacilli causing blood stream infection in patients with malignancy. Saudi Med J 2016;37:979-84.
PUBMED | CROSSREF

20. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 2003;36:1103-10.
PUBMED | CROSSREF

21. Hazan G, Ben-Shimol S, Fruchtman Y, Abu-Quider A, Kapelushnik J, Moser A, Falup-Pecurariu O, Greenberg D. Clinical and laboratory parameter dynamics as markers of blood stream infections in pediatric oncology patients with fever and neutropenia. J Pediatr Hematol Oncol 2014;36:e275-9.
PUBMED | CROSSREF

22. Chen S, Liu S, Yuan X, Wang H, Wen F. Evaluation of inflammatory biomarkers in pediatric hematology-oncology patients with bloodstream infection. J Pediatr Hematol Oncol 2021;43:e596-600.
PUBMED | CROSSREF

23. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foà R, Bassan R, Arslan Ö, Sanz MA, Bergeron J, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Brüggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47.
PUBMED | CROSSREF

24. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, Gökbuget N, O'Brien S, Wang K, Wang T, Paccagnella ML, Sleight B, Vandendries E, Advani AS. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375:740-53.
PUBMED | CROSSREF

25. Garcia-Vidal C, Cardozo-Espinola C, Puerta-Alcalde P, Marco F, Tellez A, Agüero D, Romero-Santana F, Díaz-Beyá M, Giné E, Morata L, Rodríguez-Núñez O, Martinez JA, Mensa J, Esteve J, Soriano A. Risk factors for mortality in patients with acute leukemia and bloodstream infections in the era of multiresistance. PLoS One 2018;13:e0199531.
PUBMED | CROSSREF

26. Ha YE, Kang CI, Cha MK, Park SY, Wi YM, Chung DR, Peck KR, Lee NY, Song JH. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* in patients with cancer. Int J Antimicrob Agents 2013;42:403-9.
PUBMED | CROSSREF

27. Gudiol C, Calatayud L, Garcia-Vidal C, Lora-Tamayo J, Cisnal M, Duarte R, Arnan M, Marin M, Carratalà J, Gudiol F. Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 2010;65:333-41.
PUBMED | CROSSREF

28. Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, Fadda G, Leone G, Cauda R, Pagano L. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies. J Infect 2009;58:299-307.
PUBMED | CROSSREF

29. Garnica M, Nouér SA, Pellegrino FL, Moreira BM, Maiolino A, Nucci M. Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance. BMC Infect Dis 2013;13:356.
PUBMED | CROSSREF

30. Paterson DL, Mulazimoglu L, Casellas JM, Ko WC, Goossens H, Von Gottberg A, Mohapatra S, Trenholme GM, Klugman KP, McCormack JG, Yu VL. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in *Klebsiella pneumoniae* isolates causing bacteremia. Clin Infect Dis 2000;30:473-8.
PUBMED | CROSSREF

31. Park SH, Park C, Yoo JH, Choi SM, Choi JH, Shin HH, Lee DG, Lee S, Kim J, Choi SE, Kwon YM, Shin WS. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* strains as a cause of healthcare-associated bloodstream infections in Korea. Infect Control Hosp Epidemiol 2009;30:146-55.
PUBMED | CROSSREF

32. Choi SH, Lee J, Jung J, Kim ES, Kim MJ, Chong YP, Kim SH, Lee SO, Choi SH, Woo JH, Kim YS. A longitudinal study of adult patients with *Staphylococcus aureus* bacteremia over 11 years in Korea. J Korean Med Sci 2021;36:e104.
PUBMED | CROSSREF

33. Cho SY, Lee DG, Choi SM, Kwon JC, Kim SH, Choi JK, Park SH, Park YJ, Choi JH, Yoo JH. Impact of vancomycin resistance on mortality in neutropenic patients with enterococcal bloodstream infection: a retrospective study. BMC Infect Dis 2013;13:504.
PUBMED | CROSSREF

34. Huang CT, Liu CJ, Ko PS, Liu HT, Yu YB, Hsiao LT, Gau JP, Tzeng CH, Chiou TJ, Liu JH, Yang MH, Huang LJ, Liu CY. Risk factors and characteristics of blood stream infections in patients with newly diagnosed multiple myeloma. BMC Infect Dis 2017;17:33.
PUBMED | CROSSREF

35. Okamoto A, Kanda Y, Kimura SI, Oyake T, Tamura K; from the Japan Febrile Neutropenia Study Group. Predictive and risk factor analysis for bloodstream infection in high-risk hematological patients with febrile neutropenia: post-hoc analysis from a prospective, large-scale clinical study. Int J Hematol 2021;114:472-82.
PUBMED | CROSSREF