KJIM

Prevalence and impact of extended-spectrum β-lactamase production on clinical outcomes in cancer patients with *Enterobacter* species bacteremia

Sun Jong Kim[1], Ki-Ho Park[2], Jin-Won Chung[3], Heungsup Sung[4], Seong-Ho Choi[3], and Sang-Ho Choi[5]

[1]Department of Internal Medicine, Konkuk University School of Medicine, Seoul; [2]Division of Infectious Diseases, Department of Internal Medicine, Kyung Hee University Medical Center, Seoul; [3]Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Seoul; Departments of [4]Laboratory Medicine and [5]Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Correspondence to
Seong-Ho Choi, M.D.

Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 156-755, Korea
Tel: +82-2-6299-3142
Fax: +82-2-6299-2017
E-mail: tobeservant@hotmail.com

Background/Aims: We examined the prevalence of extended-spectrum β-lactamase (ESBL) production and the impact of ESBL on clinical outcomes in cancer patients with *Enterobacter* spp. bacteremia.

Methods: Using prospective cohort data on *Enterobacter* bacteremia obtained between January 2005 and November 2008 from a tertiary care center, the prevalence and clinical impact of ESBL production were evaluated.

Results: Two-hundred and three episodes of *Enterobacter* spp. bacteremia were identified. Thirty-one blood isolates (15.3%, 31/203) scored positive by the double-disk synergy test. Among 17 isolates in which ESBL genes were detected by polymerase chain reaction and sequencing, CTX-M (n = 12), SHV-12 (n = 11), and TEM (n = 4) were the most prevalent ESBL types. Prior usage of antimicrobial agents (77.4% vs. 54.0%, *p* = 0.02) and inappropriate empirical antimicrobial therapy (22.6% vs. 3.0%, *p* < 0.001) were more commonly encountered in the ESBL-positive group than in the extended-spectrum cephalosporin-susceptible ESBL-negative group, respectively. Clinical outcomes did not differ significantly between the two groups (30-day mortality rate, 19.4% vs. 17.0%, *p* = 0.76; median length of hospital stay, 24.0 days vs. 30.5 days, *p* = 0.97). Initial presentation of severe sepsis/septic shock, pneumonia, and intra-abdominal infection were independently associated with 30-day mortality.

Conclusions: The prevalence of ESBL-producing isolates was 15.3% in cancer patients with *Enterobacter* bacteremia. Although inappropriate empirical therapy was more common in the ESBL-positive group, ESBL production was not associated with poorer outcomes.

Keywords: *Enterobacter*; Neoplasms; beta-Lactamases

INTRODUCTION

Enterobacter species are important nosocomial pathogens that have been increasingly reported to be associated with intra-abdominal, respiratory tract, urinary tract, wound, and bloodstream infections in clinical practice [1,2]. These bacteria are characterized by chromosomally-encoded AmpC β-lactamases and can develop antimicrobial resistance on exposure to broad-spectrum cephalosporins [3,4]. Moreover, recent studies have suggested the global emergence of extended-spectrum β-lactamase (ESBL)-producing *Enterobacter* spp. [5-12]. This emergence poses a serious public health threat, since only a limited number of effective antimicrobial

Table 1. Clinical characteristics and ESBL types of 17 patients with *Enterobacter* spp. bacteremia

No.	Age, yr	Sex	*Enterobacter* species	Type of ESBL	Resistance to third-generation cephalosporins	Underlying malignancy	Source of infection	60-Day mortality
1	66	Female	*E. cloacae*	TEM-52, CTX-M9	Present	Gallbladder cancer	Biliary tract	Survived
2	1	Male	*E. cloacae*	TEM-1-like, SHV-12, CTX-M9	Present	Acute leukemia	Central venous catheter	Survived
3	70	Male	*E. cloacae*	TEM-1-like, SHV-12	Present	Acute leukemia	Skin and soft tissue	Died
4	51	Male	*E. cloacae*	CTX-M9	Absent	Colon cancer	Urinary tract	Survived
5	54	Male	*E. cloacae*	CTX-M15	Present	Cholangiocarcinoma	Biliary tract	Survived
6	45	Female	*E. cloacae*	SHV-12	Present	Acute leukemia	Unknown	Survived
7	58	Female	*E. cloacae*	SHV-12	Present	Acute leukemia	Unknown	Survived
8	9	Male	*E. cloacae*	SHV-12, CTX-M9	Present	Lymphoma	Central venous catheter	Survived
9	12	Male	*E. cloacae*	SHV-12, CTX-M9	Present	Osteosarcoma	Unknown	Survived
10	1	Female	*E. cloacae*	CTX-M9	Present	Rhabdoid tumor (kidney)	Unknown	Survived
11	47	Male	*E. cloacae*	SHV-12, CTX-M9	Present	Acute leukemia	Unknown	Died
12	50	Male	*E. cloacae*	SHV-12	Present	Nasopharyngeal cancer	Lungs	Died
13	78	Male	*E. cloacae*	CTX-M15	Present	Prostate cancer	Urinary tract	Died
14	50	Female	*E. cloacae*	CTX-M15	Present	Malignant mixed Müllerian tumor	Abdomen	Died
15	43	Female	*E. cloacae*	TEM-1-like, SHV-12	Present	Acute leukemia	Unknown	Survived
16	61	Female	*E. cloacae*	SHV-12, CTX-M9	Present	Cholangiocarcinoma	Unknown	Survived
17	46	Female	*E. cloacae*	SHV-12, CTX-M14	Present	Stomach cancer	Unknown	Died

ESBL, extended-spectrum β-lactamase.

agents can be used against multidrug-resistant organisms producing both an ESBL and AmpC β-lactamase.

In patients with malignancy, who require effective antimicrobial therapy early in the course of their infection, inappropriate antimicrobial therapy due to ESBL-producing *Enterobacter* spp. may have a serious adverse impact on their clinical outcome. However, to the best of our knowledge, no reports have yet described the prevalence of ESBL-producing *Enterobacter* spp. and the impact of ESBL production on the clinical outcome of patients with malignancy.

This study investigated the prevalence and clinical impact of ESBL production in cancer patients with *Enterobacter* spp. bacteremia.

METHODS

This study follows several prospective studies performed by our group regarding AmpC β-lactamase-producing *Enterobacteriaceae*, including *Enterobacter* spp., *Serratia marcescens*, *Citrobacter freundii*, and *Morganella morgannii* [4,5,13]. We prospectively identified all patients admitted to Asan Medical Center, a 2,200-bed tertiary care university-affiliated teaching hospital in Seoul, Korea, with clinical specimens yielding AmpC β-lactamase-producing *Enterobacteriaceae*. Patient clinical data were collected, including demographic characteristics, underlying diseases or conditions, initial manifestations, antimicrobial therapies, and outcomes. The present study focused on episodes of *Enterobacter* spp. bacteremia diagnosed in patients with malignancy

Kim SJ, et al. ESBL-positive *Enterobacter* bacteremia in cancer patients

KJIM

Table 2. Baseline characteristics and clinical features of patients with *Enterobacter* bacteremia according to ESBL production or antimicrobial resistance to extended-spectrum cephalosporins

Characteristic	Group I ESBL (+) (n = 31)	Group II ESC-S/ESBL (−) (n = 100)	*p* value, I vs. II	Group III ESC-R/ESBL (−) (n = 72)	*p* value, I vs. III
Male sex	14 (45.2)	58	0.21	31 (43.1)	0.27
Median age, yr (range)	54 (1–78)	56 (4–83)	0.29	59 (neonate–82)	0.12
Underlying diseases					
Solid tumor	21 (67.7)	62	0.56	66 (91.7)	0.01
Hematologic malignancy	11 (35.5)	39	0.72	6 (8.3)	< 0.01
Biliary tract diseases	6 (19.4)	14	0.57	16 (22.2)	0.74
Diabetes	2 (6.5)	15	0.36	9 (12.5)	0.50
Dialysis	2 (6.5)	0	0.05	3 (4.2)	0.64
Stem cell transplant	2 (6.5)	6	1.00	0	0.09
Liver cirrhosis	1 (3.2)	10	0.46	6 (8.3)	0.67
Charlson's comorbidity index, median (IQR)	2.0 (2.0–6.0)	2.0 (2.0–4.0)	0.96	2.5 (2.0–6.0)	0.46
Underlying conditions					
Cancer chemotherapy[a]	17 (54.8)	50	0.64	17 (23.6)	< 0.01
White blood cell count < 4,000/μL[b]	11 (35.5)	52	0.11	17 (23.6)	0.21
Immunosuppressive agent[a]	4 (12.9)	16	0.78	7 (9.7)	0.73
Intensive care unit admission[b]	4 (12.9)	10	0.74	6 (8.3)	0.48
Surgery[a]	2 (6.5)	9	1.00	6 (8.3)	1.00
Acquisition of infection					
Hospital-acquired	25 (80.6)	79	0.84	62 (86.1)	0.56
Source of infection					
Primary bacteremia	11 (35.5)	48	0.22	17 (23.6)	0.21
Biliary tract	10 (32.3)	25	0.42	37 (51.4)	0.07
Urinary tract	3 (9.7)	5	0.39	4 (5.6)	0.43
Abdomen	2 (6.5)	9	1.00	6 (8.3)	1.00
Central venous catheter	2 (6.5)	4	0.63	2 (2.8)	0.58
Skin and soft tissue	2 (6.5)	2	0.24	0	0.09
Lungs	1 (3.2)	7	0.68	5 (6.9)	0.66
Polymicrobial infection	6 (19.4)	30	0.25	9 (12.5)	0.37
Species			0.28		0.06
Enterobacter cloacae	26 (83.9)	72		47 (65.3)	
Enterobacter aerogenes	5 (16.1)	23		25 (34.7)	
Other	0	5		0	
Initial severity of infection			0.85		0.50
No sepsis	8 (25.8)	21		13 (18.1)	
Sepsis	16 (51.6)	50		37 (51.4)	
Severe sepsis	2 (6.5)	6		12 (16.7)	
Septic shock	5 (16.1)	23		10 (13.9)	

Values are presented as number (%).

ESBL, extended-spectrum β-lactamase; ESC-S, extended-spectrum cephalosporin-susceptible; ESC-R, extended-spectrum cephalosporin-resistant; IQR, interquartile range.

[a] Within 1 month prior to the onset of *Enterobacter* bacteremia.

[b] Within 3 days prior to the onset of *Enterobacter* bacteremia.

Table 3. Antimicrobial resistances, antimicrobial therapies, and clinical outcomes of patients with *Enterobacter* bacteremia according to ESBL production or antimicrobial resistance to extended-spectrum cephalosporins

Characteristic	Group I, ESBL (+) (n = 31)	Group II ESC-S/ESBL (−) (n = 100)	*p* value, I vs. II	Group III ESC-R/ESBL (−) (n = 72)	*p* value, I vs. III
Prior antimicrobial therapy[a]	24 (77.4)	54	0.02	46 (63.9)	0.18
3rd g. cephalosporins	15 (48.4)	35	0.18	37 (51.4)	0.78
Carbapenems	6 (19.4)	22	0.75	12 (16.7)	0.74
Fluoroquinolones	3 (9.7)	17	0.40	6 (8.3)	1.00
Aminoglycosides	3 (9.7)	13	0.76	7 (9.7)	1.00
Cotrixomazole	5 (16.1)	7	0.15	2 (2.8)	0.02
Antimicrobial resistances to					
Cefotaxime	27 (87.1)	0	< 0.001	66 (91.7)	0.48
Ceftriaxone	25 (80.6)	0	< 0.001	66 (91.7)	0.18
Ceftazidime	23 (74.2)	0	< 0.001	65 (90.3)	0.06
Cefepime	13 (41.9)	0	< 0.001	13 (18.1)	0.01
Piperacillin/tazobactam	13 (41.9)	0	< 0.001	44 (61.1)	0.07
Ciprofloxacin	6 (19.4)	4	0.01	12 (16.7)	0.74
Aztreonam	24 (77.4)	3	< 0.001	60/71 (84.5)	0.39
Amikacin	1 (3.2)	0	0.24	7 (9.7)	0.43
Gentamicin	10 (32.3)	1	< 0.001	10 (13.9)	0.03
Imipenem	0	0		0	
Cotrimoxazole	9/22 (40.9)	2/95 (2.1)	< 0.001	16 (24.2)	0.13
Empirical antimicrobial therapy					
3rd g. cephalosporins	9 (29.0)	48	0.06	13 (18.1)	0.21
Cefepime	1 (3.2)	2	0.56	1 (1.4)	0.51
Piperacillin/tazobactam	2 (6.5)	8	1.00	4 (5.6)	1.00
Fluoroquinolones	4 (12.9)	13	1.00	7 (9.7)	0.73
Aminoglycosides	1 (3.2)	10	0.46	3 (4.2)	1.00
Carbapenems	17 (54.8)	28	< 0.01	38 (52.8)	0.85
Combination therapy	4 (12.9)	20	0.37	5 (6.9)	0.45
Definitive antimicrobial therapy					
3rd g. cephalosporins	1 (3.2)	50	< 0.001	3 (4.2)	1.00
Cefepime	1 (3.2)	3	1.00	1 (1.4)	0.51
Piperacillin/tazobactam	2 (6.5)	9	1.00	3 (4.2)	0.64
Fluoroquinolones	3 (9.7)	15	0.56	8 (11.1)	1.00
Aminoglycosides	1 (3.2)	10	0.46	4 (5.6)	1.00
Carbapenems	20 (64.5)	31	< 0.01	47 (65.3)	0.94
Combination therapy	1 (3.2)	22	0.02	3 (4.2)	1.00
Appropriate empirical therapy	24 (77.4)	97	< 0.001	58 (80.6)	0.72
Mortality rate					
14-Day mortality	4 (12.9)	11	1.00	8 (11.1)	0.75
30-Day mortality	6 (19.4)	17	0.76	11 (15.3)	0.61
Length of hospital stay, median days (IQR)	24.0 (13.0–51.0)	30.5 (15.2–55.5)	0.97	27.5 (16.0–41.0)	0.79
Length of hospital stay after bacteremia, median days (IQR)	16.0 (9.0–23.0)	17.0 (10.2–32.7)	0.87	18.0 (8.0–28.7)	0.95

Values are presented as number (%).

ESBL, extended-spectrum β-lactamase; ESC-S, extended-spectrum cephalosporin-susceptible; ESC-R, extended-spectrum cephalosporin-resistant; IQR, interquartile range.

[a]Within 1 month prior to the onset of *Enterobacter* bacteremia.

Table 4. Univariate analysis of risk factors for 30-day mortality among cancer patients with *Enterobacter* bacteremia

Risk factor	No. (%) of 30-day mortality	*p* value
Solid tumor		0.08
Yes	29/149 (19.5)	
No	5/54 (9.3)	
Hematologic malignancy		0.07
Yes	5/56 (8.9)	
No	29/147 (19.7)	
McCabe-Jackson criteria		0.02
Nonfatal disease	0/18	
Ultimately fatal disease	28/129 (21.7)	
Rapidly fatal disease	6/56 (10.7)	
Intensive care unit admission[a]		0.01
Yes	8/20 (40.0)	
No	26/183 (14.2)	
Pneumonia		0.01
Yes	6/13 (46.2)	
No	28/190 (14.7)	
Biliary tract infection		0.02
Yes	6/72 (8.3)	
No	28/131 (21.4)	
Intra-abdominal infection		< 0.001
Yes	9/17 (52.9)	
No	25/186 (13.4)	
Severe sepsis or septic shock		0.001
Yes	18/58 (31.0)	
No	16/145 (11.0)	
Antimicrobial resistance to any 3rd g. cephalosporin		0.83
Yes	16/99 (16.2)	
No	18/104 (17.3)	
ESBL production		0.67
Yes	6/31 (19.4)	
No	28/172 (16.3)	
Inappropriate empirical antimicrobial therapy		0.56
Yes	5/24 (20.8)	
No	29/179 (16.2)	

ESBL, extended-spectrum β-lactamase.

[a]Within 3 days prior to the onset of *Enterobacter* bacteremia.

between January 2005 and November 2008. Recurrent episodes of *Enterobacter* bacteremia in the same patient were included only if the time interval between two episodes was more than 28 days, or if different *Enterobacter* species were responsible for each episode.

Enterobacter spp. were identified using an NEG Combo Panel Type 32 (Dade Behring, Deerfield, IL, USA), and antimicrobial susceptibility was examined using the MicroScan system (Dade Behring) and standard criteria of the Clinical and Laboratory Standards Institute [14]. ESBL production was assessed by the double-disk synergy test. Briefly, the inhibitory zone diameters of disks containing 30 μg of cefatoxime, ceftazidime, or cefepime, either alone, or in combination with 10 μg of clavulanate, were compared. An ESBL production phenotype was defined as a ≥ 5 mm increase in zone diameter for at least one of the combination disks relative to its corresponding single antibiotic disk [4,15]. *Escherichia coli* strain ATCC 25922 and *Klebsiella pneumoniae* strain ATCC 700603 were used as negative and positive controls for ESBL production, respectively. Several ESBL-encoding genes (bla_{TEM}, bla_{SHV}, bla_{CTX-M}, bla_{VEB}, bla_{GES}, and bla_{PER}) were detected by polymerase chain reaction (PCR) using primers based on published sequences, followed by DNA sequencing [8,11,12,16].

A patient was considered to have malignancy if he or she had been treated for malignancy within three years prior to developing bacteremia. The McCabe-Jackson criteria, Charlson's comorbidity index scores, and systemic inflammatory response syndrome criteria were defined as described previously [17-19]. A hospital-acquired infection was defined as bacteremia occurring more than 48 hours after admission. The source of infection was defined only if it had been clinically or microbiologically documented. Prior usage of antimicrobial agents was defined as the receipt of a systemic antimicrobial agent for at least 48 hours within one month prior to the onset of bacteremia. Third-generation cephalosporins, including ceftriaxone, cefotaxime, and ceftazidime, were defined as extended-spectrum cephalosporins (ESCs). Appropriate antimicrobial therapy was defined as the receipt of *in vitro* active antimicrobial agents for at least 48 hours against the identified isolates.

A statistical analysis was performed using SPSS version 18.0 (IBM Co., Armonk, NY, USA). Binary data were

compared using the chi-square or Fisher exact test, and continuous scaled data were compared using the Student t test or Mann-Whitney U test. A logistic regression analysis was performed to investigate independent risk factors for 30-day mortality. Variables with a p value < 0.1 in univariate analyses were included in the logistic regression analysis. A p value < 0.05 was considered significant.

RESULTS

During the study period, 255 episodes of *Enterobacter* spp. bacteremia occurred in patients with malignancy. After excluding 52 episodes for which *Enterobacter* isolates were not available, 203 episodes of *Enterobacter* spp. bacteremia were finally included in the analysis. More than half of the study patients were male (113/203, 55.7%). The median patient age was 57 years. Except for malignancy, biliary tract disease was the most common underlying disease (36/203, 17.7%), followed by diabetes mellitus (26/203, 12.8%) and liver cirrhosis (17/203, 8.4%). The majority of infections (166/203, 81.8%) were hospital-acquired. *Enterobacter cloacae* isolates were responsible for the majority (145/203, 71.4%) of infections, and more than a quarter were caused by *Enterobacter aerogenes* (53/203, 26.1%). Nearly half (48.8%, 99/203) were caused by ESC-resistant isolates. ESBL production was detected in 31 isolates (15.3%). Inappropriate empirical antimicrobial therapy was observed in 24 patients (11.8%). A total of 34 patients died within 30 days after *Enterobacter* spp. bacteremia (16.7%), and the median length of hospital stay was 28 days. Of the 31 ESBL-producing isolates, 28 were used for the detection of ESBL genes. ESBL genes were detected in 17 cases: 12 were positive for CTX-M (eight CTX-M9, three CTX-M15, and one CTX-M14), 11 for SHV-12, and four for TEM (three TEM-1-like and one TEM-52) (Table 1). PER, VEB, and GES genes were not detected in any of the cases.

The clinical characteristics of the patients with *Enterobacter* bacteremia episodes caused by ESBL-producing isolates (ESBL-positive group) were compared to those of the patients with ESC-susceptible non-ESBL-producing blood isolates (ESC-S/ESBL-negative group). The ESBL-positive and ESC-S/ESBL-negative groups did not differ in their demographic characteristics or un-

derlying diseases/conditions. The acquisitions, sources, and initial severities of infection were also not different between the two groups (Table 2). Prior usage of antimicrobial agents was more common in the ESBL-positive group (77.4% vs. 54.0%, p = 0.02). The rates of antimicrobial resistance were higher in the ESBL-positive group than in the ESC-S/ESBL-negative group, except for the rate of resistance to amikacin. Carbapenems were more frequently used in the ESBL-positive group as empirical (54.8% vs. 28.0%, p < 0.01) or definitive therapy (64.5% vs. 31.0%, p < 0.01), whereas ESCs were more frequently used in the ESC-S/ESBL-negative group as empirical (48.0% vs. 29.0%, p < 0.06) or definitive therapy (50.0% vs. 3.2%, p < 0.001). The ESBL-positive group received more inappropriate empirical antimicrobial therapies than the ESC-S/ESBL-negative group (22.6% vs. 3.0%, p < 0.001). The mortalities and median lengths of hospital stay of the two groups did not differ (Table 3).

The clinical characteristics of the ESBL-positive group were also compared to those of patients with ESC-resistant non-ESBL-producing blood isolates (ESC-R/ESBL-negative group), which were thought to produce AmpC β-lactamases. The two groups did not differ in their demographic characteristics. Hematologic malignancy (35.5% vs. 8.3%, p < 0.01) and recent chemotherapy (54.8% vs. 23.6%, p < 0.01) were more common in the ESBL-positive group. The acquisition, sources, and initial severities were not different between the two groups (Table 2). Prior usage of trimethoprim-sulfamethoxazole (TMP-SMX) was more common in the ESBL-positive group (16.1% vs. 7.0%, p = 0.02). The rate of antimicrobial resistance to cefepime (41.9% vs. 18.1%, p = 0.01) and gentamicin (32.3% vs. 13.9%, p = 0.03) was higher in the ESBL-positive group than in the ESC-R/ESBL-negative group, respectively. The two groups did not differ in antimicrobial therapy, mortality, and median length of hospital stay (Table 3).

To investigate possible risk factors for 30-day mortality, univariate analyses were performed (Table 4). Independent risk factors for 30-day mortality included initial presentation of severe sepsis or septic shock (adjusted odds ratio [AOR], 2.72; 95% confidence interval [CI], 1.16 to 6.36; p = 0.02), pneumonia (AOR, 6.46; 95% CI, 1.69 to 24.76; p = 0.01), and intra-abdominal infection (AOR, 8.67; 95% CI, 2.61 to 28.80; p < 0.001).

Kim SJ, et al. ESBL-positive *Enterobacter* bacteremia in cancer patients

KJIM

DISCUSSION

Based on the results of the phenotypical ESBL tests, ESBL-producing isolates were responsible for 15.3% of the *Enterobacter* bacteremia episodes that occurred in patients with malignancy in this study. Prior usage of antimicrobial agents was more common in the ESBL-positive group than in the ESC-S/ESBL-negative group. Although the ESBL-positive group received inappropriate empirical antimicrobial therapy more often than the ESC-S/ESBL-negative group, the clinical outcomes of the two groups did not differ. Hematologic malignancy, recent chemotherapy, and prior use of TMP-SMX were more common in the ESBL-positive group than in the ESC-R/ESBL-negative group.

Previous phenotypical ESBL tests have shown that the ESBL production rate among *Enterobacter* spp. from clinical specimens ranged from 12.8% to 43.0% [5-12]. Several clinical studies regarding ESBL production in blood isolates from *Enterobacter* infections have also been published [6,7,12,20-22]. In a Korean study, ESBL production was observed in 43% of all blood isolates of *Enterobacter* spp. and 67.3% of all ESC-resistant isolates, suggesting that ESBL production is common among *Enterobacter* spp. [7]. More recently, in Korea and Taiwan, phenotypical ESBL production was found in 24 out of 99 blood isolates of *Enterobacter* spp. (23.4%) and in 123 out of 610 blood isolates of *E. cloacae* (20.2%), respectively [20,21]. In a recent study in the United States, 16 out of 159 blood isolates of *E. cloacae* produced ESBLs, as assessed by genotypic ESBL tests (10.1%) [22]. In this study, 15.3% of all blood isolates of *Enterobacter* spp. were ESBL-producers, as determined by the phenotypic ESBL test. To the best of our knowledge, this is the first study to evaluate ESBL production among blood isolates of *Enterobacter* spp. obtained from patients with malignancy. Considering the relatively low rate of ESBL production (15.3%) observed in this study, carbapenems may be infrequently required for *Enterobacter* spp. bacteremia in patients with malignancy, contrary to expectations inferred from the higher positive rates in other recent studies. However, the ESBL production rate may vary according to the regional epidemiology of resistance, the characteristics of the patients admitted to a hospital, and the effectiveness of infection control measures at each care center. Thus, the ESBL production

rate among blood isolates of *Enterobacter* spp. should be investigated in clinical studies from variable geographic regions and in different clinical settings; moreover, the ESBL production rate should be monitored continuously, especially in patients with malignancy.

In this study, previous antimicrobial therapy was more common in the ESBL-positive group than in the ESC-S/ESBL-negative group. Previous antimicrobial therapy is regarded as one of the most important risk factors for antibiotic-resistant gram-negative bacilli infections in patients with cancer [23,24]. Previous antimicrobial therapy has also been noted as a risk factor for ESBL production in studies of blood isolates of *Enterobacter* spp. [20-22].

Despite more frequent inappropriate empirical antimicrobial therapy, the mortality rate and the median length of hospital stay in the ESBL-positive group did not differ from those in the ESC-S/ESBL-negative group. In a recent study of AmpC β-lactamase-producing *Enterobacteriaceae*, in which 75.8% of all study isolates were *Enterobacter* spp., inappropriate initial antimicrobial therapy occurred more frequently in the ESBL group, but the 30-day mortality rate did not differ between the ESBL and non-ESBL groups. However, the average length of the hospital stay after bacteremia was longer in the ESBL group [20]. That study, by Cheong et al. [20], differed from ours in that malignancy was observed in only 58.9% of the study patients and inappropriate initial antimicrobial therapy was common in the ESBL group (63.3%) compared with our study (22.6%). Patients with malignancy tended to receive broad-spectrum antimicrobial agents as empirical antimicrobial therapies more frequently than those without malignancy. This tendency could have masked the adverse impact of ESBL production in our study. Another recent study also investigated the impact of ESC resistance on the clinical outcomes of adult cancer patients with *Enterobacter* spp. bacteremia, although the underlying mechanism of the resistance (e.g., ESBL or AmpC β-lactamase production) was not provided. The ESC-resistant group had a higher 30-day mortality rate than the ESC-susceptible group (30.8% vs. 16.4%, p = 0.03) [25]. These results are not consistent with our findings, in which the 30-day mortality rate was not different between ESC-susceptible and -resistant patients (17.3% vs. 16.2%, p = 0.67). Although the characteristics of the study patients were

similar to ours, antimicrobial resistance to ESCs (27.6% vs. 48.8%) and the empirical use of broad-spectrum antimicrobial agents such as carbapenems (23.1% vs. 54.5%) were less common in that study [25] than in ours, respectively. At our study center, since ESC-resistant isolates were encountered relatively commonly, the empirical use of broad-spectrum antimicrobial agents was frequent. At least in part, this might be responsible for the lack of difference in the 30-day mortality rate observed in our study. The clinical impact of ESC resistance associated with ESBL production in cancer patients with *Enterobacter* bacteremia requires further investigation. On the other hand, our explanation for the lack of differences seen in the clinical outcomes should not be taken to imply that broad-spectrum antimicrobial agents such as carbapenems are necessary as an empirical antimicrobial therapy for patients with malignancy to reduce the adverse impact of ESBLs. As a result of indiscriminate antimicrobial therapy, many clinicians have already encountered extremely multidrug-resistant Gram-negative bacilli such as carbapenemase-producing *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant *Pseudomonas aeruginosa* in clinical practice [26,27]. We may need to introduce more sophisticated therapeutic strategies, including de-escalation therapy or combination therapy with non-β-lactam antimicrobial agents, as empirical antimicrobial therapies.

The ESBL-positive group was also compared with the ESC-R/ESBL-negative group, which was thought to produce AmpC β-lactamase. Similarly, in a recent study of adult patients with *E. cloacae* bacteremia, the clinical characteristics of ESBL and cefotaxime-nonsusceptible non-ESBL groups were compared. The ESBL group had more episodes of hospital-onset and polymicrobial bacteremia, an increased severity of illness, and longer stays in hospital, but the mortality rates were similar between the two groups [21]. Their results are not directly comparable to ours because only 34.9% of the study patients had malignancy and there were methodological differences as well. Our study showed that hematologic malignancy, recent chemotherapy, and prior use of TMP-SMX were more common in the ESBL-positive group. Patients with hematologic malignancy are readily exposed to broad-spectrum antimicrobial agents due to frequent and prolonged neutropenia after bone mar-

row-toxic chemotherapy, for which the prophylactic use of TMP-SMX is commonly performed. Additionally, patients with cancer undergoing active chemotherapy may have more chance of being colonized or infected with antimicrobial-resistant bacteria compared with those who are not because they have more contact with healthcare workers and/or increased immune suppression. However, these risk factors for ESBL production over possible AmpC β-lactamase producers should be clarified in future studies.

There are several important limitations to our study. First, since our study was performed at a single large medical center our results may not be entirely applicable to different hospital settings. Second, the ESBL phenotypic test was not comprehensively performed for all consecutive *Enterobacter* spp. blood isolates, only for 79.6%. Third, the detection of ESBL genes by PCR was not performed for all ESBL-positive isolates. Fourth, pediatric and adult patient data were combined in this analysis, due to the limited number of patients with ESBL-positive *Enterobacter* bacteremia. However, only 6.9% of the patients were pediatric patients.

In conclusion, ESBL production was found in 15.3% of all *Enterobacter* spp. blood isolates obtained from patients with malignancy; moreover, inappropriate initial antimicrobial therapy was more commonly observed in the ESBL-positive group. However, ESBL production was not associated with poorer outcomes in patients with cancer and *Enterobacter* bacteremia.

KEY MESSAGE

1. Extended-spectrum β-lactamase (ESBL)-producing blood isolates were found in 15.3% of cancer patients with *Enterobacter* spp. bacteremia.
2. Empirical antimicrobial therapy was inappropriate more commonly in ESBL-positive group, but ESBL production was not associated with poorer outcomes in cancer patients with *Enterobacter* spp. bacteremia.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Kim SJ, et al. ESBL-positive *Enterobacter* bacteremia in cancer patients

KJIM

REFERENCES

1. Jarvis WR, Martone WJ. Predominant pathogens in hospital infections. J Antimicrob Chemother 1992;29 Suppl A:19-24.

2. Sanders WE Jr, Sanders CC. Enterobacter spp.: pathogens poised to flourish at the turn of the century. Clin Microbiol Rev 1997;10:220-241.

3. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991;115:585-590.

4. Choi SH, Lee JE, Park SJ, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. Antimicrob Agents Chemother 2008;52:995-1000.

5. Choi SH, Lee JE, Park SJ, et al. Prevalence, microbiology, and clinical characteristics of extended-spectrum beta-lactamase-producing Enterobacter spp., Serratia marcescens, Citrobacter freundii, and Morganella morganii in Korea. Eur J Clin Microbiol Infect Dis 2007;26:557-561.

6. Cheong HS, Ko KS, Kang CI, Chung DR, Peck KR, Song JH. Prevalence of extended-spectrum beta-lactamase among Enterobacteriacae blood isolates with inducible AmpC beta-lactamase. Infect Chemother 2010;42:280-284.

7. Pai H, Hong JY, Byeon JH, Kim YK, Lee HJ. High prevalence of extended-spectrum beta-lactamase-producing strains among blood isolates of Enterobacter spp. collected in a tertiary hospital during an 8-year period and their antimicrobial susceptibility patterns. Antimicrob Agents Chemother 2004;48:3159-3161.

8. Kim J, Lim YM. Prevalence of derepressed ampC mutants and extended-spectrum beta-lactamase producers among clinical isolates of Citrobacter freundii, Enterobacter spp., and Serratia marcescens in Korea: dissemination of CTX-M-3, TEM-52, and SHV-12. J Clin Microbiol 2005;43:2452-2455.

9. Stuart JC, Diederen B, Al Naiemi N, et al. Method for phenotypic detection of extended-spectrum beta-lactamases in enterobacter species in the routine clinical setting. J Clin Microbiol 2011;49:2711-2713.

10. Kanamori H, Yano H, Hirakata Y, et al. Molecular characteristics of Extended-spectrum beta-lactamases and qnr determinants in Enterobacter species from Japan. PLoS One 2012;7:e37967.

11. Park YJ, Park SY, Oh EJ, et al. Occurrence of extended-spectrum beta-lactamases among chromosomal AmpC-producing Enterobacter cloacae, Citrobacter freundii, and Serratia marcescens in Korea and investigation of screening criteria. Diagn Microbiol Infect Dis 2005;51:265-269.

12. Ho PL, Shek RH, Chow KH, et al. Detection and characterization of extended-spectrum beta-lactamases among bloodstream isolates of Enterobacter spp. in Hong Kong, 2000-2002. J Antimicrob Chemother 2005;55:326-332.

13. Song EH, Park KH, Jang EY, et al. Comparison of the clinical and microbiologic characteristics of patients with Enterobacter cloacae and Enterobacter aerogenes bacteremia: a prospective observation study. Diagn Microbiol Infect Dis 2010;66:436-440.

14. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility tests: 16th informational supplement, CLSI M100-S16. Wayne: Clinical and Laboratory Standards Institute, 2006.

15. Jacoby GA, Han P. Detection of extended-spectrum beta-lactamases in clinical isolates of Klebsiella pneumoniae and Escherichia coli. J Clin Microbiol 1996;34:908-911.

16. Oh CE, Hong JS, Bae IK, et al. Dissemination of CTX-M type extended-spectrum beta-lactamases and emergence of CTX-M-12 in Escherichia coli. Korean J Lab Med 2005;25:252-258.

17. McCabe WR, Jackson GG. Gram-negative bacteremia: I. etiology and ecology. Arch Intern Med 1962;110:847-855.

18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.

19. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. Chest 1992;101:1481-1483.

20. Cheong HS, Ko KS, Kang CI, Chung DR, Peck KR, Song JH. Clinical significance of infections caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae blood isolates with inducible AmpC beta-lactamase. Microb Drug Resist 2012;18:446-452.

21. Lee CC, Lee NY, Yan JJ, et al. Bacteremia due to extended-spectrum-beta-lactamase-producing Enterobacter cloacae: role of carbapenem therapy. Antimicrob Agents Chemother 2010;54:3551-3556.

22. Qureshi ZA, Paterson DL, Pakstis DL, et al. Risk factors and outcome of extended-spectrum beta-lactamase-producing Enterobacter cloacae bloodstream infections. Int J

Antimicrob Agents 2011;37:26-32.

23. Ohmagari N, Hanna H, Graviss L, et al. Risk factors for infections with multidrug-resistant Pseudomonas aeruginosa in patients with cancer. Cancer 2005;104:205-212.

24. Gudiol C, Tubau F, Calatayud L, et al. Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother 2011;66:657-663.

25. Huh K, Kang CI, Kim J, et al. Risk factors and treatment outcomes of bloodstream infection caused by extend-ed-spectrum cephalosporin-resistant Enterobacter species in adults with cancer. Diagn Microbiol Infect Dis 2014;78:172-177.

26. Kang CI, Song JH. Antimicrobial resistance in Asia: current epidemiology and clinical implications. Infect Chemother 2013;45:22-31.

27. Livermore DM. Current epidemiology and growing resistance of gram-negative pathogens. Korean J Intern Med 2012;27:128-142.