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Original Article

*Escherichia coli*와 *Klebsiella pneumoniae* 균혈증의 베타락탐 내성 추세와 세포탁심 감수성 ESBL 생성균주의 임상적 특징

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Trend of β-lactam Resistance in *Escherichia coli* and *Klebsiella pneumoniae* Bacteremia and Clinical Characteristics of Cefotaxime-susceptible Extended-spectrum β-lactamase-producing Isolates

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Background: This study aimed to evaluate the trend of β-lactam resistance in *Escherichia coli* and *Klebsiella pneumoniae* bacteremia, the prevalence of cefotaxime-susceptible extended-spectrum β-lactamase-producing (ESBL) *E. coli* and *K. pneumoniae*, and the clinical characteristics of these infections.

Methods: A retrospective study was conducted in a tertiary hospital in Korea between 2011 and 2020. All patients with *E. coli* or *K. pneumoniae* bacteremia were identified, along with the results for the antibiotic susceptibility and ESBL production test for each isolate.

Results: Of 15 706 *E. coli* and *K. pneumoniae* bacteremia episodes, only 10 (0.06%) were caused by cefotaxime-susceptible ESBL-producing isolates, and their prevalence remained low during the study period. The proportion of ESBL-producing isolates gradually increased from 23.1% to 29.5%, whereas the proportion of carbapenem-resistant isolates rapidly increased from 0.9% to 12.1%. Furthermore, the proportion of carbapenem-resistant *K. pneumoniae* increased significantly and surpassed that of carbapenem-susceptible ESBL-producing *K. pneumoniae* in 2020. In a matched case-control study, the baseline characteristics of patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia were similar to those with cefotaxime-resistant infections. There was no significant difference in 30-day mortality between patients with cefotaxime-susceptible and cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae* bacteremia.

Conclusion: The prevalence of cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia and its mortality were very low, supporting the current guidelines for elective ESBL testing. The rapidly increasing carbapenem resistance is a concern.

Key Words: Cefotaxime, ESBL, *Escherichia coli*, *Klebsiella pneumoniae*, Susceptibility

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Introduction

Broad-spectrum cephalosporins, including oxymino-β-lactam antimicrobial agents interfere with cell wall synthesis and are the main antibiotics used for treating Enterobacterales infections [1]. However, drug-resistant Enterobacterales are continuously increasing, causing high morbidity and mortality [2]. Since the initial report of extended-spectrum β-lactamase (ESBL) production in *Klebsiella pneumoniae* in 1983 [3], ESBL production has been one of the main mechanisms of drug resistance in Enterobacterales [4].

In 2010, the Clinical and Laboratory Standards Institute (CLSI) revised its guidelines for Enterobacterales by lowering MIC (minimum inhibitory concentration) interpretive thresholds for cefotaxime (or ceftriaxone) from ≤8 μg/mL to ≤1 μg/mL to indicate susceptibility and recommending reporting susceptibility results for cephalosporin "as found", removing the requirement for ESBL phenotypic testing for organisms with cefotaxime MICs ≥2 μg/mL [5]. These changes were based on pharmacokinetics/pharmacodynamic analyses of MICs and clinical outcomes in patients with ESBL-producing Enterobacterales bacteremia, where reduced clinical responses were associated with increased MICs rather than β-lactamase resistance [6,7]. However, the clinical outcomes of patients with cefotaxime-susceptible ESBL-producing Enterobacterales bacteremia were based on a limited number of studies [7-9], and the thresholds used in these studies were based on the previous guidelines [10]. Since the 2010 revision of the CLSI recommendations, several studies have advocated the need for monitoring ESBL-producing isolates with ESBL confirmation tests [11-13].

This study aimed to identify the prevalence of bacteremia caused by ESBL-producing *Escherichia coli* and *K. pneumoniae* (the family Enterobacteriaceae), cefotaxime-susceptible ESBL-producing *E. coli* and *K. pneumoniae*, and carbapenem-resistant *E. coli* and *K. pneumoniae* since the revision of the CLSI guidelines in 2010. Furthermore, we aimed to evaluate the clinical characteristics and outcomes of patients with cefotaxime-susceptible ESBL-producing *E. coli* and *K. pneumoniae* bacteremia.

Materials and Methods

1. Study population and design

This retrospective study was conducted at the Asan Medical Center, a 2700-bed tertiary center in Seoul, Korea, between January 2011 and December 2020. All patients with *E. coli* or *K. pneumoniae* bacteremia were identified. Antibiotic susceptibility results for cephalosporin and carbapenem and the status of ESBL production by each isolate were obtained. The total number of episodes of bacteremia caused by *E. coli* or *K. pneumoniae* bacteremia was analyzed to evaluate the prevalence of ESBL-producing *E. coli* and *K. pneumoniae* (ESBL Enterobacteriaceae) and carbapenem-resistant Enterobacteriaceae (CRE).

A matched case-control study within the retrospective cohort was performed, and only the first episode of bacteremia caused by an ESBL-producing isolate was included. All patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia were identified and were matched with a 1:3 ratio to control patients with cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae* bacteremia based on age, sex, ward, and case year to evaluate the clinical characteristics and outcomes of cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia. Patients who had polymicrobial bacteremia were excluded.

Clinical data were collected from electronic medical records and included the following information: demographics, preexisting medical conditions, source of bacteremia, source control measures, microbiological data, antibiotic therapy, and outcomes. This study was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2021-1568).

2. Study definitions

Bacteremia characterized by a positive blood culture obtained from a patient who had been hospitalized for at least 48 h was classified as a nosocomial infection [14]. Community-onset bacteremia characterized by a posi-

tive blood culture obtained within 48 h of hospitalization was classified as healthcare-associated or community-acquired infection, according to the definition by Friedman et al. [15]. Prognoses of underlying disease were classified according to the McCabe and Jackson system as follows: rapidly fatal (when death was expected within several months), ultimately fatal (when death was expected within four years), and non-fatal (when life expectancy was over four years) [16]. The Charlson comorbidity index was used to score the severity of the underlying disease [17]. The severity of illness at the time of bacteremia was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [18], and the severity of bacteremia was classified as sepsis, severe sepsis, and septic shock, as proposed by the International Sepsis Definitions Conference [19]. The source of bacteremia was identified according to the definition of the Centers for Disease Control and Prevention [20]. Eradicable foci and removal of eradicable foci were defined as described in a previous study [21]. Appropriate empirical treatment was defined as the use of an antimicrobial agent in a susceptible pathogen within 24 h of the index blood culture. Appropriate definitive treatment was defined as the use of an in vitro active antimicrobial agent within 5 days of the acquisition of the first positive blood culture and treatment for more than 48 h after antimicrobial susceptibility data became available [9]. β-lactam/β-lactamase inhibitor combinations were considered appropriate if the agent had an in vitro activity on the susceptibility test. The main outcome of bacteremia was 30-day mortality after its onset.

3. Microbiological data and identification of beta-lactamases

Species and antimicrobial susceptibilities were determined using a MicroScan WalkAway 96 plus System and Neg Combo Panel Type 44 or 72 (Beckman Coulter, Brea, CA, USA), according to the standard criteria of the CLSI [22]. The clinical microbiology laboratory in our hospital reported the results of phenotypic detection of ESBL using the MicroScan ESBL detection test (included in the Neg Combo Panel), which included testing with cefotaxime and ceftazidime alone or together with a fixed concentration of clavulanate. CRE was defined as a member of the family Enterobacteriaceae (*E. coli* and *K. pneumoniae* in this study) demonstrating resistance to any carbapenem (ertapenem, meropenem, or imipenem), based on antimicrobial susceptibility testing [23]. Six out of the ten isolates of cefotaxime-susceptible ESBL Enterobacteriaceae were collected, and ESBL production was phenotypically determined by the combined disk test using cefotaxime and ceftazidime alone and in combination with clavulanic acid, according to the CLSI guidelines [22].

4. Statistical analysis

Trend analysis of prevalence rates of ESBL-producing isolates and CRE isolates was evaluated using Poisson regression models. The Student's t-test or Mann–Whitney U test was used to compare continuous variables, and the Pearson chi-squared test or Fisher's exact test was used to compare corresponding categorical variables, as appropriate. A two-tailed P-value<0.05 was considered statistically significant. Analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA).

5. Ethics statement

This study was conducted according to the research protocol approved by the Asan Medical Center IRB in accordance with the Declaration of Helsinki and the Good Clinical Practice set by the Korea Food and Drug Administration. Identifying information in the electronic database was encrypted to protect personal privacy. Given the retrospective and observational nature of the study, written informed patient consent was waived by the IRB of the Asan Medical Center as no intervention was involved and no patient-identifying information was included.

Results

1. Trends in the prevalence of cefotaxime-susceptible ESBL isolates, ESBL isolates, and CRE isolates

A total of 10 205 episodes of *E. coli* bacteremia and 5501 episodes of *K. pneumoniae* bacteremia were identified during the study period. Of these, 32.5% (3183/10 205) of the *E. coli* isolates and 24.2% (1332/5501) of the *K. pneumoniae* isolates were ESBL-producing. A total of 10 (0.06% [10/15 706], 95% confidence interval [CI], 0.03%-0.12%) episodes of bacteremia with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* were identified from January 2011 to December 2020 (Fig. 1). The number of bacteremias caused by cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* remained low, and there was no significant change in the prevalence over the study period (P=0.43 for trend). All six cefotaxime-susceptible ESBL isolates collected during the study period were confirmed as ESBL producers by the combined disk test.

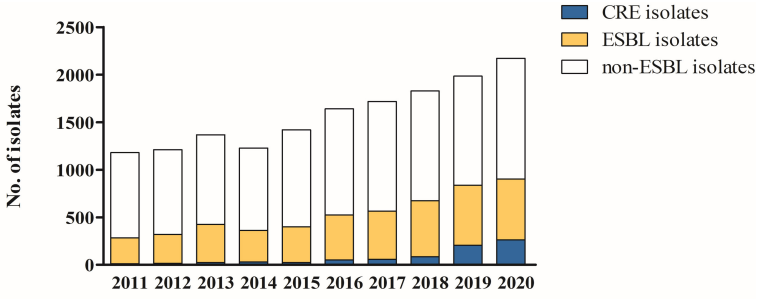
The total number of episodes of bacteremia caused by *E. coli* and *K. pneumoniae* increased from 2011 to 2020 (P<0.001 for trend), as shown in Fig. 1. The proportions of ESBL-producing isolates and CRE isolates also increased (both P<0.001 for trend). The proportion of ESBL-producing isolates gradually increased from 23.1% in 2011 to 29.5% in 2020 (incidence rate ratio [IRR], 1.03; 95% CI, 1.02-1.04), whereas the proportion of carbapenem-resistant isolates increased rapidly from 0.9% in 2011 to 12.1% in 2020 (IRR, 1.37; 95% CI, 1.33-1.42). Furthermore, the proportion of carbapenem-resistant *K. pneumoniae* increased rapidly and surpassed that of ESBL-producing *K. pneumoniae* in 2020 (Fig. 2).

2. Characteristics of patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia

The baseline and clinical characteristics of patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia are shown in Table 1. Only one patient (10%) had community-acquired infection, and the majority had healthcare exposure (90%) and previous antibiotic use within 3 months (90%). The antibiotic susceptibility test reported susceptibility for cefotaxime in these 10 isolates; however, none of the patients received cephalosporin as definitive treatment, and half received antibiotics other than carbapenem (Table 2). None of the patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia died within 30 days of the initial positive culture.

3. Comparison of clinical characteristics and treatment outcomes between cefotaxime-susceptible and cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae* bacteremia

Patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia were compared with those with cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae* bacteremia. The two groups were largely comparable in terms of demographic and underlying variables (Table 1).



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	
No. of CTX-susceptible ESBL isolates	0	0	0	1	2	2	1	1	1	2	(P = 0.43 for trend)
Proportion of CRE isolates (%)	0.9	1.2	1.8	2.4	1.6	3.2	3.4	4.6	10.3	12.1	(P <0.001 for trend)
Proportion of ESBL isolates (%)	23.1	25.1	29.5	26.9	26.5	28.8	29.4	32.2	31.9	29.5	(P <0.001 for trend)

Fig. 1. Ten-year trends of bacteremia caused by ESBL-producing and carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae*. ESBL indicates carbapenem-susceptible ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*.
Abbreviations: CTX, cefotaxime; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase.

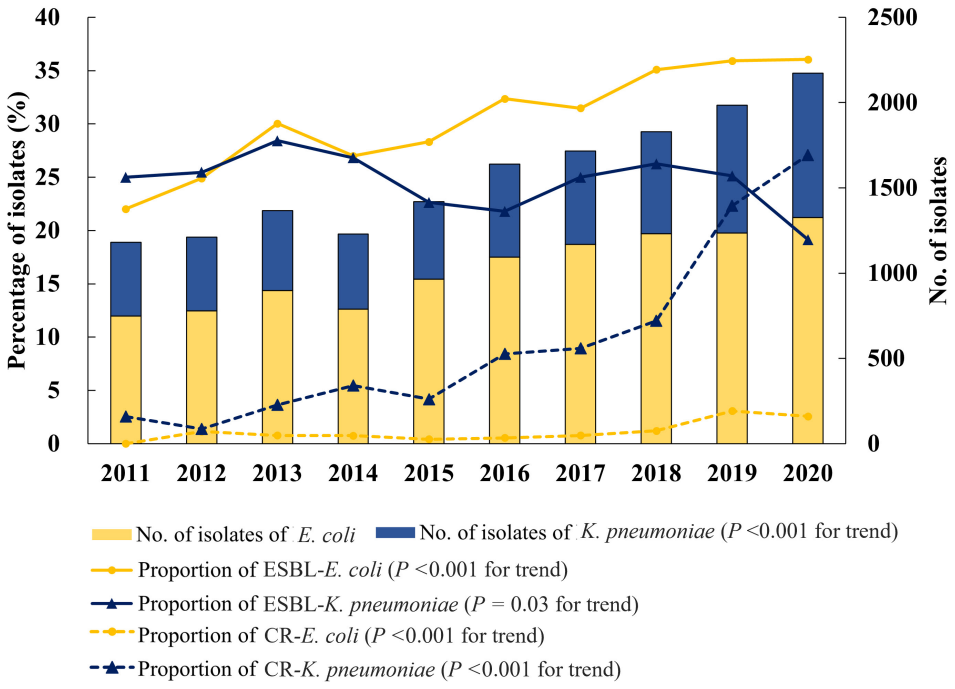


Fig. 2. Ten-year trends in proportions of ESBL-production and carbapenem-resistance in *Escherichia coli* and *Klebsiella pneumoniae* bacteremia. Abbreviations: ESBL, extended-spectrum β-lactamase; CR, carbapenem-resistant.

They displayed similar patterns in terms of site of acquisition and previous antibiotic use (both *P*=0.44). The Charlson comorbidity index scores, severity of sepsis, and APACHE II scores were also comparable. Approximately 70% of the patients in both groups received appropriate empirical treatment, and most received appropriate definitive treatment. Patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia tended to receive carbapenem less frequently for definitive treatment than those with cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae* bacteremia (*P*=0.09). There was no significant difference in 30-day mortality in patients with cefotaxime-susceptible and cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae* bacteremia (0% [0/10] vs. 23% [7/30], *P*=0.16).

Discussion

The numbers of ESBL-producing *E. coli* and *K. pneumoniae* and CRE bacteremia increased; however, cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia remained rare over the study period. The CLSI recommends that susceptibility results for cephalosporin be reported "as found" without a mandatory requirement for ESBL testing. In this study, the microbiology laboratory in our hospital identified ESBL production via an automated antimicrobial susceptibility test (MicroScan Neg Combo Panel) in all the Enterobacteriaceae isolates. Previous studies have reported the specificity of the ESBL confirmation panel in MicroScan to be 73-97% [24, 25]. We performed ESBL confirmation tests on the six available isolates to exclude any false positives. Infante et al. [26] reported the incidence of very major errors (VME) for cefotaxime susceptibility testing using MicroScan to be 0.63%, and Chung et al. [27] reported 0% VME for cefotaxime in our hospital. Therefore, we considered the possibility of false positives in cefotaxime-susceptible isolates to be low.

The underlying diseases/conditions and severities of infection in patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia were similar to those of patients with cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae*, particularly in terms of healthcare and antibiotic exposure. These epidemiological characteristics were more similar to those of cefotaxime-resistant ESBL *E. coli* and *K. pneumoniae* compared with those of ESBL-non-producing *E. coli* and *K. pneumoniae* [28,29]. Half of the cefotaxime-susceptible patients received antibiotics other than carbapenem, and their mortality was numerically lower than that of the cefotaxime-resistant

Table 1. Baseline and clinical characteristics of patients with ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia according to cefotaxime susceptibility

Characteristic	Cefotaxime-susceptible (n=10)	Cefotaxime-resistant (n=30)	*P*-value
Age (yr), median (IQR)	55.0 (44.0-60.3)	53.5 (48.0-60.3)	0.99
Male	4 (40.0)	15 (50.0)	0.72
Site of acquisition			
Community-acquired infection	1 (10.0)	1 (3.3)	0.44
Healthcare-associated infection	2 (20.0)	4 (13.3)	0.63
Nosocomial infection	7 (70.0)	25 (83.3)	0.39
McCabe and Jackson classification			0.89
Nonfatal	3 (30.0)	6 (20.0)	
Ultimately fatal	5 (50.0)	20 (66.7)	
Rapidly fatal	2 (20.0)	4 (13.3)	
Charlson comorbidity index, median (IQR)	6 (2-8)	6 (3-8)	0.88
Previous antibiotic within 3 months	9 (90.0)	29 (96.7)	0.44
Cephalosporin	5 (50.0)	23 (76.7)	0.11
Carbapenem	3 (30.0)	15 (50.0)	0.46
β-lactam/β-lactamase inhibitor	6 (60.0)	13 (43.3)	0.47
Quinolone	2 (20.0)	11 (36.7)	0.45
Indwelling device	8 (80.0)	22 (73.3)	>0.99
Preexisting medical condition	9 (90.0)	29 (96.7)	0.44
Previous surgery within 3 months	3 (30.0)	10 (33.3)	>0.99
Diabetes mellitus	4 (40.0)	10 (33.3)	0.72
End-stage liver disease	3 (30.0)	7 (23.3)	0.69
End-stage renal disease	3 (30.0)	3 (10.0)	0.15
Congestive heart failure	0	1 (3.3)	>0.99
Solid cancer	4 (40.0)	15 (50.0)	0.72
Hematologic malignancy	3 (30.0)	7 (23.3)	0.69
Chemotherapy within 6 months	4 (40.0)	14 (46.7)	>0.99
Immunosuppressant use	4 (40.0)	10 (33.3)	0.72
Corticosteroid use	3 (30.0)	6 (20.0)	0.67
Solid organ transplant	3 (30.0)	8 (26.7)	>0.99
Neutropenia	3 (30.0)	7 (23.3)	0.69
APACHE II score, median (IQR)	15.0 (11.5-18.3)	15.0 (10.8-25.3)	0.41
Severity of sepsis			0.57
Without SIRS	0	1 (3.3)	
Sepsis	3 (30.0)	6 (20.0)	
Severe sepsis	3 (30.0)	7 (23.3)	
Septic shock	4 (40.0)	16 (53.3)	
Site of infection			0.99
Primary bacteremia[a]	4 (40.0)	8 (26.7)	
Intra-abdominal infection	3 (30.0)	7 (23.3)	
Biliary tract infection	2 (20.0)	5 (16.7)	
Urinary tract infection	1 (10.0)	6 (20.0)	
Catheter-related infection	0	3 (10.0)	
Pneumonia	0	1 (3.3)	

Data are presented as number of patients (with percentage in parentheses), unless otherwise specified.
[a]Of the 12 patients, 4 had typhlitis with neutropenic fever.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range.

group. Our results are consistent with previous studies suggesting that cefotaxime MIC, rather than ESBL production, is associated with mortality [7-9,30]. However, we failed to demonstrate a statistically significant difference in mortality between the two groups due to the limited number of patients with cefotaxime-susceptible iso-

Table 2. Clinical management and outcomes of patients with ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia

Characteristic/outcome	Cefotaxime-susceptible (n=10)	Cefotaxime-resistant (n=30)	*P*-value
Microbiology			>0.99
E. coli	2 (20.0)	6 (20.0)	
K. pneumoniae	8 (80.0)	24 (80.0)	
No. patients with eradicable foci	4 (40.0)	14 (46.7)	>0.99
Removal of eradicable focus within 7 days	4/4 (100.0)	10/14 (71.4)	0.52
Appropriate empirical treatment	7 (70.0)	22 (73.3)	>0.99
Empirical antibiotics regimen			
Cephalosporin	0	7 (23.3)	0.16
Carbapenem	6 (60.0)	15 (50.0)	0.72
β-lactam/β-lactamase inhibitor	4 (40.0)	8 (26.7)	0.45
Appropriate definitive treatment	9 (90.0)	28 (93.3)	>0.99
Definitive antibiotic regimen			
Cephalosporin	0	2 (6.7)	>0.99
Carbapenem	5 (50.0)	25 (83.3)	0.09
β-lactam/β-lactamase inhibitor	2 (20.0)	3 (10.0)	0.58
Quinolone	3 (30.0)	0	0.01
Recurrence within 1 month	0	1 (3.3)	>0.99
7-day mortality	0	3 (10.0)	0.56
14-day mortality	0	4 (13.3)	0.56
30-day mortality	0	7 (23.3)	0.16

Data are presented as number of patients (with corresponding percentage in parentheses), unless otherwise specified.

lates. Multicenter studies with larger numbers of patients are required. Furthermore, studies comparing the clinical outcomes of antibiotics other than carbapenem in patients with cefotaxime-susceptible ESBL isolates are required.

We found that the prevalence of cefotaxime-susceptible ESBL isolates since the revision of the CLSI recommendations was 0.06% over 10 years. Ku et al. [30] reported a prevalence of 0.38% over the five years from 2006-2010. The low prevalence in both studies supports the CLSI guidelines, which recommend reporting cefotaxime susceptibility "as found," without mandatory ESBL confirmation tests.

Since the first detection of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* in 2010 in Korea [31], a rising trend of carbapenemase-producing Enterobacteriaceae has been reported on sentinel surveillance conducted by the Korea Disease Control and Prevention [32]. Noteworthy, the proportion of CRE surpassed that of ESBL among *K. pneumoniae* in our study.

Our study had several limitations. First, none of the patients received cephalosporin as a definitive treatment despite their susceptibility. Therefore, we were unable to evaluate whether clinical outcomes differed if patients with cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia received extended-spectrum cephalosporin based on the susceptibility test. Second, we could not perform ESBL confirmation tests on four of the cefotaxime-susceptible ESBL isolates since they were not collected and stored. Furthermore, we could not perform the broth test for cefotaxime; therefore, we cannot exclude the possibility of false negative results for cefotaxime susceptibility, although the VME for cefotaxime in our hospital was low. Third, we reviewed antibiotic use within 3 months based on electronic medical records; however, we cannot exclude antibiotic use prescribed outside the hospital, which was not recorded in our charts. Fourth, the study consisted of patients from a single center, indicating potential selection bias. Therefore, a larger study including more diverse hospital settings is required.

In conclusion, our study indicates that the prevalence of cefotaxime-susceptible ESBL *E. coli* and *K. pneumoniae* bacteremia and its mortality are low. These results support the current CLSI recommendation for elective ESBL

testing. The rapidly increasing carbapenem resistance, particularly in *K. pneumoniae*, is a potential concern.

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Disclosure of Conflict of Interest

The authors have no potential conflict of interest to disclose.

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