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Risk Factors for Mortality in Patients with *Klebsiella pneumoniae* Carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia

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ABSTRACT

Background: *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacterales bacteremia is associated with significant mortality; however, no optimal antibiotic strategy is available. We aimed to evaluate the clinical outcomes according to the antibiotic regimens and identify risk factors for mortality in patients with KPC-producing *K. pneumoniae* and *Escherichia coli* bacteremia.

Materials and Methods: This retrospective cohort study included all adult patients with monomicrobial bacteremia (KPC-producing *K. pneumoniae* or *E. coli*) between January 2011 and March 2021 at a 2,700-bed tertiary center.

Results: Ninety-two patients were identified; 7 with *E. coli* bacteremia, and 85 with *K. pneumoniae* bacteremia. Thirty-day mortality was 38.0% (35/92). Non-survivors were more likely to have had nosocomial infection (88.6% *vs.* 63.2%, *P* = 0.01), high APACHE II scores (mean [interquartile range], 22.0 [14.0 - 28.0] *vs.* 14.0 [11.0 - 20.5], *P* <0.001), and septic shock (51.4% *vs.* 26.3%, *P* <0.001) and less likely to have been admitted to the surgical ward (5.7% *vs.* 22.8%, *P* = 0.04), undergone removal of eradicable foci (61.5% *vs.* 90.6%, *P* = 0.03), and received appropriate combination treatment (57.1% *vs.* 78.9%, *P* = 0.03) than survivors. No significant difference in mortality was observed according to combination regimens including colistin, aminoglycoside, and tigecycline. In multivariable analysis, high APACHE II scores (adjusted odds ratio [aOR], 1.14; 95% confidence interval [CI], 1.06 - 1.23, *P* <0.001), and appropriate definitive treatment (aOR, 0.25; CI, 0.08 - 0.74, *P* = 0.01) were independent risk factors for mortality.

Conclusion: High APACHE II scores and not receiving appropriate definitive treatment were associated with 30-day mortality. Mortality did not significantly differ according to combination regimens with conventional drugs such as aminoglycoside and colistin.

Keywords: *Klebsiella pneumoniae* Carbapenemase; Mortality; *Klebsiella pneumoniae*; *Escherichia coli*; Bacteremia

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INTRODUCTION

Klebsiella pneumoniae carbapenemase (KPC)-producing Enterobacterales has become a major cause of nosocomial infection worldwide since its first detection in the Unites States in 2001 [1]. Lee et al. reported rising trends of carbapenemase producing Enterobacterales (CPE) based on sentinel surveillance conducted by the Korea Disease Control and Prevention Agency (KDCA) from 5,962 in 2018 to 8,887 in 2019 [2]. KPC has been the most prevalent carbapenemase in Korea which comprises almost 70% of carbapenemases, and the number of KPC isolates has been increasing from 4,132 in 2018 to 6,309 in 2019 [2]. KPC-producing Enterobacterales bacteremia is associated with a significant mortality of 22% to 72% [3, 4].

Previous studies have reported that combination therapy is associated with a survival benefit in patients with KPC-producing Enterobacterales bacteremia, especially in severely ill patients [3, 5-8]. However, ideal combination strategies are yet to be identified. Furthermore, previous studies defined combination therapy differently, and increasing numbers of patients with KPC-producing Enterobacterales bacteremia have demonstrated multi-drug resistance including tigecycline and colistin [4, 9, 10]. Therefore, options involving more than two susceptible antibiotics are usually limited in real clinical settings.

Novel antibiotics such as ceftazidime-avibactam or meropenem-vaborbactam have been used against KPC-producing organisms since 2015 [11]. However, many countries have limited access to these novel antimicrobial agents, including Korea. Therefore, we aimed to evaluate clinical outcomes according to antibiotic regimens in a situation in which novel antibiotics are unavailable, as well as to identify risk factors for mortality in patients with KPC-producing *K. pneumoniae* and *Escherichia coli* bacteremia.

MATERIALS AND METHODS

1. Study population and design
This retrospective observational study was performed at Asan Medical Center, a 2,700-bed tertiary referral center in Seoul, Korea. All patients with monomicrobial bacteremia (KPC-producing *K. pneumoniae* or *E. coli*) between January 2011 and March 2021 were included in this study, and only the first episode of bacteremia occurred in each patient was included in the analysis. Patients were excluded if they (1) were aged <18 years, (2) had polymicrobial bacteremia, defined as isolation of at least two different organisms from the same blood sample at the time of first positive culture with KPC-producing *K. pneumoniae* and *E. coli*, or (3) had KPC-producing Enterobacterales other than *K. pneumonia* or *E. coli.* Clinical data were collected from electronic medical records, including demographic information, preexisting medical conditions, antibiotic exposure within 3 months, microbiological data, antibiotic therapy, source of bacteremia, source control measures, and outcomes. This study was approved by the institutional review board of Asan Medical Center (approval no. 2020-0874).

2. Study definitions
The onset of bacteremia was defined as the date of blood collection for the first culture that yielded the study organisms. The bacteremia was classified as a nosocomial infection in cases in which a positive blood culture was obtained from patients who had been hospitalized for >48 h. Community-onset healthcare-associated infection was classified as healthcare-associated or community-acquired according to the definition provided by Friedman et al [12].
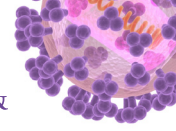
The Charlson comorbidity index was used to score the severity of the underlying conditions [13]. The prognosis of underlying condition was classified as rapidly fatal (when death was expected within several months), ultimately fatal (when death was expected within 4 years), and nonfatal (when life expectancy was >4 years), in accordance with the McCabe and Jackson classification [14]. The severity of illness at the time of bacteremia was assessed using the acute physiology and chronic health evaluation II (APACHE II) score [15]. Furthermore, the severity of bacteremia was distinguished into without systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock, as proposed by the international sepsis definitions conference [16]. The suspected source of bacteremia was identified using the definition from the Centers for Disease Control and Prevention [17]. Immunosuppressive medication was defined as described in a previous study [18]. Eradicable foci and removal of eradicable foci were defined as previously described [19]. Briefly, eradicable foci included surgically removable infections or drainable abscess, as well as indwelling foreign bodies such as central venous catheters [20]. Source control was defined as the removal of eradicable infection foci within the first 3 days from the date of the positive isolation of organism from blood samples. Appropriate empirical treatment was defined as the use of an antimicrobial agent to which the causative pathogen is susceptible within 24 h of the index blood culture [21]. Appropriate definitive treatment was defined as the administration of an *in vitro* active antimicrobial agent within 7 days of the first positive blood culture, after the availability of antimicrobial susceptibility data and treatment for >48 h [5]. Combination therapy was defined as a regimen of one *in vitro* active agent combined with one or more antimicrobials with Gram-negative activity regardless of *in vitro* susceptibility in which the duration of each antimicrobial agent overlapped for >48 h [22]. The treatment outcome of bacteremia was evaluated on the basis of 30-day mortality after the onset of bacteremia.

3. Microbiological data and identification of carbapenemase

Species identification and antimicrobial susceptibility determination were performed using the MicroScan WalkAway 96 plus system and Neg Combo Panel Type 72 (Beckman Coulter, Brea, CA, USA) and the standard criteria set by the Clinical and Laboratory Standards Institute published in 2012 [23]. Carbapenem-resistant Enterobacterales (CRE) was defined as Enterobacterales isolates demonstrating resistance to any carbapenem (ertapenem, meropenem, or imipenem) based on antimicrobial susceptibility testing [21], and all CRE isolates underwent modified Hodge test and carbapenemase inhibition test using phenylboronic acid and EDTA for the phenotypic detection of carbapenemase [24]. The presence of carbapenemase genes including KPC was evaluated using NG-Test Carba 5 (NG Biotech, Guipry, France) [25]. When CPE was identified, the clinical microbiology laboratory in our center reported the tigecycline susceptibility in available isolates using Neg Breakpoint Combo Panel Type 44 (Beckman Coulter, USA) according to the criteria set by European committee on antimicrobial susceptibility testing [26].

4. Statistical Analysis

Student's *t*-test or the Mann-Whitney *U* test was used to compare differences between continuous variables, and the Pearson chi-square test or Fisher's exact test was used to compare the respective categorical variables, as appropriate. Multivariable analyses were performed to identify risk factors for 30-day mortality in patients with KPC-producing *K. pneumoniae* or *E. coli* bacteremia. All variables with a *P*-value of <0.1 in the univariate analysis and other variables of clinical importance were included in a multiple logistic regression model. A two-tailed *P* <0.05 was considered statistically significant. Kaplan-Meier survival curves for 30-day mortality according to the definitive treatment were constructed and

analyzed using the log-rank test. Analyses were performed using GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA) and SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics and clinical outcomes

A total of 106 patients with KPC-producing Enterobacterales bacteremia were identified during the study period. Of these, 14 were excluded; 1 was under 18 years old, 1 had KPC-producing *Citrobacter freundii* bacteremia, and 12 had polymicrobial infection. Of the 92 patients included the study, 85 (92.4%) had *K. pneumoniae* bacteremia and 7 (7.6%) had *E. coli* bacteremia. The demographics and clinical characteristics of the 92 patients with KPC-producing *K. pneumoniae* and *E. coli* bacteremia are shown in **Table 1**. The mean patient age was 61.4 years, and 66.3% were male. Most of the patients (97.8%) had healthcare-associated or nosocomial infection, and solid cancer and recent surgical history were frequent underlying medical conditions.

Table 1. Baseline, clinical characteristics, and management of patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia

Characteristic/outcome	Nonsurvivors (n = 35)	Survivors (n = 57)	*P*-value
Age (yr), median (IQR)	64.0 (56.0 - 74.0)	62.0 (54.5 - 68.0)	0.44
Male sex	22 (62.9)	39 (68.4)	0.58
Site of acquisition			
Community-acquired infection	0	2 (3.5)	0.52
Healthcare-associated infection	4 (11.4)	19 (33.3)	0.03
Nosocomial infection	31 (88.6)	36 (63.2)	0.01
Charlson comorbidity index, median (IQR)	7 (6 - 9)	6 (4 - 9)	0.09
McCabe and Jackson classification			0.78
Non-fatal	7 (20.0)	8 (14.0)	
Ultimately fatal	24 (68.6)	48 (84.2)	
Rapidly fatal	4 (11.4)	1 (1.8)	
Preexisting medical condition			
Solid cancer	18 (51.4)	27 (47.4)	0.71
Hematologic malignancy	8 (22.9)	9 (15.8)	0.40
Solid organ transplant	9 (25.7)	19 (33.3)	0.44
Recent surgery within 6 months	15 (42.9)	31 (54.4)	0.28
Diabetes mellitus	13 (37.1)	24 (42.1)	0.64
Liver cirrhosis	12 (34.3)	20 (35.1)	0.94
Chronic kidney disease	13 (37.1)	14 (24.6)	0.20
End-stage renal disease requiring renal replacement therapy	8 (22.9)	6 (10.5)	0.11
Congestive heart failure	1 (2.9)	2 (3.5)	>0.99
Immunosuppressant use	20 (57.1)	24 (42.1)	0.16
Recent chemotherapy within 6 months	14 (40.0)	20 (35.1)	0.64
Neutropenia	8 (22.9)	7 (12.3)	0.18
Previous antibiotics within 3 months	33 (94.3)	55 (96.5)	0.63
Previous carbapenem use within 3 months	22 (62.9)	34 (59.6)	0.76
Indwelling device	33 (94.3)	52 (91.2)	0.71
Ward at bacteremia onset			
Intensive care unit	10 (28.6)	13 (22.8)	0.54
Medical ward	23 (65.7)	32 (56.1)	0.36
Surgical ward	2 (5.7)	13 (22.8)	0.04
APACHE II score, median (IQR)	22.0 (14.0 - 28.0)	14.0 (11.0 - 20.5)	<0.001
Severity of sepsis			<0.001
Without SIRS	0	2 (3.6)	
Sepsis	8 (22.9)	30 (52.6)	
Severe sepsis	9 (25.7)	10 (17.5)	
Septic shock	18 (51.4)	15 (26.3)	

Table 1. (Continued) Baseline, clinical characteristics, and management of patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia

Characteristic/outcome	Nonsurvivors (n = 35)	Survivors (n = 57)	*P*-value
Site of infection			
Biliary infection	10 (28.6)	20 (35.1)	0.52
Abdominal infection	10 (28.6)	19 (33.3)	0.63
Pneumonia	6 (17.1)	4 (7.0)	0.17
Urinary tract infection	2 (5.7)	6 (10.5)	0.71
Catheter-related infection	1 (2.9)	3 (5.3)	>0.99
Primary infection	6 (17.1)	5 (8.8)	0.23
Microbiology			0.71
Escherichia coli	2 (5.7)	5 (8.8)	
Klebsiella pneumoniae	33 (94.3)	52 (91.2)	
Meropenem minimum inhibitory concentration, µg/mL			0.30
2	1 (2.9)	2 (3.5)	
4	3 (8.6)	4 (7.0)	
8	4 (11.4)	6 (10.5)	
>8	27 (77.1)	45 (78.9)	
No. of patients with eradicable foci	13 (37.1)	32 (56.1)	0.08
Removal of eradicable foci within 3 days	8/13 (61.5)	29/32 (90.6)	0.03
Appropriate empirical treatment	17 (48.6)	19 (33.3)	0.15
Inappropriate definitive treatment	14 (40.0)	10 (17.5)	0.02
Appropriate definitive treatment	21 (60.0)	47 (82.5)	0.02
Monotherapy	1 (2.9)	2 (3.5)	>0.99
Combination therapy	20 (57.1)	45 (78.9)	0.03
Combination regimen (mutually exclusive)			
Colistin-based[a]	9/20 (45.0)	19/45 (42.2)	0.84
Aminoglycoside-based[b]	8/20 (40.0)	18/45 (40.0)	>0.99
Aminoglycoside with colistin[c]	3/20 (15.0)	7/45 (15.6)	>0.99
Tigecycline-based[d]	0/20	1/45 (2.2)	>0.99

Data are presented as the number of patients (percentage), unless otherwise specified.
[a]Colistin-based regimen was defined as colistin combination without aminoglycoside.
[b]Aminoglycoside-based regimen was defined as aminoglycoside combination without colistin.
[c]Aminoglycoside with colistin was defined as aminoglycoside and colistin combination.
[d]Tigecycline-based regimen was defined as tigecycline combination without colistin and aminoglycoside.
IQR, interquartile range; APACHE II, acute physiology and chronic health evaluation II; SIRS, systemic inflammatory response syndrome.
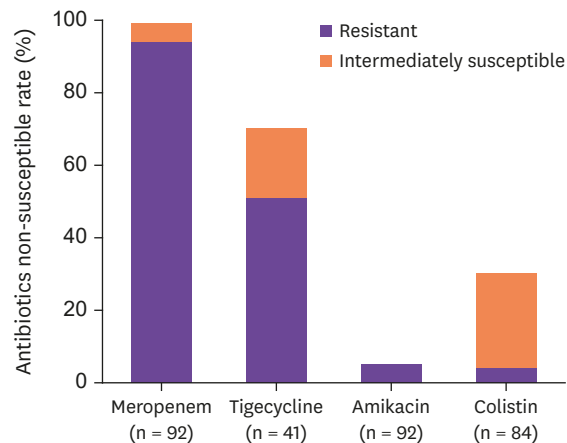
Figure 1. Meropenem, tigecycline, amikacin and colistin resistance rates among *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* isolates. Numbers are patients that susceptibility tests were available for each antimicrobial agent.

Resistance rates for each antimicrobial agent are shown in **Figure 1**. 70.7% (29/41) of patients with KPC-producing *K. pneumoniae* and *E. coli* bacteremia were non-susceptible to tigecycline, and 31.0% (26/84) to colistin. Only 5.4% (5/92) of patients were non-susceptible to amikacin.

In terms of treatment, 36 patients (39.1%) received appropriate empirical treatment and 68 patients (73.9%) received appropriate definitive treatment (**Table 1**). Thirty-day mortality was 38.0% (35/92).

2. Clinical characteristics associated with 30-day mortality

No significant differences in 30-day mortality were observed between the *E. coli* and *K. pneumoniae* groups: 2/7 (28.6%) and 33/85 (38.8%), respectively (*P* = 0.71). Patients who died were more likely to have had nosocomial infection (88.6% *vs.* 63.2%, *P* = 0.01), higher APACHE II score (median, 22.0 [interquartile range, 14.0 - 28.0] *vs.* 14.0 [11.0 - 20.5], *P* <0.001), and septic shock (51.4% *vs.* 26.3%, *P* <0.001) than patients who survived. Nonsurvivors were also less likely to have been admitted to the surgical ward at the onset of bacteremia (5.7% *vs.* 22.8%, *P* = 0.04), undergone removal of eradicable foci (61.5% *vs.* 90.6%, *P* = 0.03), and received appropriate definitive treatment (60.0% *vs.* 82.5%, *P* = 0.02) and combination therapy (57.1% *vs.* 78.9%, *P* = 0.03). The Kaplan-Meier curves according to the definitive treatment are presented in **Supplementary Figure 1** (*P* <0.001 by log rank test).

3. Anti-KPC antibiotic strategies and risk factor analysis

To compare the efficacy of anti-KPC antibiotic strategies, we classified all anti-KPC antibiotic regimens that were considered appropriate definitive combination treatments into mutually exclusive groups (**Table 1**). In addition, we analyzed 30-day mortality according to the antimicrobial regimens used (**Supplementary Table 1**). Colistin-based and aminoglycoside-based regimens were the most frequently used combination treatments. Aminoglycoside with colistin was associated with the lowest 30-day mortality (3/10, 30.0%) in groups with ≥10 patients. However, there were no significant differences in 30-day mortality according to each combination regimen (colistin-based regimen *vs.* aminoglycoside-based regimen *vs.* aminoglycoside with colistin *vs.* tigecycline-based regimen, *P* = 0.89).

Significant variables in the univariate analysis (**Table 1**) were included in a logistic regression model to identify independent risk factors for 30-day mortality (**Table 2**). Because of the significant correlations between variables that reflect the severity of bacteremia, we retained APACHE II score but not severity of sepsis. Furthermore, because of the inverse correlation between nosocomial infection and healthcare-associated infection, we retained only nosocomial infection. As combination therapy was correlated with appropriate definitive treatment, we retained only appropriate definitive treatment. Consequently, we used nosocomial infection, Charlson comorbidity index, surgical ward, eradicable focus control, APACHE II score, and appropriate treatment in the multivariable analysis. Multivariable analysis indicated that a high APACHE II score (adjusted odds ratio [aOR], 1.14; 95% confidence interval [CI], 1.06 - 1.23; *P* <0.001) and appropriate definitive treatment (aOR, 0.25; 95% CI, 0.08 - 0.74; *P* = 0.01) were independent risk factors for 30-day mortality.

Table 2. Results of analyses of risk factors for 30-day mortality in patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Nosocomial infection	4.52 (1.40 - 14.60)	0.01		
Charlson comorbidity index	1.15 (0.98 - 1.36)	0.09		
Surgical ward	0.21 (0.04 - 0.97)	0.046		
Eradicable focus control	0.29 (0.11 - 0.74)	0.01		
APACHE II score	1.13 (1.06 - 1.21)	<0.001	1.14 (1.06 - 1.23)	<0.001
Appropriate definitive treatment	0.32 (0.12 - 0.83)	0.02	0.25 (0.08 - 0.74)	0.01

OR, odds ratio; CI, confidence interval; APACHE II, acute physiology and chronic health evaluation II.

Table 3. Univariate and multivariate analyses of the associations between different definitive combination regimens and 30-day mortality in patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia (n = 64)[a]

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Nosocomial infection	6.33 (0.76 - 52.95)	0.09	4.74 (0.48 - 46.98)	0.18
Charlson comorbidity index	1.20 (0.98 - 1.45)	0.07	1.18 (0.93 - 1.50)	0.18
Eradicable focus control	0.39 (0.13 - 1.21)	0.10	0.68 (0.17 - 2.67)	0.58
APACHE II score	1.13 (1.04 - 1.22)	0.01	1.11 (1.00 - 1.23)	0.045
Colistin-based combination[b]	(reference)		(reference)	
Aminoglycoside-based combination[c]	0.94 (0.30 - 2.96)	0.91	0.80 (0.20 - 3.31)	0.76
Aminoglycoside with colistin[d]	0.91 (0.19 - 4.34)	0.90	0.47 (0.07 - 3.43)	0.46

[a]Of 65 patients who received appropriate definitive combination therapy, 1 patient who received tigecycline-based combination therapy was excluded.
[b]Colistin-based combination was defined as colistin combination without aminoglycoside.
[c]Aminoglycoside-based combination was defined as aminoglycoside combination without colistin.
[d]Aminoglycoside with colistin was defined as aminoglycoside and colistin combination.
OR, odds ratio; CI, confidence interval; APACHE II, acute physiology and chronic health evaluation II.

Different anti-KPC regimens among patients who received appropriate definitive combination therapy were compared after adjusting for confounding factors (**Table 3**). Tigecycline-based combination therapy was excluded because of the small number (n = 1). In multivariable analysis, patients who received an aminoglycoside-based combination (aOR 0.80; 95% CI, 0.20 - 3.31, *P* = 0.76), or aminoglycoside with colistin (aOR, 0.47; 95% CI, 0.07 - 3.43, *P* = 0.46) showed no significant differences in 30-day mortality from those who received a colistin-based combination regimen.

We compared the number of susceptible or intermediate susceptible antibiotics between nonsurvivors and survivors who received appropriate definitive treatments (**Supplementary Table 2**). Of 68 patients who received appropriate definitive treatment, 19 received two or more susceptible or intermediate susceptible antibiotics, while 49 received only one susceptible or intermediate susceptible antibiotics. Although 30-day mortality were numerically lower in patients who received two or more susceptible or intermediate susceptible antibiotics (4/19, 21.1%) than in those who received only one susceptible or intermediate susceptible antibiotic (17/49, 34.7%), the two groups showed no significant differences (*P* = 0.38).

DISCUSSION

In the present study, high APACHE II score and not receiving appropriate definitive treatment were independent risk factors for 30-day mortality in patients with KPC-producing *K. pneumoniae* and *E. coli* bacteremia. Mortality showed no significant difference according to the definitive combination regimens used. Carbapenem-containing combination therapy was associated with low mortality in patients with KPC-producing *K. pneumoniae* bacteremia in previous studies [4, 5, 7]. However, the benefit of carbapenem-containing combination therapy was identified only when the meropenem MIC was ≤8 mg/L, and Daikos et al. recommended considering carbapenem therapy for carbapenemase-producing *K. pneumoniae* infection when the carbapenem MIC is ≤4 mg/L [27]. A wide variation of carbapenem MICs in KPC-producing isolates had been observed [27]. Moreover, although Tumbarello et al. reported that 36.8% (243/661) of patients with KPC-producing *K. pneumoniae* had a meropenem MIC of ≤8 mg/L [4], we had reported that a high proportion (76.2 - 88.0%) of patients with KPC-producing isolates demonstrated a meropenem MIC of >8 mg/L [19, 28].
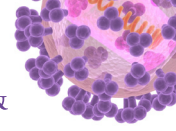
Therefore, carbapenem-containing regimens were less likely to be effective in our center, and other antimicrobial strategies for KPC-producing isolates were needed. Falcon et al. identified colistin-based combination as the best-available therapy for KPC-producing *K. pneumoniae* infection in a previous study [29]. However, when we compared the clinical efficacy of definitive combination regimens, colistin-based regimens were not associated with a mortality benefit.

Previous studies recommended combination therapy for KPC-producing *K. pneumoniae* infection [3, 5-8]; however, the definitions for combination therapy varied. Tumbarello et al. and Tzouvelekis et al. defined combination therapy as the administration of at least two antibiotics with *in vitro* activity [3, 4, 8], whereas Gutiérrez-Gutiérrez et al. defined it as a regimen including more than one in vitro active antibiotic [6]. Qureshi et al. defined combination therapy as the administration of two antimicrobials with Gram-negative activity regardless of *in vitro* susceptibility [7]. However, as increasing numbers of KPC-producing Enterobacterales had developed colistin and/or tigecycline resistance, and even pan-drug-resistant isolates had been observed [4, 9, 10, 27], the combination of more than two antibiotics with *in vitro* activity is not always feasible. We compared the clinical outcomes according to the number of susceptible or intermediate susceptible antibiotics used. No significant mortality benefit was noted in patients who received two or more susceptible or intermediate susceptible antibiotics compared with those who received only one susceptible or intermediate susceptible antibiotic. As this study analyzed a small number of patients, larger studies are needed to confirm our findings.

In the current study, the mortality of patients who received combination treatment was approximately 30%, and it was similar between patients who received colistin-based regimens and those who received aminoglycoside-based regimens. Shields et al. reported that 30-day mortality in patients with carbapenem-resistant *K. pneumoniae* bacteremia, mainly KPC-producing isolates (97%), was 8% when patients received ceftazidime-avibactam, whereas the mortality of patients who received conventional regimens including carbapenem, aminoglycoside, or colistin was approximately 30% [30]. Furthermore, Tumbarello et al. reported there was a significant mortality benefit in patients with KPC-producing *K. pneumoniae* when they received ceftazidime-avibactam salvage treatment with at least one antimicrobial agent with *in vitro* activity compared to when they received other antimicrobial agents other than ceftazidime-avibactam (36.5% *vs.* 55.8%, $P = 0.005$) [31]. In a randomized clinical trial, Wunderink et al. compared meropenem-vaborbactam and best-available therapy with colistin, aminoglycoside, tigecycline, and carbapenem in patients with carbapenem-resistant Enterobacteriaceae infection [32]. Although 64% of the patients in this study had KPC-producing *K. pneumoniae* infection, 28-day mortality in patients with carbapenem-resistant *Enterobacteriaceae* bacteremia was 22.2% in the meropenem-vaborbactam group, compared with 44.4% in the best-available therapy group. The results of our study highlight the limitation of currently available antimicrobial treatments, including classic agents such as carbapenem, colistin, and aminoglycoside, in Korea. Thus, the introduction of novel antimicrobial agents is urgently needed.

Our study had several limitations. First, we excluded tigecycline-based combination therapy in the evaluation of 30-day mortality according to different definitive combination regimens owing to the small number (n = 1). As data from a tigecycline susceptibility test were unavailable in 55.4% (51/92) of the patients in our study, the number of patients with appropriate definitive treatment who received a tigecycline-based regimen could have been

underestimated. Second, owing to the observational nature of the study, a selection bias may exist. Third, this study included a small number of patients from a single tertiary center in Korea. Finally, as it is difficult to apply the modified Hodge test in general hospitals, further multicenter randomized studies in different settings are needed.

In conclusion, high APACHE II score and not receiving appropriate definitive treatment were associated with 30-day mortality. Novel antimicrobial agents are needed to reduce the mortality of KPC-producing Enterobacterales bacteremia because there are very few susceptible antimicrobial agents, and it is difficult to select an appropriate antimicrobial agent.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Clinical outcomes of patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia according to antimicrobial regimens

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Supplementary Table 2

Comparison of the number of susceptible or intermediate susceptible antibiotics between nonsurviving and surviving patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia who received appropriate definitive treatment

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Supplementary Figure 1

Kaplan-Meier survival curves for patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* and *Escherichia coli* bacteremia according to the definitive treatment. The continuous and dotted lines depict the survival curves for patients who received appropriate definitive treatment and inappropriate definitive treatment, respectively. The log rank test showed significant difference in 30-day mortality (P <0.001).

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