Difference in the Clinical Outcome of Bloodstream Infections Caused by *Klebsiella aerogenes* and *Enterobacter cloacae* Complex

Minji Jeon,[1] **Kyungmin Huh,**[1] **Jae-Hoon Ko,**[1] **Sun Young Cho,**[1] **Hee Jae Huh,**[2] **Nam Yong Lee,**[2] **Cheol-In Kang,**[1] **Doo Ryeon Chung,**[1] **and Kyong Ran Peck**[1]

[1]Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Irwon-dong, Gangnam-gu, Seoul, Republic of Korea,
[2]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Irwon-dong, Gangnam-gu, Republic of Korea

Background. The difference in clinical outcomes between *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*) bacteremia (KAB) and *Enterobacter cloacae* complex bacteremia (ECB) is controversial.

Methods. We compared the clinical outcomes of patients with KAB and ECB and examined the risk factors associated with mortality. We conducted a retrospective case-control study of hospitalized patients with monobacterial KAB and ECB between January 2011 and June 2020. The primary outcome measure was 30-day all-cause mortality. Multiple logistic regression and propensity-score (PS) matching were used to identify independent risk factors for mortality. The models included demographic characteristics, comorbidities, recent healthcare contact, patient status at the onset of bacteremia, and severity of infection as covariates.

Results. A total of 282 patients with KAB or ECB were included, among whom 194 patients were selected after PS matching. The 30-day all-cause mortality rate was higher in the ECB group than in the KAB group (24.1% vs 10.6%, *P* = .003). In a multivariable model, ECB was an independent risk factor for 30-day mortality in both overall and PS-matched cohorts (adjusted odds ratio, 3.528; 95% confidence interval, 1.614–7.714; *P* = .002). Stay in the intensive care unit at the onset of bacteremia and higher Pitt bacteremia score were found to be independent risk factors for 30-day mortality.

Conclusions. In our study, mortality was significantly higher in patients with ECB than in those with KAB. Further studies are warranted to clarify the virulence mechanisms of *E cloacae* complex.

Keywords. bacteremia; *Enterobacter cloacae* complex; *Klebsiella aerogenes*.

Enterobacter is a genus of Gram-negative, facultatively anaerobic, rod-shaped, nonspore-forming bacteria of the family Enterobacterales. *Enterobacter* species are associated with wound, intra-abdominal, respiratory, urinary, and bloodstream infections, representing an increasingly important nosocomial pathogen [1]. These species have intrinsic resistance to penicillin and early cephalosporin mediated by a chromosomal (*ampC*) beta-lactamase, and further resistance is rapidly induced upon exposure to beta-lactams, resulting in limited therapeutic options [2, 3].

Whole genome sequence-based bacterial phylogenetics demonstrated that *Enterobacter aerogenes* is more closely related to *Klebsiella pneumoniae* than other *Enterobacter* species. Therefore, the species formerly known as *E aerogenes* was reclassified as *Klebsiella aerogenes* [4]. However, the differences in clinical outcomes between infections caused by *K aerogenes* and other *Enterobacter* species are unclear.

Some studies have suggested a difference in clinical outcomes between *K aerogenes* bacteremia (KAB) and *Enterobacter cloacae* complex bacteremia (ECB). However, inconsistent results have been reported for the mortality of KAB and ECB in previous studies. In one study, there was no significant difference in overall in-hospital mortality between KAB and ECB; in contrast, bacteremia-related mortality was higher in KAB than ECB [5]. However, another study reported that there was no significant difference in both all-cause mortality and bacteremia-attributable mortality [6].

The purpose of this study was to compare the clinical outcomes of patients with KAB and ECB and to elucidate the risk factors associated with poor prognosis.

METHODS

Study Design and Patient Population

A retrospective, single-center, case-control study was conducted at the Samsung Medical Center, a tertiary-care hospital in the

Republic of Korea. Study subjects included hospitalized adults (aged ≥18 years) who had at least 1 positive blood culture for *K aerogenes* or *E cloacae* complex between January 2010 and June 2020. Only the first episode of bacteremia in each patient during the study period was included. Patients with polymicrobial bacteremia or whose cultures were drawn in an outpatient setting were excluded. Each case of KAB was matched with one age- and sex-matched case of ECB, with priority to the temporally closest episode of bacteremia.

Patient Consent Statement

This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. 2020-12-096-001) with waiver of consent.

Microbiological Methods

For species identification and antimicrobial susceptibility testing, a VITEK II automated system (bioMérieux, Marcy-l'Étoile, France) was used, utilizing a standard identification card and the modified broth microdilution method. Susceptibility was determined according to the recommendations of the Clinical and Laboratory Standards Institute guidelines [7]. Intermediate susceptibility was considered as resistance. Phenotypic or genetic tests for extended-spectrum beta-lactamase production were not performed according to the routine protocol of our institution.

Data Collection

We retrospectively collected the following data from medical records: age, sex, comorbid medical conditions, Charlson comorbidity index [8], source of infection, healthcare-associated acquisition, administration of immunosuppressive drugs, surgery within 3 months before the onset of bacteremia, and empirical and definitive antimicrobial regimens, duration of bacteremia, duration of susceptible antibiotic administration, susceptibility to antibiotics, and source control procedure. Other conditions when the blood culture was taken were also reviewed, including presentation with septic shock, Pitt bacteremia score [9], presence of an indwelling catheter, mechanical ventilation, tracheostomy, and hemodialysis. The primary outcome measure was 30-day all-cause mortality. The secondary outcome measure was the infection-attributable mortality at 30 days. In addition, the clinical response after 14 days was assessed.

Definition

Healthcare-associated infection was defined as bacteremia that occurred ≥48 hours after admission, ≤2 weeks after discharge, or that occurred in patients with prior healthcare contact [10]. Prior healthcare contact is defined as the presence of the following in the preceding 3 months: hospitalization for more than 2 days, residence in a nursing home or other long-term care facilities, receipt of home infusion therapy or home wound

care, and chronic dialysis [11]. Active cancer was defined as any type of cancer (except basal cell or squamous cell carcinoma of the skin, or primary brain tumor) that met at least 1 of the following: diagnosis within 6 months before the onset of bacteremia, receiving anticancer treatment at the time of bacteremia, any treatment for cancer during the 6 months before bacteremia, or recurrent locally advanced or metastatic cancer [12]. The administration of immunosuppressive drugs was defined as exposure to doses greater than the equivalent of 20 mg of prednisone per day for more than 14 days or antineoplastic chemotherapy within the previous month. Prior antibiotic exposure was defined as exposure to antibiotics within 90 days before the onset of bacteremia. Septic shock was defined as sepsis with systolic blood pressure <90 mmHg that did not respond to adequate fluid resuscitation and required the use of a vasopressor [13]. Patients without any identifiable source of infection were classified as having primary bacteremia. Catheter-related infections were defined using guidelines from the Infectious Disease Society of America (IDSA) [14].

Empirical antibiotic therapy was defined as initial antibiotic therapy started within 24 hours after blood culture. Definitive antibiotic therapy was defined as antibiotics administered within 24 hours after the result of blood culture, and antibiotic susceptibility tests have been reported. Antibiotic therapy was considered appropriate if the isolate was susceptible to any of the antibiotics administered at the optimal doses and route of administration. The duration of antibiotic therapy was defined as the period of administration of susceptible antibiotics from the date of initial positive blood culture. Source control was defined as an adequate removal or drainage of the focus of infection, which included removal of the indwelling catheter in catheter-related infection, insertion of a percutaneous urinary catheter, percutaneous or endoscopic biliary drainage, and percutaneous drainage/aspiration of abscess. Primary bacteremia or urinary tract infection that did not require such intervention was considered to have controlled the source.

Clinical response was classified as complete response (resolution of fever, bacteremia, and all other signs of infection), partial response (improvement of the above, but not complete resolution), and treatment failure (persistent fever or bacteremia, clinical deterioration, or death). Mortality attributable to bacteremia was defined as death with positive blood cultures for *K aerogenes* or *E cloacae* complex or persistent signs or symptoms of infection, but no other definitive causes of death. The duration of bacteremia was calculated only in cases in which follow-up blood cultures were taken within 72 hours after the initial positive culture, as the time interval from the initial positive culture to the first negative culture.

Statistical Analysis

Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Continuous variables were compared as

the mean ± standard deviation or median (interquartile range) using a 2-sample Student *t* test or the Mann-Whitney *U* test. The crude 30-day all-cause mortality of patients with KAB and ECB was compared using the Kaplan-Meier curve with a log-rank test.

A multiple logistic regression model was used to identify independent risk factors associated with mortality in patients with KAB and ECB in both the original and propensity score (PS)-matched cohorts. Variables with a *P* value less than .20, in the univariable analysis, were subjected to further selection using a backward logistic procedure.

Propensity score matching was conducted to further mitigate the differences in baseline characteristics between patients with KAB and those with ECB (Supplementary Table 1). Each PS was calculated using a multivariable logistic regression model in which the dependent variable was a binary indicator of KAB or ECB. Covariates with a *P* < .2, as determined by univariate analysis, were used to generate the PS, which included underlying renal disease, administration of immunosuppressive therapy or corticosteroids within 30 days, active cancer, intensive care unit care, healthcare-associated infection, primary bacteremia, and urinary tract infection. In addition, age and sex were included in the matching variables, considering the possibility of imbalance after PS matching. We performed 1:1 greedy matching with a calliper of 0.2. The standardized mean difference of covariates was tested to ensure balance after PS matching between the KAB and ECB groups (Supplementary Figure 1).

All tests were 2-tailed, and a *P* < .05 was considered statistically significant. Statistical analysis was performed using SPSS (version 25.0; IBM, Armonk, NY) and SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

Study Population
A total of 682 patients with monomicrobial KAB (n = 141) or ECB (n = 541) were identified during the study period; of these, 282 patients were included in the analysis after 1:1 age and sex matching. The PS-matched cohort included 194 patients.

The baseline characteristics of patients with KAB or ECB in the overall and PS-matched cohorts are summarized in Table 1. Active cancer was the most common underlying disease in both groups (KAB, 70.9% vs ECB, 78.0%). Patients with ECB were more likely to have underlying renal disease, administration of immunosuppressive therapy or corticosteroids. Healthcare-associated acquisition of bacteremia was more likely to occur in patients with ECB (KAB, 71.6% vs ECB, 83.0%; *P* = .023). In terms of the focus of infection, hepatobiliary infection was the most common in both groups. Primary bacteremia was more commonly associated with ECB. Urinary tract infection was more commonly associated with KAB. There were no significant differences in the appropriateness of empirical or definitive

antimicrobial treatment, septic shock, Pitt bacteremia score, or source control. Resistance rates to antibiotics were similar in the 2 groups, except for imipenem (KAB, 27.0% vs ECB, 12.1%; *P* = .002) and ciprofloxacin (KAB, 2.8% vs ECB, 9.2%; *P* = .021). During the entire study period, the rate of resistance to third-generation cephalosporins and imipenem was higher in the KAB group (see Supplementary Table 2). In terms of definitive antibiotics, third-generation cephalosporins and carbapenems were similarly used in both groups (see Supplementary Table 3).

In the PS-matched cohort, 97 pairs of patients with KAB and ECB were included. The standardized mean differences were less than 10% after matching (see Supplementary Figure 1). There were no significant differences between the KAB and ECB groups in baseline characteristics, except for resistance rate to cefepime, imipenem, and ciprofloxacin.

Clinical Outcomes and Risk Factor of 30-Day Mortality
Clinical outcomes of the KAB and ECB groups in both the overall and PS-matched cohorts are presented in Table 2. The 30-day all-cause mortality was significantly higher in the ECB group (24.1%) than in the KAB group (10.6%, *P* = .003) in the overall cohort. In the PS-matched cohort, the 30-day all-cause mortality was higher in the ECB group (24.7%) than in the KAB group (11.3%, *P* = .015). Kaplan-Meier survival analysis also revealed that the ECB group had higher mortality than the KAB group in both cohorts (Figure 1). In a multivariable model, ECB was an independent risk factor for mortality both in overall (adjusted odds ratio [aOR], 3.528; 95% confidence interval [CI], 1.614–7.714; *P* = .002) and PS-matched cohorts (aOR, 4.135; 95% CI, 1.619–10.558; *P* = .003) (Table 3). Infection-attributable mortality of ECB group was also marginally higher than those of KAB group in overall cohort (KAB, 4.3% vs ECB, 9.2%; *P* = .096). There were no significant differences in the length of hospital stay, length of stay in the intensive care unit, or treatment failure by day 14 between the overall and PS-matched cohorts. The duration of bacteremia was similar in the PS-matched cohort (median, 2 days; *P* = .661).

The baseline characteristics of patients according to survival at 30 days after positive blood culture are presented in Table 4. The inappropriateness of definitive antibiotics was marginally associated with 30-day mortality in the original cohort (*P* = .055), but no significant association was observed after matching (*P* = .637). The variables associated with 30-day all-cause mortality both before and after matching were ECB, presence of urinary catheter, stay in the intensive care unit at the onset of bacteremia, dialysis, healthcare-associated infection, septic shock at presentation, and a higher Pitt bacteremia score. Source control did not show a significant association with mortality in our study. In addition, there were no significant differences in prognosis between infections with easily controllable sources (such as catheter-related infection and urinary tract infection) and infections requiring invasive source control. In a

Table 1. Baseline Characteristics of Patients With *Klebsiella aerogenes* Bacteremia and Patients With *Enterobacter cloacae* Complex Bacteremia

Characteristics	Overall			PS-Matched		
	K aerogenes (n = 141)	E cloacae complex (n = 141)	P	K aerogenes (n = 97)	E cloacae complex (n = 97)	P
Age, years (mean ± SD)[a]	60.1 ± 14.4	60.1 ± 14.4	.994	60.0 ± 14.2	59.6 ± 14.1	.801
Male sex[a]	86 (61.0)	86 (61.0)	>.999	58 (59.8)	58 (59.8)	>.999
Underlying Disease						
Cardiovascular disease	17 (12.1)	20 (14.2)	.597	11 (11.3)	12 (12.37)	.835
Neurologic disease	22 (15.6)	16 (11.3)	.295	14 (14.4)	11 (11.3)	.513
Pulmonary disease	4 (2.8)	5 (3.5)	>.999	2 (2.1)	2 (2.1)	>.999
Liver disease	42 (29.8)	50 (35.5)	.310	27 (27.8)	35 (36.1)	.217
Renal disease[a]	29 (20.6)	46 (32.6)	.022	26 (26.8)	26 (26.8)	>.999
Diabetes mellitus	34 (24.1)	35 (24.8)	.890	23 (23.7)	25 (25.8)	.739
Active cancer[a]	100 (70.9)	110 (78.0)	.172	76 (78.4)	79 (81.4)	.591
Transplantation[b]	14 (9.9)	21 (14.9)	.206	12 (12.4)	13 (13.4)	.827
Charlson comorbidity index (median, IQR)	6 (4–9)	7 (4–9)	.424	6 (4–9)	7 (5–9)	.617
Comorbid Condition						
Surgery within 30 days	30 (21.3)	23 (16.3)	.286	19 (19.6)	19 (19.6)	>.999
Receipt of immunosuppressive therapy or corticosteroid within 30 days[a]	44 (31.2)	72 (51.1)	.001	38 (39.2)	42 (43.3)	.450
Central venous catheter	40 (28.4)	48 (34.0)	.304	30 (30.9)	28 (28.9)	.754
Biliary drainage catheter	43 (30.5)	35 (24.8)	.287	29 (29.9)	27 (27.8)	.751
Urinary catheter	30 (21.3)	177 (25.0)	.452	20 (20.6)	21 (21.6)	.860
ICU care[a]	19 (13.5)	12 (8.5)	.183	12 (12.4)	11 (11.3)	.796
Mechanical ventilation	11 (7.8)	11 (7.8)	>.999	7 (72)	10 (10.3)	.405
Tracheostomy	7 (5.0)	5 (3.5)	.555	5 (5.2)	4 (4.1)	.733
Dialysis	7 (5.0)	11 (7.8)	.330	6 (6.2)	8 (8.3)	.564
Healthcare-associated acquisition[a]	101 (71.6)	117 (83.0)	.023	76 (78.4)	76 (78.4)	>.999
Septic shock at presentation	36 (25.5)	38 (27.0)	.787	25 (25.8)	29 (30.0)	.505
Pitt bacteremia score (median, IQR)	1 (0–3)	1 (0–3)	.965	1 (0–3)	1 (0–3)	.530
Focus of infection						
Primary bacteremia[a]	12 (8.5)	31 (22.0)	.002	12 (12.4)	12 (12.4)	>.999
Catheter related	21 (14.9)	17 (12.1)	.485	17 (175)	10 (10.3)	.127
Respiratory tract	7 (5.0)	12 (8.5)	.235	4 (4.1)	8 (8.3)	.206
Hepatobiliary	51 (36.2)	43 (30.5)	.312	32 (33.0)	35 (36.1)	.612
Intra-abdominal	20 (14.2)	19 (13.5)	.863	15 (15.5)	15 (15.5)	>.999
Urinary tract[a]	26 (18.4)	13 (9.2)	.025	15 (15.5)	13 (13.4)	.667
Others	5 (3.5)	5 (3.5)	>.999	3 (3.1)	3 (3.1)	>.999
Appropriateness of empirical antibiotics	107 (75.9)	112 (79.4)	.475	78 (80.4)	74 (76.3)	.480
Appropriateness of definitive antibiotics	134 (95.0)	138 (97.9)	0.198	92 (94.9)	94 (96.9)	.414
Definitive Antibiotic Regimen						
3rd-generation cephalosporin	16 (11.3)	9 (6.4)	.143	10 (10.3)	8 (8.2)	.621
4th-generation cephalosporin	22 (15.6)	32 (22.7)	.130	16 (16.5)	18 (18.6)	.706
Piperacillin/tazobactam	32 (22.7)	34 (24.1)	.778	23 (23.7)	23 (23.7)	>.999
Quinolone	32 (22.7)	39 (27.7)	.337	20 (20.6)	29 (29.9)	.137

Table 1. Continued

Characteristics	Overall			PS-Matched		
	K aerogenes (n = 141)	E cloacae complex (n = 141)	P	K aerogenes (n = 97)	E cloacae complex (n = 97)	P
Carbapenem	41 (29.1)	37 (26.2)	.594	31 (32.0)	25 (25.8)	.342
Duration of susceptible antibiotics, days (median, IQR)	14 (10–17)	14 (10–17)	.939	14 (10–18)	14 (11–18)	.398
Source control	101 (71.6)	92 (65.2)	.249	57 (58.8)	58 (59.8)	.884
Resistance Rate						
3rd-generation cephalosporin	46 (32.6)	37 (26.2)	.240	31 (32.0)	26 (26.8)	.431
4th-generation cephalosporin	6 (4.3)	14 (9.9)	.063	3 (3.1)	11 (11.3)	.026
Piperacillin/tazobactam[c]	43 (30.5)	29 (20.6)	.075	29 (29.9)	22 (22.9)	.271
Imipenem	38 (27.0)	17 (12.1)	.002	29 (29.9)	12 (12.4)	.003
Aztreonam	40 (28.4)	33 (23.4)	.341	27 (27.8)	25 (25.8)	.746
Ciprofloxacin[d]	4 (2.8)	13 (9.2)	.021	2 (2.3)	10 (10.9)	.022

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PS, propensity score; SD, standard deviation.

[a]Variables used for propensity score matching.

[b]Included both bone marrow transplantation and solid organ transplantation.

[c]One isolate was not tested for susceptibility to piperacillin/tazobactam.

[d]Twenty-seven isolates and 15 isolates, respectively, were not tested for susceptibility to ciprofloxacin among overall (n = 205) and PS-matched (n = 179) cohorts.

Table 2. Clinical Outcomes of Patients With *Klebsiella aerogenes* Bacteremia and Those With *Enterobacter cloacae* Complex Bacteremia in Overall and PS-Matched Cohorts

Outcome	Overall				PS-Matched			
	K aerogenes (n = 141)	E cloacae Complex (n = 141)	OR (95% CI)	P	K aerogenes (n = 97)	E cloacae Complex (n = 97)	OR (95% CI)	P
30-day all-cause mortality	15 (10.6)	34 (24.1)	2.669 (1.380–5.164)	.003	11 (11.3)	24 (24.7)	2.570 (1.180–5.601)	.015
Infection attributable mortality	6 (4.3)	13 (9.2)	2.285 (0.843–6.194)	.096	4 (4.1)	9 (9.3)	2.378 (0.707–8.001)	.151
Treatment failure at 14 day	16 (11.3)	25 (17.7)	1.684 (0.856–3.312)	.128	11 (11.3)	18 (18.6)	1.781 (0.793–4.004)	.159
Length of stay[a], median, (range), day	12 (1–1380)	12 (1–427)		.788	12.5 (1–225)	11.0 (1–427)		.751
ICU length of stay, median, (range), day	3.5 (0–1380)	3.0 (1–45)		.817	3.0 (0–540)	3.0 (0–45)		.871
Duration of bacteremia[b], median, (range), day	2 (1–9)	2 (1–5)		.003	2 (1–4)	2 (1–5)		.661

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PS, propensity score.

[a]One patient remained admitted in the hospital until the end of this study.

[b]Sixty and 41 cases for whom follow-up blood cultures were not performed within 72 hours after initial blood culture were excluded among overall (n = 222) and PS-matched (n = 153) cohorts.
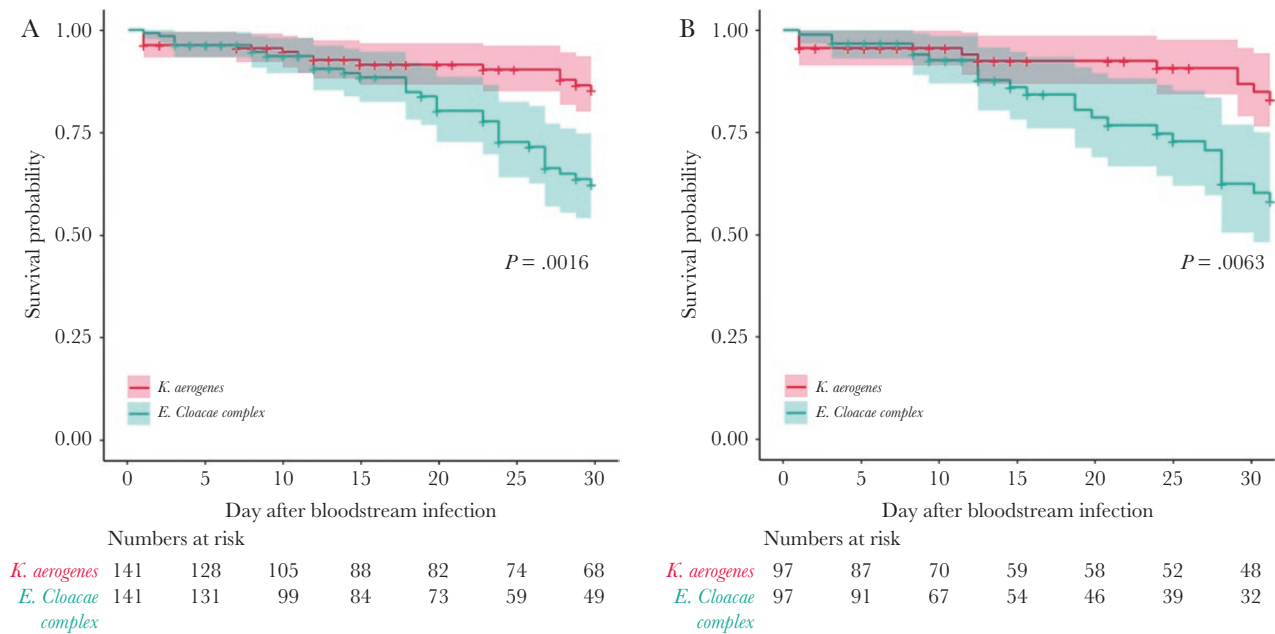
Figure 1. A survival curve of the patients with *Klebsiella aerogenes* and *Enterobacter cloacae* complex bacteremia. (A) Overall cohort; (B) propensity score-matched cohort.

multivariable model, stay in the intensive care unit at the onset of bacteremia and higher Pitt bacteremia scores were also independent risk factors for 30-day mortality in both the overall and PS-matched cohorts.

The causes of death are summarized in Supplementary Table 4. Infection-attributable mortality was higher in the ECB group, although the difference was not significant. In a multivariable model of the overall cohort, ECB was associated with 30-day infection-attributable mortality (aOR, 3.562; 95% CI, 1.007–12.600; *P* = .049). However, after PS matching, ECB was not associated with the secondary outcomes. Administration of immunosuppressive therapy or corticosteroids and the inappropriateness of definitive antibiotics were independent risk factors for 30-day infection-attributable mortality (Supplementary Table 5).

DISCUSSION

We found that the 30-day all-cause mortality in the ECB group was higher than that in the KAB group. The infection-attributable mortality of the ECB group tended to be higher than that of the KAB group, although the difference was not statistically significant.

These findings are different from those of previous studies on *Enterobacter* species bloodstream infections. A previous study reported that the 28-day mortality was higher in KAB than in ECB (KAB, 14.9% vs ECB, 8.1%) [5]. Another previous study reported that in-hospital mortality was 28% in the KAB group and 21% in the ECB group [6]. In our study, the 30-day all-cause mortality was 14.6% in the KAB group and 24.3% in the ECB group.

Several factors may have influenced these differences. First, there were differences in the severity of infection and the proportion of appropriate antibiotic therapy by species in different studies. Song et al [5] reported that KAB commonly presented as septic shock and was associated with a higher rate of bacteremia-related mortality than ECB. However, these investigators did not compare the appropriateness of empirical antibiotic therapy. Appropriate empirical antibiotic therapy is one of the most critical factors in the outcome of bloodstream infection; therefore, unobserved differences in the appropriateness of empirical antibiotic therapy might have influenced the results of the study. In this study, a lower proportion of KAB patients received appropriate overall antimicrobial therapy (ECB, 92.4% [159 of 172] vs KAB, 85.1% [57 of 67], *P* = .083). The authors showed that patients who died within 24 hours after the onset of bacteremia did not receive adequate antibiotics and explained that most KAB patients with fatal outcomes (died in the early phase after bacteremia) were classified as being given inappropriate antibiotics. In our study, the proportion of septic shock at the time of bacteremia and Pitt bacteremia score were similar between the KAB and ECB groups, and the ECB group had a worse outcome. This was different from previous studies that reported that the proportion of septic shock was higher in the KAB group than in the ECB group [5, 6]. This difference suggests the possibility that the severity of the infection itself, rather than species, influenced the outcome.

Second, the difference in baseline characteristics between the study cohorts may have resulted in differences in mortality. For example, in a previous study that reported that KAB was associated with poor clinical outcomes, the median age and the

Table 3. Patient Characteristics by 30-Day in-Hospital Mortality

Characteristic	Overall				PS-Matched			
	Survival (n = 233)	Death (n = 49)	OR (95% CI)	P	Survival (n = 159)	Death (n = 35)	OR (95% CI)	P
Enterobacter cloacae complex	107 (45.9)	34 (69.4)	2.669 (1.380–5.164)	.003	73 (45.9)	24 (68.6)	2.570 (1.180–5.601)	.015
Age (mean ± SD)	60.2 ± 14.1	59.2 ± 15.9		.630	60.1 ± 13.4	58.5 ± 17.1		.592
Male	141 (60.5)	31 (63.3)	0.890 (0.470–1.683)	.720	96 (60.4)	20 (57.1)	1.143 (0.545–2.398)	.724
Underlying disease								
Cardiovascular disease	26 (11.2)	11 (22.4)	2.305 (1.051–5.054)	.033	16 (10.1)	7 (20.0)	2.234 (0.842–5.931)	.107
Neurologic disease	31 (13.3)	7 (14.3)	1.086 (0.448–2.631)	.855	20 (12.6)	5 (14.3)	1.158 (0.403–3.331)	.785
Pulmonary disease	8 (3.4)	1 (2.0)	0.586 (0.072–4.795)	>.999	4 (2.5)	0 (0.0)	N/A	N/A
Liver disease	74 (31.8)	18 (36.7)	1.248 (0.656–2.373)	.500	50 (31.4)	12 (34.3)	1.137 (0.524–2.267)	.745
Renal disease	53 (22.7)	22 (44.9)	2.767 (1.458–5.253)	.001	39 (24.5)	13 (37.1)	1.818 (0.838–3.947)	.131
Diabetes mellitus	58 (24.9)	11 (22.4)	0.873 (0.419–1.819)	.718	41 (25.8)	7 (20.0)	0.720 (0.292–1.772)	.473
Active cancer	178 (76.4)	42 (85.7)	1.854 (0.788–4.361)	.152	125 (78.6)	30 (85.7)	1.632 (0.589–4.525)	.343
Transplantation[a]	33 (14.2)	2 (4.1)	0.258 (0.060–1.113)	.052	23 (14.5)	2 (5.7)	0.358 (0.080–1.597)	.178
Charlson comorbidity index (median, IQR)	6 (4–9)	8 (6–10)		.005	6 (4–9)	8 (6–10)		.082
Comorbid Condition								
Surgery within 30 days	44 (18.9)	9 (18.4)	0.966 (0.437–2.138)	.933	32 (20.1)	6 (17.1)	0.821 (0.314–2.146)	.332
Receipt of immunosuppressive therapy or corticosteroid within 30 days	93 (39.9)	23 (46.9)	1.332 (0.717–2.474)	.364	63 (39.6)	17 (48.6)	1.439 (0.690–3.002)	.332
Central venous catheter	65 (27.9)	23 (46.9)	2.286 (1.218–4.292)	.009	43 (27.0)	15 (42.9)	2.023 (0.951–4.306)	.064
Biliary drainage catheter	65 (27.9)	13 (26.5)	0.933 (0.465–1.872)	.846	47 (29.6)	9 (25.7)	0.825 (0.359–1.894)	.649
Urinary catheter	37 (15.6)	18 (36.7)	3.076 (1.560–6.064)	.001	26 (16.4)	15 (42.9)	3.837 (1.740–8.457)	.001
ICU care	18 (7.7)	13 (26.5)	4.313 (1.946–9.560)	<.001	13 (8.2)	10 (28.6)	4.492 (1.778–11.353)	.002
Mechanical ventilation	14 (6.0)	8 (16.3)	3.052 (1.204–7.740)	.014	11 (6.9)	6 (17.1)	2.783 (0.954–8.127)	.061
Tracheostomy	10 (4.3)	2 (4.1)	0.949 (0.201–4.473)	.947	7 (4.4)	2 (5.7)	1.316 (0.262–6.623)	.666
Dialysis	11 (4.7)	7 (14.3)	3.364 (1.233–9.174)	.013	8 (5.0)	6 (17.1)	3.905 (1.261–12.097)	.018
Healthcare-associated infection	171 (73.4)	47 (95.9)	8.520 (2.009–36.128)	.001	120 (75.5)	32 (91.4)	3.467 (1.006–11.948)	.049
Septic shock at presentation	52 (22.3)	22 (44.9)	2.836 (1.493–5.389)	.001	34 (21.4)	20 (57.1)	4.902 (2.271–10.580)	<.001
Pitt bacteremia score (median, IQR)	1 (0–3)	3 (1–4)		<.001	1 (0–2)	3 (1–5)		<.001
Focus of Infection								
Primary bacteremia	32 (13.7)	11 (22.4)	1.818 (0.844–3.918)	.123	17 (10.7)	7 (20.0)	2.088 (0.792–5.503)	.136
Catheter related	32 (13.7)	6 (12.2)	0.876 (0.345–2.226)	.781	23 (14.5)	4 (11.4)	0.763 (0.246–2.365)	.639
Respiratory tract	11 (4.7)	8 (16.3)	3.983 (1.493–10.385)	.003	9 (5.7)	3 (8.6)	1.562 (0.401–6.095)	.521
Hepatobiliary	83 (35.6)	11 (22.4)	0.523 (0.254–1.078)	.075	59 (37.1)	8 (22.9)	0.502 (0.214–1.177)	.113
Intraabdominal	31 (13.3)	8 (16.3)	1.271 (0.545–2.965)	.578	22 (13.8)	8 (22.9)	1.845 (0.744–4.576)	.186
Urinary tract	35 (15.0)	4 (8.2)	0.503 (0.170–1.487)	.206	24 (15.1)	4 (11.4)	0.726 (0.235–2.243)	.578
Others	9 (3.9)	1 (2.0)	0.519 (0.064–4.190)	.531	5 (3.1)	1 (2.9)	0.906 (0.103–8.005)	>.999
Inappropriateness of empirical antibiotics	51 (21.9)	12 (24.5)	1.157 (0.563–2.381)	.691	35 (22.0)	7 (20.0)	0.886 (0.357–2.199)	.794
Inappropriateness of definitive antibiotics	6 (2.6)	4 (8.2)	3.363 (0.912–12.401)	.055	6 (3.8)	2 (5.7)	1.545 (0.299–7.998)	.637
Definitive antibiotic regimen								
3rd-generation cephalosporin	22 (9.4)	3 (6.1)	0.625 (0.180–2.178)	.588	16 (10.1)	2 (5.7)	0.542 (0.119–2.471)	.537
4th-generation cephalosporin	47 (20.2)	7 (14.3)	0.660 (0.279–1.561)	.341	29 (18.2)	5 (14.3)	0.747 (0.267–2.090)	.578
Piperacillin/tazobactam	51 (21.9)	15 (30.6)	1.574 (0.796–3.115)	.190	38 (23.9)	8 (22.9)	0.943 (0.396–2.250)	.896
Quinolone	59 (25.3)	12 (24.5)	0.956 (0.468–1.955)	.903	41 (25.8)	8 (22.9)	0.853 (0.359–2.026)	.718
Carbapenem	61 (26.2)	17 (34.7)	1.498 (0.777–2.889)	.226	41 (25.8)	15 (42.9)	2.159 (1.012–4.606)	.044
Duration of susceptible antibiotics, days (median, IQR)	14 (11–18)	11 (5–16)		.464	14 (11–19)	12 (6–16)		.020

Table 3. Continued

Characteristic	Overall				PS-Matched			
	Survival (n = 233)	Death (n = 49)	OR (95% CI)	P	Survival (n = 159)	Death (n =35)	OR (95% CI)	P
Source control	165 (70.8)	28 (57.1)	0.549 (0.292–1.034)	.061	95 (59.7)	20 (57.1)	0.898 (0.428–1.884)	.776
Resistance rate								
3rd-generation cephalosporin	69 (29.6)	14 (28.6)	0.951 (0.481–1.878)	.884	47 (29.6)	10 (28.6)	0.953 (0.425–2.140)	.907
4th-generation cephalosporin	15 (6.4)	5 (10.2)	1.652 (0.571–4.780)	.360	10 (6.3)	4 (11.4)	1.923 (0.566–6.528)	.286
Piperacillin/tazobactam[b]	60 (25.8)	12 (24.5)	0.961 (0.470–1.967)	.232	42 (26.4)	9 (26.5)	1.003 (0.433–2.322)	.995
Imipenem	47 (20.2)	8 (16.3)	0.772 (0.339–1.757)	.537	36 (22.6)	5 (14.3)	0.569 (0.206–1.574)	.273
Aztreonam	59 (25.3)	14 (28.6)	1.180 (0.594–2.344)	.637	42 (26.4)	10 (28.6)	1.114 (0.494–2.514)	.794
Ciprofloxacin[c]	11 (4.7)	6 (12.2)	2.783 (0.972–7.972)	.130	7 (4.8)	5 (15.2)	3.546 (1.050–11.979)	.047

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; N/A, not applicable; OR, odds ratio; PS, propensity score; SD, standard deviation.

[a]Included both bone marrow transplantation and solid organ transplantation.

[b]One isolate was not tested for susceptibility to piperacillin/tazobactam.

[c]Twenty-seven isolates and 15 isolates, respectively, were not tested for susceptibility to ciprofloxacin among overall (n = 205) and PS-matched (n = 179) cohorts.

proportion of healthcare-associated infections were higher in the KAB group [6]. Although the difference was not statistically significant, the study might have been underpowered to detect such differences. In addition, more cases with ECB were caused by catheter-related infection and urinary tract infection, which are known to be associated with better outcomes [15, 16]. We performed PS matching to mitigate baseline imbalances in characteristics that are likely to affect the outcome, and no variables showed significant differences between the KAB and ECB groups after matching.

The higher mortality in the ECB in this study may have been attributed to the virulent potential of *E cloacae* complex. *Enterobacter* species harbor a variety of virulence mechanisms, including heavy metal resistance, efflux pumps that result in a wide array of antimicrobial resistance, and additional siderophore assembly kits to gain a fitness advantage that facilitates their survival in diverse environments [17, 18]. Flynn et al [19] prospectively studied *Enterobacter* colonization in cardiac surgery patients receiving cefazolin prophylaxis. *Enterobacter cloacae* was isolated 4 times more frequently than *K aerogenes*, and it led to invasive infections more often than *K aerogenes*. This result suggests that the virulence factor, such as fitness, of *E cloacae* increases the infection rate and results in a poor prognosis. According to studies on virulence gene detection in *Enterobacter* species in Italy, Iraq, and Egypt, several virulence genes encoding siderophores and adhesins were detected in *E cloacae* isolates [20–22]. These findings are different from those of a previous study in Brazil, which reported that virulence genes were detected only in *K aerogenes* isolates, whereas no *E cloacae* isolate harbored virulence genes [23]. Considering the characteristics of *Enterobacter* species that can acquire plasmid-mediated antibiotic resistance genes, the epidemiology of virulent genes may vary depending on regional characteristics, so the detection rate of virulence genes may differ between countries. Thus, it is necessary to study the molecular epidemiology of virulence genes of *E cloacae* complex isolates and *K aerogenes* isolates from various countries.

In our study, the use of antibiotics with in vitro susceptibility was defined as appropriate even when third-generation cephalosporins were used. There is a controversy about the optimal antibiotic therapy for infections caused by AmpC-producing organisms. The emergence of resistance against broad-spectrum cephalosporins during treatment have been reported, but whether the treatment with a third-generation cephalosporin is associated with poor outcome remains controversial. Various studies reported comparable outcomes between broad-spectrum cephalosporins and carbapenems [24–26]. We analyzed the clinical outcome by specific antibiotic agents using our dataset. The 30-day all-cause mortality in the overall cohort was 12.0% (3 of 25, $P = .588$) in the patients who were treated with third-generation cephalosporin and 21.8% (17 of 78, $P = .226$) in those with carbapenem. In the PS-matched cohort, the use of carbapenem as a definitive antibiotic was an independent risk

Table 4. Multivariable Logistic Regression Analysis for the Risk Factors Associated With 30-Day All-Cause Mortality

Risk Factor	Overall		PS-Matched	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Enterobacter cloacae complex	3.528 (1.614–7.714)	.002	4.135 (1.619–10.558)	.003
Underlying renal disease	2.360 (1.151–4.839)	.019		
Transplantation[a]	0.167 (0.034–0.813)	.027	0.167 (0.028–0.984)	.048
ICU care	3.070 (1.170–8.052)	.023	8.504 (1.182–61.200)	.034
Pitt bacteremia score	1.364 (1.142–1.629)	.001	1.453 (1.170–1.803)	.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PS, propensity score.
[a]Included both bone marrow transplantation and solid organ transplantation.

factor associated with mortality. Surely this difference is likely to be due to the severity of infection rather than the weaker efficacy of carbapenem, but our results do not show that the use of third-generation cephalosporin is associated with poor outcomes. Furthermore, the proportion of patients who were treated with third-generation cephalosporins was low (8.9% in the overall cohort and 9.2% in the PS-matched cohort).

Our study has several limitations. First, since our study was conducted at a single tertiary care center, the results may not be generalizable. Second, the study was performed retrospectively. Although we tried to control for confounders using PS matching and multiple logistic regression, the possibility of bias by unobserved variables cannot be excluded. In addition, among 682 patients with KAB or ECB who were initially screened, only 282 were included after age and sex matching. There thus remains a possibility that an unobserved bias was introduced during matching. However, we only used age, sex, and temporal proximity to cases with KAB for initial matching. Consequently, there was no significant difference in the 30-day all-cause mortality between the patients with ECB who were initially identified (112 of 541, 20.7%) and those who were included in the analysis (34 of 141, 24.1%; *P* = .381), suggesting that the risk of selection bias is low. Third, only bloodstream infections were included in our study. Therefore, the results may not be applicable to localized infections without bacteremia.

CONCLUSIONS

In conclusion, ECB was independently associated with higher 30-day all-cause mortality than KAB. Further studies are warranted to clarify the virulence mechanisms of *E cloacae* complex.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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