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The effect of colistin resistance and other predictors on fatality among patients with bloodstream infections due to *Klebsiella pneumoniae* in an OXA-48 dominant region

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ABSTRACT

Background: The aim of this study was to determine the effect of colistin resistance and other predictors on fatality among patients with *Klebsiella pneumoniae* bloodstream infections (Kp-BSI) and to describe the effect of amikacin and tigecycline on the outcome in an OXA-48 dominant country.
Method: This was a retrospective study performed among patients >16 years of age in a tertiary hospital with 465 beds. All cases had ≥1 positive blood culture for *K. pneumoniae* 48 h after admission.
Results: Among 210 patients with Kp-BSI, the 30-day mortality rate after isolation of the microorganism was 58%. The rate of carbapenem resistance was higher (64% vs. 38%, $p < 0.001$) and the colistin minimum inhibitory concentration (MIC) was elevated (7 vs. 4, $p < 0.029$) among the patients who died. Among the colistin-resistant *K. pneumoniae*, the rates of OXA-48, ST101, and NDM-1 were 78%, 67%, and 35%, respectively. Amikacin was added to the treatment of 13 patients with carbapenem and colistin-resistant Kp-BSI and 77% survived ($p < 0.001$). Tigecycline was added to the treatment of 24 patients with carbapenem and colistin-resistant Kp-BSI, and the 30-day mortality rate was 71% ($p = 0.576$). In the multivariate analysis, carbapenem resistance (odds ratio (OR) 5.2, 95% confidence interval (CI) 2.47–10.9, $p < 0.001$) and increasing APACHE II score (OR 1.19, 95% CI 1.12–1.26, $p < 0.001$) were significantly associated with 30-day mortality. The addition of amikacin to the treatment regimen (OR 0.05, 95% CI 0.01–0.23, $p < 0.001$) was significantly beneficial.
Conclusions: Carbapenem resistance, increasing MIC of colistin, and the lungs as the source of the infection were significantly associated with 30-day mortality. The empirical use of combined active aminoglycosides was found to be beneficial in the treatment of colistin-resistant *K. pneumoniae* infections.
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Introduction

Multidrug-resistant gram-negative bacteria remain the leading cause of infections worldwide, with a high fatality rate and with limited treatment options (Aydin et al., 2018; Isler et al., 2019). Colistin is one of the drugs of choice among the limited options for carbapenemase-producing *Enterobacteriaceae*. However, in recent years, an increasing rate of resistance to colistin among *Enterobacteriaceae* from human and animal sources has been reported, and the highest rate has been detected among *Klebsiella spp* in Asian and Southern European countries (Giamarellou, 2016). At the end of 2015, a transferable gene (*mcr-1*) encoded on a plasmid conferring resistance to colistin was discovered in gram-negative bacteria in China (Liu et al., 2016), following which a substantial number of publications appeared reporting a similar colistin resistance profile and gene in Europe, Africa, and Asia (Schwarz and Johnson, 2016; Skov and Monnet, 2016).

Although the increasing colistin resistance appears to be a clinical problem, especially in the countries of Southern Europe (Giamarellou, 2016), there is controversy in the literature

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regarding its clinical impact on fatality (Olaitan et al., 2016). This study was performed to describe the effect of colistin resistance on fatality among patients with *Klebsiella pneumoniae* blood stream infections (Kp-BSI). In addition, the effect of combination with amikacin and tigecycline was examined.

Methods

Study design

This was a retrospective study performed among adult patients older than 16 years of age in a tertiary hospital with 465 beds, covering the period January 1, 2011 to September 1, 2017. All patients had ≥1 positive blood culture for *K. pneumoniae* 48 h after admission. Patients with community-acquired infections, those who had been transferred and had started therapy before admission, and all patients <16 years of age were excluded. The following information was collected using a structured electronic form: demographic data, source of bacteremia, causative microorganisms, antimicrobial resistance, empiric antibiotic therapy, length of stay in the intensive care unit (ICU), operations performed within 1 month, time to the first positive blood culture after admission, mean C-reactive protein (CRP) level, procalcitonin level, leukocyte count, mean time to appropriate antibiotic initiation, death rate, and the APACHE II score (Acute Physiology and Chronic Health Evaluation).

Whether the bacteremia was primary or secondary (urinary, respiratory, catheter-related, abdominal, skin and soft tissue infections) was determined in accordance with definitions of the US Centers for Disease Control and Prevention (CDC). Appropriate empiric antibiotic therapy was defined as the administration of an empiric agent within 48 h, which was active in vitro, based on susceptibility test results.

Microbiological studies

Only the clinically significant (defined according to the CDC criteria) blood culture isolates were included in the study. The identification of organisms was conducted using the Vitek 2 automated system (bioMérieux). Antimicrobials in the analysis included carbapenems (ertapenem, meropenem, and imipenem), third- and fourth-generation cephalosporins (ceftriaxone, ceftazidime, and cefepime), fluoroquinolones (ciprofloxacin), aminoglycosides (amikacin and gentamicin), and polymyxin (colistin). Antibiotic susceptibility was determined by disk diffusion method or minimum inhibitory concentration (MIC) tests according to the Clinical and Laboratory Standards Institute (CLSI) guidelines; resistance was defined according to the CLSI criteria (2010). Carbapenem resistance was defined as resistance to any carbapenem. Polymicrobial infection was defined as the isolation of any bacteria other than Klebsiella, 7 days before and 7 days after the isolation of *K. pneumoniae*.

Colistin-resistant *K. pneumoniae* isolates were selected for molecular studies. The carbapenemase type was detected by multiplex PCR, as described previously (Poirel et al., 2011). Multilocus sequence typing was performed according to the protocol published on the Pasteur Institute website by comparing seven housekeeping genes (*pho*E, *gap*A, *rpo*B, *ton*B, *inf*,*mdh*, and *pgi*) (http://bigsdb.pasteur.fr/klebsiella/klebsiella.html). The sequence types (ST) were determined using BioNumerics version 7.6 software (Applied Maths).

Statistical analysis

The Student *t*-test was used for the analysis of continuous variables and the Chi-square test for categorical variables. For non-parametric comparisons, the two-sample Wilcoxon rank sum test (Mann–Whitney test) was used. In the multivariate analysis, logistic analysis with backward selection was performed for the predictors of the 30-day mortality rates. Variables included in the model were carbapenem resistance, colistin resistance, APACHE score, adding amikacin to the regimen, and the lungs as the source of infection. Stata version 11 (StataCorp., College Station, TX, USA) was used for the analysis, and statistical significance was set at $p < 0.05$. The Institutional Review Board of Kartal Koşuyolu Training and Research Hospital approved the study.

Results

The study included 210 patients with Kp-BSI; 182 patients were in the ICU and 28 patients were on the wards. Comorbidities are presented in Table 1. The overall mortality rate was 71%, and the 30-day mortality rate after isolation of the microorganism was 58% (Table 1). The number of patients with polymicrobial isolation was 54. In the univariate analysis, a higher mean APACHE score (23 vs. 15, $p < 0.001$), higher mean colistin MIC (7 vs. 4, $p < 0.029$), higher

Table 1
Predictors of 30-day mortality among patients with *Klebsiella pneumoniae* bloodstream infections.

	Survived ($n = 89$), n (%)	30-day mortality ($n = 121$), n (%)	p-Value
Female sex	34 (38)	60 (50)	0.101
Mean age (SD) (min–max)	58 (SD 14) (16–86)	61 (SD 15) (16–90)	0.117
Comorbidities			
Chronic renal failure	7 (8)	15 (12)	0.289
DM	32 (27)	21 (24)	0.614
COPD	7 (8)	12 (10)	0.608
Transplant	2 (2)	4 (3)	0.649
Malignancy	6 (8)	12 (10)	0.417
Mean APACHE score	15 (SD 5.9)	23 (SD 7.5)	<0.001
Mean CRP (normal: <0.3 mg/dL)	12 (SD 11)	14 (SD 9)	0.048
Mean procalcitonin (ng/mL)	14 (SD 26)	21 (SD 29)	0.16
Median leukocyte count (14.227×10^9/L)	14 227	18 369	0.278
Median platelet count (227.52×10^9/L)	227 520	150 562	<0.001
Carbapenem resistance	34 (38)	77 (64)	<0.001
Colistin resistance	20 (23)	40 (33)	0.103
Mean colistin MIC	4	7	0.029
Polymicrobial infection	18 (21)	36 (30)	0.13
Lungs as the source of infection	13 (15)	33 (31)	0.005

SD, standard deviation; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; MIC, minimum inhibitory concentratio.

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rate of carbapenem resistance (64% vs. 38%, $p < 0.001$), and higher percentage of patients with the lungs as the source of infection were found among those who died compared to those who survived (Table 1). Among the colistin-resistant *K. pneumoniae* strains, OXA-48 was detected in 78% and NDM in 35% of the strains. The most common ST was ST101 in 67% of colistin-resistant *K. pneumoniae*, followed by ST295 (13%), ST147 (8%), and ST395 (8%).

Patients who received empiric colistin therapy had a higher colistin resistance than those who did not (71% vs. 23%, $p < 0.001$). In blood cultures, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas spp*, and *Acinetobacter spp* were isolated along with *Klebsiella pneumoniae*, and no association of their presence with 30-day mortality was observed ($p > 0.05$). The rate of appropriate empiric antibiotic initiation was lower in the patients who died than in the patients who survived (31% vs. 45%, $p = 0.034$). Amikacin was added to the treatment of 13 patients with carbapenem and colistin-resistant Kp-BSI and 77% survived ($p < 0.001$). Tigecycline was added to the treatment of 24 patients with carbapenem and colistin-resistant Kp-BSI, and the 30-day mortality rate was 71% ($p = 0.576$). Amikacin was started empirically for five patients and according to culture results within 7 days in eight patients. Tigecycline was started empirically for nine patients and according to culture results for the others, within 3 days after culture.

The multivariate analysis revealed that carbapenem resistance (odds ratio (OR) 5.2, 95% confidence interval (CI) 2.47–10.9, $p < 0.001$) and increasing APACHE score (OR 1.19, 95% CI 1.12–1.26, $p < 0.001$) increased the 30-day mortality rate significantly, whereas the addition of amikacin to the treatment regimen (OR 0.05, 95% CI 0.01–0.23, $p < 0.001$) decreased the 30-day mortality rate significantly.

Discussion

Colistin resistance is an emerging problem, especially in the countries of Southern Europe. Italy (36%) (Capone et al., 2013) and Greece (14%) (Mavroidi et al., 2016) have the highest rates of colistin resistance in *K. pneumoniae*. In Turkey, the prevalence of colistin resistance increased from 6% in 2013 to 16% in 2014–2015 among Kp-BSI (Ergonul et al., 2016). In this study, the rate of colistin resistance was 29% among Kp-BSI overall and 53% among the strains with carbapenem resistance. Previous studies performed in the USA, Italy, and Greece have reported rates of colistin resistance ranging between 10% and 54.7% among the carbapenem-resistant strains (Capone et al., 2013; Daikos et al., 2014; Gomez-Simmonds et al., 2016; Nguyen et al., 2010; Papadimitriou-Olivgeris et al., 2017a; Papadimitriou-Olivgeris et al., 2014; Rojas et al., 2017; Tumbarello et al., 2015; Tumbarello et al., 2012; Vardakas et al., 2015; Zarkotou et al., 2011).

The overall fatality rate was 71%, and the 30-day mortality rate after isolation of the microorganism was 58% (Table 1). The 30-day mortality rate was calculated to be 69% among those with carbapenem-resistant Kp-BSI; however, previous studies have reported 30-day mortality rates among those with carbapenem-resistant Kp-BSI of 33% to 54.3% (Giacobbe et al., 2015; Hussein et al., 2013; Nguyen et al., 2010; Papadimitriou-Olivgeris et al., 2014; Qureshi et al., 2012; Tumbarello et al., 2012). The 30-day mortality rate among patients with colistin-resistant Kp-BSI was calculated to be 67%, and recent studies have reported 30 day-mortality rates ranging from 30.8% to 51% (Giacobbe et al., 2015; Machuca et al., 2017).

The present study was performed in a region where OXA-48 is dominant and this was detected in 78% of the *K. pneumoniae*; however, the majority of studies have been reported from regions where KPC is more prevalent. In a previous study, OXA types were reported to be more fatal among those with bacteremia caused by *Enterobacteriaceae* (Gutierrez-Gutierrez et al., 2017). In the present study, ST101 was also high (67%). A recent study in Turkey reported that *K. pneumoniae* with the ST101 clone was associated with higher mortality (Can et al., 2018).

This study found that an increased mean colistin MIC was significantly associated with 30-day mortality (MIC 7 vs. 4, $p = 0.029$; Table 1). The MIC of colistin increased from 0.5 in 2011 up to 16 in 2017 among the patients who died. Some authors have indicated an association between colistin resistance and fatality (Giacobbe et al., 2015; Tumbarello et al., 2015), while others have reported no significant association (Gomez-Simmonds et al., 2016; Papadimitriou-Olivgeris et al., 2017b; Sbrana et al., 2013; Zarkotou et al., 2011). Some studies have reported that pneumonia as the source of infection is associated with increased fatality (Giacobbe et al., 2015; Qureshi et al., 2012). In the present study, pneumonia as the source of infection was associated with fatality in the univariate analysis (Table 1), but not in the multivariate analysis (Table 2).

Colistin resistance was higher among the patients who had received empiric colistin than among the patients who had not (71% vs. 23%, $p < 0.001$), and similar findings have been reported previously (Giacobbe et al., 2015; Papadimitriou-Olivgeris et al., 2014). However, a recent study reported that the presence of colistin-resistant bacteria can occur without any prior colistin use (Olaitan et al., 2016; Rojas et al., 2017).

The detection of carbapenem and colistin resistance urges the clinician to seek alternative combination therapies. Usually, despite the resistance, carbapenems, colistin, fluoroquinolones, tigecycline, and aminoglycosides remain the components of combination therapy with the expectation of synergistic action. The beneficial use of different antibiotic combinations remains to be clarified and there is no standard approach to extensively resistant or pan-resistant Klebsiella infections. One of the most significant findings of this study was the detection of the beneficial effect of adding amikacin to the regimen against colistin-resistant *K. pneumoniae*. Therapy with an aminoglycoside alone against colistin-resistant *K. pneumoniae* has been reported to be the most efficacious monotherapy, and therapeutic schemes including an aminoglycoside and a carbapenem have appeared to be the most effective combinations (Daikos et al., 2014; Gomez-Simmonds et al., 2016; Tzouvelekis et al., 2014; Zarkotou et al., 2011). Tigecycline combinations were not found to be effective.

Table 2
Multivariate analysis for 30-day mortality among patients with *Klebsiella pneumoniae* blood stream infections.

	Crude analysis			Adjusted analysis (with backward selection)		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Carbapenem resistance	2.8	1.6–4.98	<0.001	5.2	2.47–10.9	<0.001
Colistin resistance	1.7	0.89–3.14	0.105	-	-	-
APACHE score	1.19	1.13–1.25	<0.001	1.19	1.12–1.26	<0.001
Adding of amikacin to the regimen	0.16	0.04–0.59	0.006	0.05	0.01–0.23	<0.001
Lung as the source of infection	2.7	1.32–5.4	0.025	-	-	-

OR, odds ratio; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation.

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Recently, novel treatment options such as ceftazidime/avibactam, meropenem/vaborbactam, ceftolozane/tazobactam, plazomicin, and eravacycline have become available, providing much-awaited resources for effectively counteracting some severe multidrug-resistant gram-negative bacteria infections. However, their optimal use should be developed in the long term. The treatment of severe multidrug-resistant gram-negative bacteria infections in critically ill patients in the near future will require expert and complex clinical reasoning (Bassetti et al., 2019).

Limitations of this study are the retrospective design and being performed in a single center of cardiovascular surgery, although this is an important cardiovascular surgery center. The study was retrospective but presents data on the OXA-48 type of *K. pneumoniae* that were lacking in the literature.

In conclusion, carbapenem resistance, increasing MIC of colistin, and the lungs as the source of infection were significantly associated with 30-day mortality. The empirical use of combined active aminoglycosides should be recommended for colistin-resistant *Klebsiella pneumoniae* infections.

Author contributions: Şirin Menekşe: Study design, data collection, writing; Yasemin Çağ: study design, data collection; Mehmet Emirhan Işık: study design, data collection; Suzan Şahin: study design, data collection; Demet Hacıseyitoğlu: data collection; Fusun Can: data analysis, writing; Onder Ergonul: study design, data analysis, writing.

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Ethical approval

The Institutional Review Board of Kartal Koşuyolu Training and Research Hospital approved the study.

Informed consent

Not applicable.

Conflict of interest

None to declare.

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