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Original Article

Evaluation of Risk Factors for Carbapenem-Resistant *Klebsiella Pneumoniae* Bacteremia

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ABSTRACT

Objective: In recent years, carbapenem-resistant *Klebsiella pneumoniae* infections have become an important health problem in our country and all over the world. In this study, we aimed to identify the risk factors of carbapenem-resistant *K. pneumoniae* bacteremia.

Methods: Patients who suffered from Klebsiella pneumoniae bacteremia between December 2016 and May 2018 were included prospectively in this study. Patients were divided into groups according to carbapenem resistance and risk factors were analyzed under variable and multivariable logistic regression model.

Results: Of the fifty-three patients were included in this study, 27 patients infected with carbapenem-resistant *K. pneumoniae* and 26 patients infected with carbapenem-suspectible *K. pneumoniae*. Risk factors for carbapenem-resistant *K. pneumoniae* bacteremia according to univariate analysis were listed prior hospitalization (p=0.043; OR=3.20; 95% CI: 1.04–9.85), admission to intensive care unit (p=0.001; OR=10.91; 955 CI: 2.61–45.6), use of beta-lactams/beta-lactamase inhibitor combination (p<0.001; OR=41.67; 95% CI: 7.57–229.2) and use of glycopeptides (p=0.001; OR=7.92; 95% CI: 2.31–27.1). Before hospitalization (p=0.016; OR=9.64; 95% CI: 1.54–60.46) and use of beta-lactams/beta-lactamase, inhibitor combination (p<0.001; OR=38.45; 95% CI: 6.04–244.85) were identified as independent risk factors for carbapenem resistance in multivariate analysis.

Conclusion: According to our study, before hospitalization, the use of beta-lactams/beta-lactamase inhibitor combination was the major risk factor for carbapenem-resistant *Klebsiella pneumoniae* bacteremia.

INTRODUCTION

Bloodstream infections that arise from Gram-negative bacteria are infections that need to be diagnosed and treated quickly. In recent years, it has become an important problem due to increased antimicrobial resistance.[1] *Klebsiella pneumoniae* isolates lead to nosocomial infections, such as bloodstream infection, pneumonia, and urinary tract infection.[2] In recent years, with increasing resistance rates in our country and all over the world, *K. pneumoniae* infections have been associated with high mortality and morbidity and have become an important health problem.[3,4] Carbapenems are the most commonly used antibiotics for multi-drug resistant *Enterobacteriaceae* infections. Especially, they are the first treatment option for infections that arises from extended-spectrum beta-lactamase producing strains.[5] Carbapenem resistance was first detected in 1997 in *Klebsiella pneumoniae* strains.[6] In September 2001, the OXA48 enzyme was defined in carbapenem-resistant *Klebsiella pneumoniae* isolates in our country for the first time.[7] Nosocomial outbreaks with carbapenem-resistant strains have been reported all around the world.[8,9]

Among the members of the *Enterobacteriacae* family, the most susceptible bacterium which develops carbapenem resistance is *K. pneumoniae*. Since carbapenem-resistant isolates inhibit almost all beta-lactams, treatment options are quite limited in the infections caused by them and optimal treatment has not been determined for certain. Therefore, it is important to investigate the risk factors for the development of carbapenem resistance and to take necessary measures against these risk factors. In this study, we aimed to investigate the risk factors in carbapenem- resistant *Klebsiella pneumoniae* bacteremias.

MATERIALS AND METHODS

Patients aged 18 and over who had *Klebsiella pneumoniae* growth in their blood cultures, and treated in the inpatient services of our hospital between December 2016 and May 2018, were included in this study. Data regarding age, gender, hospitalization in the intensive care unit, accompanying comorbidities, history of antibiotic use, hospitalization, operation and use of invasive tools within the last 90 days were recorded in the case report forms.

An automated system (VITEK2 Compact, bioMerieux, France) was used for determining bacteriological identification and carbapenem susceptibilities of *Klebsiella pneumoniae* isolate growing in blood culture, and also European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards was used.[10] Isolates with imipenem/meropenem minimum inhibitory concentration (MIC) values of ≤2 mg/L and ertapenem MIC value of ≤0.5 mg/L were included in the carbapenem susceptible group. Isolates moderately sensitive or resistant to at least one of these antibiotics were included in the carbapenem- resistant group.

For statistical analysis, SPSS 22.0 Software (Chicago, IL, USA) program was used. Average, standard deviation, median, minimum, maximum, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. Mann-Whitney U test was used in the analysis of quantitative independent data. In the analysis of qualitative independent data, the chi-square test was used, and when chi-square test conditions were not met, Fisher's exact test was employed. The effect level was investigated by univariate and multivariate regression analysis. P<0.05 values were considered statistically significant.

RESULTS

Fifty-three patients with *Klebsiella pneumoniae* growth in blood culture between December 2016 and May 2018 were included in this study. Carbapenem resistance was found in 27 (50.9%) of the isolates and 26 of them were susceptible to carbapenem. In addition, antibacterial resistance were detected against ceftriaxone in 42 (79.2%), piperacillin/tazobactam in 31 (58.5%), amikacin in16 (30.2%), gentamicin in 25 (47.2%), cefepime in 28 (52.8%) and ciprofloxacin in 32 (60.4 %) isolates.

Fifty-three cases included in our study consisted of 21 (39.6%) female and 32 (60.4%) male with a mean age of 58.4±15.8 years. (median age, 60 years). The respective number of patients had a history of hospitalization (n=28: 52.8%), operation (n=22: 41.5%) within 30, and antibiotic use within 90 days (n=35: 66.0%). Twenty-five (47.2%) patients had been hospitalized in the intensive care unit at the onset of bacteremia. Central catheter was detected in 27 (50.9%), urinary catheter in 43 (81.1%), and drainage catheter in 10 (18.9%) patients, while 25 (47.2%) patients were connected to mechanical ventilator. Comparison of demographic characteristics of the patients according to carbapenem resistance status is given in Table 1.

The same isolate (*Klebsiella pneumoniae*) was grown in the urine culture of 21, sputum / bronchoalveolar lavage culture in 5, the blood culture obtained through central venous catheter in 3, and wound culture, in 5 in patients. The foci of infection were urinary tract infection in 28, respiratory tract infection in 8, catheter-related bloodstream infection in 3, soft tissue infection in 5, and cholecystitis/cholangitis in 5 cases. According to the results of univariate analysis hospitalization (p=0.043; OR=3.20; 95% CI 1.04–9.85), intensive care unit stay (p=0.001; OR=10.91; 95% CI 2.61–45.6), beta-lactam/beta -lactamase inhibitor combination use (p<0.001; OR=41.67; 95% CI 7.57–229.2), glycopeptide use (p=0.001; OR=7.92; 95% CI 2.31–27.1) all of them within 30 days were determined to be statistically significant risk factors for carbapenem resistance in *Klebsiella pneumoniae* bacteremias I (Table 2).

In the further multivariate analysis of the results, the use of carbapenem hospitalization (p=0.016; OR=9.64; 95% CI 1.54–60.46), and use of beta-lactam/beta-lactamase inhibitor combination (p<0.001; OR=38.45; 95% CI 6.04–244.85) within 30 days were found to be significant independent risk factors as for carbapenem resistance (Table 2).

DISCUSSION

In this study, which was carried out to determine risk factors due to increasing carbapenem resistance in *Klebsiella pneumoniae* strains, hospitalization, intensive care unit stay, use of beta-lactam/beta-lactamase inhibitor combination, and/or glycopeptide use within 30 days were determined as risk factors for the development of carbapenem resistance according to univariate analysis. Also, in our study, hospitalization and use of beta-lactam/beta-lactam inhibitor combination within 30 days were determined as independent risk factors for carbapenem resistance in advanced multivariate analysis.

As a risk factor for carbapenem resistance in *Enterobacteriaceae* infections in different studies, mostly emphasized and the important issue was the history of antibiotic use and hospitalization.[11–13] In accordance with these findings, in our study, hospitalization history was determined as an independent risk factor for carbapenem resistance in both univariate and multivariate analyses. In our study, a statistically significant relationship was found between hospitalization in the intensive care unit, the use of glycopeptide and carbapenem resistance. In a case-control study conducted by Akgül et al., acute renal failure, steroid use, diarrhea, mechanical ventilation, presence of tracheostomy, urinary catheterization, central venous catheterization, nasogastric catheter use, emergency surgical intervention, total parenteral nutrition, hospitalization history, carbapenem, glycopeptide, colistin and piperacillin/tazobactam use were found to be risk factors for the development of carbapenem- resistant *Klebsiella pneumoniae* infection in univariate statistical analysis.

Table 1. Demographic characteristics of the patients with *Klebsiella pneumoniae* bacteremias according to their carbapenem resistance

	Carbapenem resistant (n=27)	Carbapenem sensitive (n=26)	p*
Age, median (mean±SD)	62 (61.3±16.6)	59.5 (55.3±14.6)	0.197**
Female/male	10/17 (37–63%)	11/15 (42.3–57. 7%)	0.695
Hospitalization in the intensive care unit, n (%)	16 (59.3)	9 (34.6)	0.072
Comorbidities, n (%)			
Diabetes mellitus	7 (25.9)	5 (19.2)	0.560
Chronic renal failure	3 (11.1)	4 (15.4)	0.646
Acute renal failure	10 (37)	11 (42.3)	0.695
Chronic liver disease	0 (0)	1 (3.8)	0.304
Malignancy	9 (33.3)	14 (53.8)	0.132
Coronary artery disease	4 (14.8)	2 (7.7)	0.413
Hypertension	14 (51.9)	8 (30.8)	0.119
Cerebrovascular disease	3 (11.1)	1 (3.8)	0.317
Chronic pulmonary disease	2 (7.4)	0 (0)	0.491
History, n (%)			
Antibiotic use within 90 days	24 (88.9)	11 (42.3)	0.000
Hospitalization within 30 days	18 (66.7)	10 (38.5)	0.040
Surgery within 30 days	12 (44.4)	10 (38.5)	0.659
Previous antibiotic use, n (%)			
Cephalosporins	3 (11.1%)	1 (3.8)	0.317
Quinolones	4 (14.8)	2 (7.7)	0.413
Glycopeptides	19 (70.4)	6 (23.1)	0.001
Beta-lactam/beta-lactamase inhibitor combination	25 (92.6)	6 (23.1)	<0.001
Presence of invasive device, n (%)			
Central catheter	17 (63)	10 (38.5)	0.074
Urinary catheter	23 (85.2)	20 (76.9)	0.442
Mechanical ventilator	16 (59.3)	9 (34.6)	0.072
Drainage catheter	4 (14.8)	6 (23.1)	0.442

*Chi-square test (Fisher's exact test); **Mann-Whitney U test. SD: Standard deviation.

Table 2. Univariate and multivariate analyses of risk factors for carbapenem resistance in *Klebsiella pneumoniae* bacteremias

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95 %CI	p
Hospitalization within 30 days	3.20	1.04–9.85	0.043	9.64	1.54–60.46	0.016
Hospitalization in the intensive care unit	10.91	2.61–45.6	0.001			
Previous use of antibiotics						
Beta-lactam/beta-lactam inhibitor combination	41.67	7.57–229.2	<0.001	38.45	6.04–244.85	<0.001
Glycopeptides	7.92	2.31–27.1	0.001			

OR: Odds ratio; CI: Confidence interval.

Nonusage of glycopeptide (OR=0.143; 95% CI 0.031–0.674; p<0.05), steroid (OR=0.244; 95% CI 0.072–0.822; p<0.05) and absence of tracheostomy (OR=0.06; 95% CI 0.006–0.614; p<0.05) were determined as protective factors against the development of carbapenem resistance in multivariate regression analysis.[14]

In a meta-analysis that included sixteen studies, being in the hospital for a long time (OR=12.92), staying in the intensive care unit (OR=2.48), history of hospitalization (OR=1.85), duration of hospitalization in the intensive care unit (OR=4.58), organ transplant (OR=2.01), steroid use (OR=1.43), presence of central venous catheter (OR=2.30), mechanical ventilation (OR=2.54), presence of tracheostomy (OR=3.63), total parenteral nutrition (OR=2.38), history of antibiotic use (OR=3.31), including carbapenem (OR=4.01), aminoglycoside (OR=2.05), glycopeptide (OR=2.40), quinolone (OR=2.28), and an-

tipseudomonal penicillin (OR=2.67), have been identified as risk factors for carbapenem resistance in *Klebsiella pneumoniae* infections.[15]

In different studies, exposure to glycopeptides has been found to be an independent risk factor for carbapenem resistance in *Klebsiella pneumoniae* infections.[16,17] In a study by Pultz et al.[18] on mice, vancomycin and linezolid therapy have been shown to disrupt anaerobic intestinal flora and lead to colonization of *Klebsiella pneumoniae.* Colonization rate increased due to a high dose and prolonged vancomycin treatment time. The suppression of gram-positive bacteria in the intestinal flora with the use of glycopeptides leads to the proliferation of gram-negative bacteria. Although it is thought that mutations resulting from this rapid growth in gram-negative bacteria may increase the expression of genes associated with carbapenem resistance and contribute to the spread of carbapenemases. However, further studies are needed in this regard.

As in our study, the use of beta-lactam/beta-lactamase inhibitor combination (OR=4.765, 95% CI 1.508–15.055; p=0.008) was found as a risk factor in both uni-, and multivariate analyses for carbapenem resistance in *Klebsiella pneumonia*e infections in a retrospective case-control study conducted in China. In addition, being hospitalized in the intensive care unit (OR=15.486; 95% CI 3.175–75.541; p<0.001), cephalosporin (OR=8.033; 95% CI 1.623–39.763; p=0.011), and/or fluoroquinolone use (OR=6.090; 95% CI 1.343–27.613; p=0.019) and the presence of urinary catheter (OR=6.164; 95% CI 1.847–20.578; p=0.003) were also identified as independent risk factors in this study.[19] In another retrospective study conducted by Jiao et al.[12] uses of glycopeptide (OR=43.84; 95% CI 1.73–1111.91; p=0.020), cefoperazone/sulbactam combination (OR=49.56; 95% CI 1.42–1726.72; p=0.030), presence of tracheostomy (OR=677.82; 95% CI 2.76–1667; p=0.020) were found to be independent risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization.

According to the annual report of Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) 2018, carbapenem resistance is increasing in *K. pneumonae* strains in our country; imipenem/meropenem resistance (moderately sensitive+resistant) was found in 38% and ertapenem resistance in 43% of the cases.[3] Multidrug resistance rates also increased in *K. pneumonae* strains compared to the previous year (35%) but were reported as 38 percent. In our study, carbapenem resistance was found in 50.8% of our *K. pneumoniae* isolates grown in blood culture.

In conclusion, carbapenem- resistant *K. pneumoniae* infections have become an important health problem in our country and in the world with increasing resistance rates. Therefore, considering the risk factors for carbapenem resistance, unnecessary use of antibiotics, especially the combination of glycopeptide, beta-lactam/beta-lactamase inhibitor, should be avoided. In addition, the possibility of carbapenem resistance should be taken into account when starting empirical antimicrobial therapy in bacteremias in patients who are hospitalized in the intensive care unit or who have a history of hospitalization.

Ethics Committee Approval

Approved by the local ethics committee (date: 13.12.2016, no: 2016/514/97/6).

Informed Consent

Prospective study.

Peer-review

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Authorship Contributions

Concept: P.K., S.G., A.B.; Design: P.K., S.G., A.B.; Supervision: P.K., S.G., A.B.; Fundings: P.K., S.G., A.B.; Materials: P.K., S.G., A.B.; Data: P.K., S.G., A.B.; Analysis: P.K., S.G., A.B.; Literature search: P.K., S.G., A.B.; Writing: P.K.; Critical revision: P.K.

Conflict of Interest

None declared.

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Klebsiella Pneumoniae Bakteriyemilerinde Karbapenem Direnci İçin Risk Faktörlerinin Değerlendirilmesi

Amaç: Son yıllarda artan karbapenem direnci ile birlikte *Klebsiella pneumoniae* enfeksiyonları ülkemizde ve tüm dünyada önemli bir sağlık problemi haline gelmiştir. Bu çalışmada, *Klebsiella pneumoniae* bakteriyemilerinde karbapenem direnci için risk faktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: Aralık 2016–Mayıs 2018 tarihleri arasında kan kültüründe *Klebsiella pneumoniae* üremesi olan hastalar ileriye yönelik olarak çalışmaya dahil edildi. Olgular karbapenem direnç durumuna göre gruplara ayrılarak; tek ve çok değişkenli regresyon modeli ile karbapenem direnci için risk faktörleri analiz edildi.

Bulgular: Çalışmaya dahil edilen 53 olgunun; 27'si karbapenem dirençli, 26'sı ise karbapenem duyarlı *Klebsiella pneumoniae* izolatı ile enfekte idi. Yapılan tek değişken analiz sonuçlarına göre; hastaneye yatış öyküsü [p=0.043; Odds ratio (OR)=3.20; %95 güven aralığı (%95 GA): 1.04–9.85], yoğun bakım ünitesinde (YBÜ) yatıyor olmak (p=0.001; OR=10.91; %95 GA 2.61–45.6), beta-laktam/beta-laktam inhibitörü kombinasyonu kullanımı (p<0.001; OR=41.67; %95 GA 7.57–229.2), glikopeptid kullanımı (p=0.001; OR=7.92; %95 GA 2.31–27.1) *Klebsiella pneumoniae* bakteriyemilerinde karbapenem direnci için istatistiksel olarak anlamlı bulundu. Çok değişkenli analiz sonucunda ise; hastaneye yatış öyküsü (p=0.016; OR=9.64; %95 GA: 1.54–60.46), beta-laktam/beta-laktam inhibitörü kombinasyonu kullanımı (p<0.001; OR=38.45; %95 GA 6.04–244.85) karbapenem direnci açısından anlamlı bağımsız risk faktörü olarak saptandı.

Sonuç: Yaptığımız çalışmada, hastanede yatış öyküsü, beta-laktam/beta-laktamaz inhibitörü kombinasyonu kullanımı *Klebsiella pneumoniae* bakteriyemilerinde karbapenem direnci için en önemli risk faktörü olarak bulunmuştur.

Anahtar Sözcükler: Bakteriyemi; karbapenem; *Klebsiella pneumoniae*; risk faktörleri.