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Risk factors for mortality in healthcare-associated infections caused by Klebsiella pneumoniae

Klebsiella pneumoniae: Resistance and mortality risks

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Abstract
Aim: Healthcare-associated infections (HAIs) are a major cause of morbidity and mortality in hospitals. This study aimed to evaluate the antibiotic resistance profiles and mortality risk factors associated with Klebsiella pneumoniae in healthcare-associated infections.
Material and Methods: This cross-sectional, retrospective study was conducted between January 1, 2018, and January 1, 2024. Adult individuals who had K. pneumoniae isolated from clinical samples taken 48 hours after hospitalization and who met healthcare-associated infection criteria were included in the study. The risk factors associated with mortality were evaluated.
Results: A total of 84 cases of HAIs caused by K. pneumoniae were included in the study, 47 (56%) of whom were male. Among these, 73.8% exhibited carbapenem-resistant Klebsiella pneumoniae (CRC-Kp). Univariate logistic regression identified chronic obstructive pulmonary disease (COPD), absence of fever response on the fifth day, and CRC-Kp growth as significant mortality predictors. Multivariate analysis revealed patients not on hemodialysis (HD) and absence of fever response on the fifth day as significantly associated with mortality, with 23.774 and 121.620 times higher risk, respectively.
Discussion: These findings underscore the threat posed by K. pneumoniae infections due to antibiotic resistance and mortality, highlighting the urgent need for effective infection control measures and targeted treatment strategies.

Keywords
Carbapenem Resistance, Klebsiella Pneumoniae, Hospital Infections, Mortality, Risk Factor

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Introduction

Healthcare-associated infections (HAI) are a significant cause of morbidity and mortality in hospitals, particularly in intensive care units (ICUs) [1]. 'Nosocomial infections' or HAIs are defined as infections that occur in patients receiving medical care in a hospital or another healthcare facility and were not present or incubating at the time of admission. These infections can occur even after patients have been discharged (available at: https://www.who.int/news-room/feature-stories/detail/the-burden-of-health-care-associated-infection-worldwide). Modern invasive devices, such as catheters and ventilators, which are inserted into sterile spaces, contribute to the increased incidence of these infections (available at: https://www.cdc.gov/hai/infectiontypes.html). One of the most important factors leading to these infections, which are becoming increasingly difficult to treat due to antibiotic resistance, is gram-negative bacilli from the Enterobacterales family. Klebsiella species within this family, like other members of Enterobacterales, develop resistance to beta-lactam antibiotics through hydrolysis by beta-lactamases. They particularly exhibit resistance to beta-lactam agents through extended-spectrum beta-lactamase (ESBL) production and resistance to carbapenems through carbapenemase production. Klebsiella strains that develop carbapenem resistance are microorganisms that are difficult to treat, even with broad-spectrum antibiotics such as third- and fourth-generation cephalosporins, imipenem, and meropenem (available at: https://www.cdc.gov/hai/organisms/cre/cre-clinicians.html). Over the years, the need for new antibiotics has increased due to changes in resistance genes, and new agents have been developed and used in their treatment, as the effectiveness of currently used antibiotics has decreased [2, 3]. Therefore, it is essential for each physician to be aware of the resistance profile of the infectious organisms in their particular hospitalization unit to choose the best empirical antibiotic therapy and reduce mortality. This study aims to determine the antibiotic resistance profiles of Klebsiella pneumoniae strains and the risk factors associated with mortality in healthcare-associated infections caused by these microorganisms in a secondary care state hospital over the past six years.

Material and Methods

This cross-sectional, retrospective study was conducted at a secondary-level state hospital using data obtained from patient records and laboratory results-based surveillance from January 1, 2018, to January 1, 2024.

Cases with a diagnosis of HAIs in which K. pneumoniae strains were isolated from various samples (such as blood, wound, abscess, sputum, tracheal aspirate, etc.) were examined. The identification of HAIs was performed according to the surveillance diagnostic criteria established by the Centers for Disease Control and Prevention (CDC) of the United States (available at: https://www.cdc.gov/healthcare-associated-infections/about/index.html). Adult patients who had positive K. pneumoniae growth from samples taken 48 hours after hospital admission, considered as pathogens associated with infection focus, and who received antibacterial treatment, were included in the study. Data on patients and the microorganisms cultured from their samples were accessed through the hospital's infection control committee surveillance system and the Public Health Management System (PHMS). Patients' chronic illnesses, infection sites, fever responses on the fifth day, and antimicrobial resistance patterns of K. pneumoniae strains were recorded. Following a 30-day follow-up after infection, patients were divided into two groups: those who survived and those who died. Culture processes of the collected clinical materials and identification of microorganisms grown in culture were performed at the microbiology laboratory of the study center. Identification of strains was carried out using conventional microbiological methods and the automated bacterial identification system VITEK 2 (bioMérieux, Marcy-L'Étoile, France). The results were evaluated according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (available at: http://www.eucast.org).

Statistical Analysis

All data were analyzed using the SPSS program. Continuous variables were presented as mean ± standard deviation, while nominal variables were presented as case number and percentage (%). Chi-square analysis was used to evaluate relationships between categorical variables, and univariate and multivariate logistic regression analyses were used to determine factors affecting mortality. Variables found to be statistically significant in univariate logistic regression analysis ($p < 0.20$) were included in multivariate logistic regression analysis to determine odds ratio (OR) and 95% confidence interval (95% CI). A significance level of $p < 0.05$ was considered statistically significant.

Ethical Approval

This study was approved by the Non-Interventional Ethics Committee of Izmir Katip Celebi University (Date: 2024-01-18, No: 0031).

Results

The study comprised 84 cases with HAI diagnoses, 47 of whom (56%) were male. The mean age of the cases was 71.9 ± 13.3 years. Among the cases, 43 (51.2%) had bloodstream infections, 31 (36.9%) had urinary system infections, 5 (6%) had pneumonia, and 5 (6%) had wound infections (Table 1). Of the Klebsiella pneumoniae strains, 22 (26.2%) were only ESBL positive, while 62 (73.8%) were carbapenem-resistant. The lowest resistance rates were observed for amikacin (57.1%) and gentamicin (58.3%), while the highest resistance rates were observed for cefepime (89.3%), ciprofloxacin (84.5%), and piperacillin-tazobactam (81%). The resistance profiles of K. pneumoniae are presented in Figure 1.

Table 1. Distribution of K. pneumoniae infections

Infection Focus	K. pneumoniae n (%)
Bloodstream Infection	43 (51,2%)
Urinary Tract Infection	31 (36,9%)
Pneumonia	5 (6%)
Wound Infection	5 (6%)
Total	84 (100%)

n: Count %: Percentage

Table 2. Risk Factors Analysis for 30-day Mortality in Patients with K. pneumoniae

Characteristics	Survivors n=34	Deceased n=50	p	Univariate analysis OR (95% CI)	p	Multivariate analysis OR (95% CI)	p
Age	65.1 ± 15.9	76.5 ± 8.8	0.000				
Gender							
Female	18 (%48.6)	19 (51.4)	0.176				
Male	16 (34)	31 (66)					
Demantia	10 (47.6)	11 (52.4)	.441				
Malignancy	1 (25)	3 (75)	.644				
Hemodialysis	5 (83.3)	1 (16.7)	.038	8.448 (0.940-75.910)	0.057	23.774 (1.177 -480.404)	0.039
Diabetes	4 (26.7)	11 (73.3)	.229				
COPD*	2 (14.3)	12 (85.7)	.029	5.053 (1.052-24.264)	.043	8.535 (0.758 - 96.113)	0.083
Chronic Kidney Disease	2 (15.4)	11 (84.6)	.045	4.513 (0.932 - 21.855)	.061	5.937 (0.244 - 144.319)	0.274
Hypertension	7 (28)	18 (72)	.129				
Heart Failure	1 (14.3)	6 (85.7)	.233				
Cerebrovascular Disease	4 (30.8)	9 (69.2)	.438				
Coronary Artery Disease	2 (16.7)	10 (83.3)	.111				
Secondary Bloodstream Infection	4(66.7)	2 (33.3)	.216				
Fever response on the 5th day	32 (86.5)	5 (13.5)	.000	93.00 (20.695-417.918)	.000	121.620 (22.222 - 665.602)	0.000
Concomitant Infection	22 (41.5)	31 (58.5)	.801				
ESBL**	16 (72.7)	6 (27.3)	.000	0.153 (0.052 - 0.455)	.001		
CRKP***	18 (29.0)	44 (71.0)	.000	6.519 (2.199- 19.325)	.001		
Urinary Tract Infection	18 (58.1)	13 (41.9)	.012	0.312 (0.124 - 0.786)	.014		
Wound Infection	2 (40)	3 (60)	1.00				
Pneumonia	1 (20)	4 (80)	.644				
Bloodstream Infection	13 (30.2)	30 (69.8)	.049	2.243 (0.991 - 5.922)	.052	0.600 (0.084 - 4.291)	0.611

n: Count %: percentage OR: Odds ratio, CI: Confidence interval *: Chronic Obstructive Pulmonary Disease ** Extended-Spectrum Beta-Lactamase ***Carbapenem-Resistant Klebsiella pneumoniae

Table 3. Relationship between K. pneumoniae antibiotic resistance and fifth day fever response

Antibiotics	Fever response on the fifth day		
	Present	Absent	p
Ciprofloxacin resistance	27 (38)	44 (62)	.009
Ertapenem resistance	22(33.3)	44 (66.7)	.000
Meropenem resistance	21 (33.9)	41 (66.1)	.002
Imipenem resistance	20 (31.7)	43 (68.3)	.000
Cefepime resistance	28 (37.3)	47 (62.7)	.000
Gentamicin resistance	18 (36.7)	31 (63.3)	.110
Amikacin resistance	15 (31.3)	33 (68.8)	.006
Trimethoprim-Sulfamethoxazole resistance	21 (35)	39 (65)	.008
Piperacillin-tazobactam resistance	25 (36.8)	43 (63.2)	.006

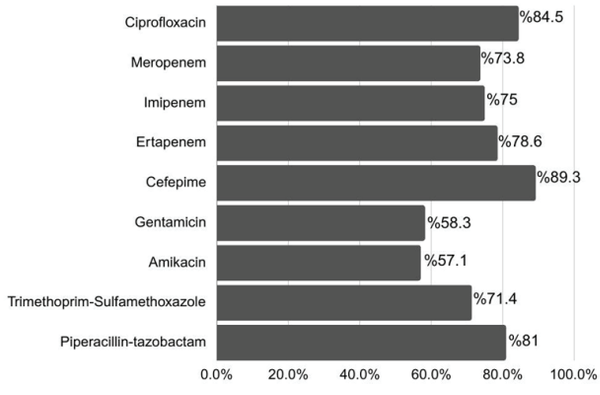


Figure 1. Antibiotic resistance rates of K. pneumoniae

When examining risk factors for 30-day mortality, advanced age, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and bloodstream infections were found to be more common (p-values; p=0.000, p=0.029, p=0.045, p=0.049, respectively). When examining the resistance profile, the presence of CR-Kp strains was found to be significantly associated with mortality (p=0.000). In univariate logistic regression analysis to assess factors predicting mortality, COPD in cases, absence of fever response on the 5th day, and presence of CR-Kp growth were found to be significant (p-values; p=0.043, p=0.000, p=0.001, respectively) (Table 2).

According to the results of univariate binary logistic regression analysis, when evaluating the main factors related to mortality, the variables with p-value<0.20, namely the presence of COPD and CKD, presence of bloodstream infection, not receiving hemodialysis (HD), and absence of fever response on the fifth day, were included in the multivariate logistic regression model. According to the final results of multivariate logistic regression analysis, not undergoing HD (p=0.039) and absence of fever response on the fifth day (p=0.000) were found to have a significant impact on mortality. The presence of COPD (p=0.083), presence of CKD (p=0.274), and presence of bloodstream infection (p=0.611) were found to have insignificant effects. The risk of mortality for those not undergoing HD was found to be 23.774 times higher compared to those undergoing HD, and for those without fever response on the fifth day, it was found to be 121.620 times higher compared to those with a response. These data are presented in Table 2. In the analyses conducted to assess the effect of culture antibiotic susceptibility on clinical response, except for

gentamicin resistance, it was found that there was a lower fever response on the fifth day in cultures with resistance to antibiotics ($p < 0.05$). These findings are presented in Table 3.

Discussion

Recent reports indicate an increasing prevalence of Klebsiella pneumoniae-associated infections, high antibiotic resistance rates, and rising mortality rates, especially in HAI settings [4, 5]. Consistent with these trends, our study found high antibiotic resistance rates and a 30-day mortality rate of 59.5% among patients diagnosed with HAIs caused by Klebsiella pneumoniae. The most significant factors predicting mortality were determined to be COPD, absence of fever response on the 5th day, not undergoing HD among CKD patients, and the presence of CR-Kp. A meta-analysis covering the years 2005-2019 reported antibiotic resistance rates of K. pneumoniae at 2.9% for colistin and 40.8% for amikacin, with the highest resistance rates observed for cefotaxime (79.2%), ceftazidime (75.7%), and cefepime (72.6%) [5]. Consistent with this meta-analysis, our study found a low resistance rate to amikacin and a high resistance rate to cefepime. Studies conducted in Turkey examining Enterobacterales resistance have also shown that Klebsiella strains have the lowest resistance rates for amikacin and carbapenems [6, 7]. In our study, all Klebsiella isolates were ESBL positive, and compared to resistance studies conducted in previous years, the rate of CR-Kp was higher. Compared to current studies, the rate of CR-Kp was also found to be higher in our study [8, 9]. The results of these studies support the increasing trend of carbapenem resistance [10, 11]. In a study of patients with bloodstream infections due to CR-Kp, a 28-day mortality rate of 56% was reported, and absence of clinical response on the fifth day was found to be one of the factors predicting mortality [12]. These findings, similar to the mortality rate in our study, support the predictive value of the absence of fever response on the fifth day for mortality. In our study, a significant relationship was observed between antibiotic resistance and the absence of fever response on the fifth day. A study by Eren et al. also found an association between colistin resistance and clinical non-response [12]. A meta-analysis of 157 studies, including seven studies from Turkey, found that CR-Kp and ESBL K. pneumoniae bacteremia were associated with high mortality rates in ICU-acquired and healthcare-associated K. pneumoniae infections [13]. In our study, a higher frequency of mortality was found in patients with bloodstream infections caused by CR-Kp. A comprehensive meta-analysis examining the relationship between CR-Kp and mortality, with a detailed examination of patients' comorbidities, identified septic shock, COPD, CKD, diabetes, mechanical ventilation, and inappropriate empirical antibiotic use described as risk factors for mortality [14]. In our study, the presence of COPD and CKD comorbidities was found to be a risk factor for mortality in patients, emphasizing the importance of controlling chronic diseases in these patients. In our study, mortality was found to be higher in patients not undergoing hemodialysis, and multivariate logistic regression analyses showed that not undergoing HD had a significant effect on mortality (Table 2). We believe that regulating kidney function through hemodialysis may reduce mortality. As is known, patients with COPD are predisposed to infection and biofilm formation through various mechanisms, resulting in high rates of antimicrobial resistance [15]. Therefore, prolonged and prophylactic antibiotic use is common in these patients. All these suggest that the lung tissue of these individuals is more prone to infection, and the existence of antibiotic resistance complicates therapy, which is why having COPD raises the risk of infection and mortality [15]. To elucidate this, more comprehensive and prospective studies are needed in patients with COPD. In our study, mortality was found to be lower in patients diagnosed with urinary system infections. A study by Sönmez et al. involving 94 patients with ESBL-positive E. coli and K. pneumoniae bacteremia also reported an inverse relationship between 30-day mortality and urinary system infection [16]. As is known, urinary system infection, asymptomatic bacteriuria, and colonization distinctions are challenging clinically and laboratorial. Colonization is inevitable in patients followed up with long-term urinary catheterization, and it can result in infection at later stages [17]. Diagnosing urinary system infections is particularly challenging in elderly patients, chronically catheterized patients, and ICU patients with impaired consciousness [18]. Therefore, more comprehensive prospective studies are needed to elucidate the relationship between Klebsiella pneumoniae growth in urinary system infections and mortality.

Limitation

One of the most significant limitations of our study is that it was conducted retrospectively and in a single center. Additionally, it is possible that the coronavirus pandemic caused a drop in surveillance reports and a lower number of cases. However, the strengths of our study include the detailed access to patients' chronic diseases and fever responses on the fifth day, allowing for an examination of their relationship with mortality in addition to Klebsiella pneumoniae antibiotic resistances.

Conclusion

The escalating antibiotic resistance of Klebsiella pneumoniae presents a formidable challenge to public health, exacerbating mortality and morbidity rates. Particularly alarming is the heightened mortality risk observed in patients with co-existing conditions such as chronic obstructive pulmonary disease, chronic kidney disease, and those afflicted by carbapenem-resistant Klebsiella pneumoniae strains. This underscores the urgent need for robust interventions targeting infection control and innovative treatment strategies to mitigate the devastating impact of these infections on patient outcomes and public health.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Colpan A, Akinci E, Erbay A, Balaban N, Bodur H. Evaluation of risk factors for mortality in intensive care units: a prospective study from a referral hospital in Turkey. Am J Infect Control. 2005;33(1):42-7.

2. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother. 2010;54(3):969-76.

3. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem/relebactam against Enterobacteriaceae and Pseudomonas aeruginosa isolated from intraabdominal and urinary tract infection samples: SMART Surveillance United States 2015-2017. J Glob Antimicrob Resist. 2020;21:223-8.

4. Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. Ann Clin Microbiol Antimicrob. 2017;16(1):18.

5. Effah CY, Sun T, Liu S, Wu Y. Klebsiella pneumoniae: an increasing threat to public health. Ann Clin Microbiol Antimicrob. 2020;19(1):1.

6. Mirza HC, Sancak B. Bir üniversite hastanesinde kan kültürlerinden izole edilen enterobacterales takımı üyelerinin dağılımının ve antimikrobiyal duyarlılıklarının incelenmesi [Distribution and Antimicrobial Susceptibilities of Members of Enterobacterales Isolated from Blood Cultures in a University Hospital]. Turk Mikrobiyol Cemiy Derg. 2021;51(4):348-53.

7. Kula Atik T, Uzun B. Kan kültürlerinden izole edilen Enterobacteriaceae türlerinin antibiyotik duyarlılıklarının araştırılması [Investigation of Antimicrobial Susceptibility in Enterobacteriaceae Species Isolated From Blood Cultures]. ANKEM Derg. 2020;34(2):33-40.

8. Duman Y, Kuzucu C, Tekerekoglu MS, Cakil B, Yakupogullari Y, Kaysadu H. Changing trends of carbapenem resistance of Escherichia coli and Klebsiella pneumoniae strains isolated from intensive care units, inpatient services and outpatient's clinics: a five years retrospective analysis. MedScience 2018;7:536-9.

9. Tümtürk A, Tezer Tekçe AY, Şanal L. Nozokomiyal infeksiyon etkeni Gram negatif bakterilerdekarbapenem direnç oranları: üçüncü basamak birhastaneden retrospektif bir çalışma [Carbapenem resistance rates in Gram-negative bacteria as causative agents of nosocomial infections: A retrospective study from a tertiary care hospital]. Ortadoğu Tıp Dergisi 2019;11:422-6.

10. Telli M. Klebsiella pneumoniae klinik suşlarında, 2012-2020 yılları arasında karbapenem direnç oranlarındaki değişimin ve direnç genlerinin araştırılması [Investigetion of Carbapenem Resistance Ratio Changes and Resistange Genes in Clinical Isolates of Klebsiella pneumoniae Between 2012 to 2020]. Turk Mikrobiyol Cemiy Derg. 2022;52(2):95-102.

11. Mermutluoğlu Ç, Çiftçi EZ, Özcan N, Dayan S. Klinik Örneklerden İzole Edilen Karbapenem Dirençli Klebsiella pneumoniae ve Escherichia coli Suşlarında Antibiyotik Duyarlılıklarının Araştırılması: Kapsamlı Bir Sağlık Kuruluşunda Dört Yıllık Analiz [Investigation of Antibiotic Susceptibilities in Carbapenem-Resistant Klebsiella pneumoniae and Escherichia coli Strains Isolated from Clinical Samples: A Four Year Analysis in a Comprehensive Healthcare Facility]. Van Tıp Dergisi, 2023;30(4):374-81.

12. Eren E, Ulu-Kılıç A, Türe Z, Cevahir F, Kılıç H, Alp-Meşe E. [Risk Factors of Mortality in Patients with Bloodstream Infections Due to Carbapenem Resistant Klebsiella pneumoniae]. Klimik Derg. 2021;34(1):56-60. Turkish.

13. Li D, Huang X, Rao H, Yu H, Long S, Li Y et al. Klebsiella pneumoniae bacteremia mortality: a systematic review and meta-analysis. Front Cell Infect Microbiol. 2023;13:1157010.

14. Qian Y, Bi Y, Liu S, Li X, Dong S, Ju M. Predictors of mortality in patients with carbapenem-resistant Klebsiella pneumoniae infection: a meta-analysis and a systematic review. Ann Palliat Med. 2021;10(7):7340-50.

15. Smith D, Gill A, Hall L, Turner AM. Prevalence, Pattern, Risks Factors and Consequences of Antibiotic Resistance in COPD: A Systematic Review. COPD. 2021;18(6):672-82.

16. Sönmez U, Çalık Ş, Çayıröz MU, Olut AI, Arı A, Tosun S, et al. Determination of the Risk Factors Associated with Mortality in Bacteraemia due to Extended Spectrum Beta-lactamase Producing Klebsiella pneumoniae and Escherichia coli and Comparison of Empirical Piperacilin-Tazobactam Versus Carbapenem Treatment. Ankem Derg 2018;32(1):1-8.

17. Gaston JR, Johnson AO, Bair KL, White AN, Armbruster CE. Polymicrobial Interactions in the Urinary Tract: Is the Enemy of My Enemy My Friend?. Infect Immun. 2021;11:IAI.00652-20.

18. Nicolle LE. Catheter-related urinary tract infection: practical management in the elderly. Drugs Aging. 2014;31(1):1-10.

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