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Evaluation of Antimicrobial Resistance Rates in *Klebsiella* Isolates

Klebsiella İzolatlarının Antimikrobiyal Direnç Oranlarının Değerlendirilmesi

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Abstract

Introduction: Bacteria of the genus *Klebsiella* are important causes of nosocomial infections. These bacteria may develop resistance in different ways, with extended-spectrum beta-lactamase (ESBL) production being the most common. The aim of this study was to evaluate resistance status of *Klebsiella* isolates obtained from different intensive care units and various clinical samples.
Materials and Methods: Resistance rates of *Klebsiella* spp. strains isolated from bacteriologic cultures of patients in intensive care units between 2014 and the first six months of 2017 were evaluated retrospectively. Blood, urine, bronchoalveolar lavage, cerebrospinal fluid, and tracheal aspirate samples were cultured. Intensive care patients aged ≥18 years were included. Only the first isolate from each patient was included; subsequent isolates from the same patient were excluded.
Results: A total of 443 patients were included in the study. Of the *Klebsiella*-positive samples, 31.8% (n=141) were tracheal aspirate, 23.7% (n=105) were blood, 23.3% (n=103) were urine, 9.0% (n=40) were sputum, and 12.2% (n=54) were other samples. The majority of cases were *K. pneumoniae* (89.7%, n=397), followed by *K. oxytoca* (7%, n=31), *K. ozaenae* (2.9%, n=13), *K. granulomatis* (0.2%, n=1), and *K. ornithinolytica* (0.2%, n=1). Of the 443 isolates, 54.4% (n=241) were ESBL-producing while 45.6% (n=202) were non-ESBL-producing. Mortality rates were 60% among patients with ESBL-positive *Klebsiella* and 47.5% among patients with ESBL-negative *Klebsiella* (p=0.008).
Conclusion: The antibiotic resistance of ESBL-positive *Klebsiella* isolates in our hospital was higher than resistance rates in the literature. To overcome this resistance issue, each hospital must know its own resistance rates and establish policies for the rational use of antibiotics.
Keywords: Extended-spectrum beta-lactamase, *Klebsiella*, ciprofloxacin, colistin, tigecycline

Öz

Giriş: *Klebsiella* cinsi bakteriler nozokomiyal enfeksiyonların önemli bir nedenidir. Bu bakteriler farklı şekillerde direnç geliştirebilirler. Genişlemiş spektrumlu beta-laktamaz (GSBL) yapımı bunların başında gelmektedir. Bu çalışmada, farklı yoğun bakım ünitelerinden ve çeşitli klinik örneklerden elde edilen *Klebsiella* izolatlarının direnç durumlarının değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: Çalışmada 2014-2017 (ilk 6 ay) tarihleri arasında yoğun bakım ünitelerinde yatan hastaların bakteriyolojik kültüründen izole edilen *Klebsiella* spp. kökenlerinin direnç oranları retrospektif olarak incelendi. Kan, idrar, bronkoalveolar lavaj, beyin omurilik sıvısı trakeal aspirat gibi örnekler kullanıldı. Çalışmaya ≥18 yaş yoğun bakım hastaları dahil edildi. Hastalardan ilk izole edilen suş çalışmaya alınırken aynı hastaya ait mükerrer izolatlar çalışma dışı tutuldu.
Bulgular: Çalışmaya 443 olgu dahil edildi. *Klebsiella* izole edilen örnekler incelendiğinde %31,8'inin (n=141) trakeal aspirat kültürü, %23,7'sinin (n=105) kan, %23,3'ünün (n=103) idrar, %9,0'ının (n=40) balgam ve %12,2'sinin (n=54) diğer örneklerden oluştuğu tespit edilmiştir. *Klebsiella* türlerinin dağılımı incelendiğinde olguların büyük bir kısmını %89,7 (n=397) ile *Klebsiella pneumoniae* oluşturmaktaydı. Sonrasında sırası ile *K. oxytoca* %7 (n=31), *K. ozaenae* %2,9 (n=13), *K. granulomatis* %0,2 (n=1) ve *K. ornithinolytica* %0,2 (n=1) saptanmıştır. Olguların %54,4'ü (n=241) GSBL (+) iken %45,6'sının (n=202) GSBL (-) olduğu tespit edilmiştir. ESBL-pozitif *Klebsiella* enfeksiyonlu hastalarda mortalite %60 iken, ESBL negatif kökenlere bağlılarda %47,5 idi (p=0,008).
Sonuç: Hastanemizde GSBL (+) *Klebsiella* izolatlarına ait antibiyotik direncinin literatürdeki direnç oranlarından daha yüksek olduğu saptanmıştır. Bu direnç sorununun üstesinden gelebilmek için her hastane kendi direnç oranlarını bilmeli ve akılcı antibiyotik kullanım politikaları geliştirmelidir.
Anahtar Kelimeler: Genişlemiş spektrumlu beta-laktamaz, *Klebsiella*, siprofloksasin, kolistin, tigesiklin

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Introduction

Klebsiella is an important genus of the *Enterobacteriaceae* family which causes community-acquired infections as well as nosocomial infections[1]. Present in small amounts in normal flora, *Klebsiella* spp. may cause colonization and subsequent infection in cases of prolonged hospitalization, invasive procedures such as urinary or central venous catheterization, history of prior surgery, or use of broad-spectrum antibiotics[2,3]. It has been known for the last four or five decades that Gram-negative bacteria are more common causes of nosocomial infections[4]. Today, knowing the resistance pattern of the bacterial agent has become more important than knowing whether it is Gram-negative or Gram-positive.

Klebsiella bacteria may develop different mechanisms of antibiotic resistance. Among them, the most common is extended-spectrum beta-lactamase (ESBL) production[5]. Another form is carbapenem resistance[6]. Resistant bacteria lead to prolonged hospitalization, loss of labor, high costs, and high mortality.

Intensive care patients are critical patterns who require early and effective treatment. Therefore, each hospital must be aware of its specific bacterial resistance rates and initiate empirical treatment accordingly. The aim of this study was to determine the resistance profiles of *Klebsiella* bacteria isolated from various sample types in various clinical samples in the intensive care units (ICUs) of our setting and contribute to policies regarding the appropriate use of antibiotics.

Materials and Methods

Resistance rates of *Klebsiella* spp. strains isolated from clinical samples of patients residing in ICUs of the Kahramanmaraş Sütçü İmam University Faculty of Medicine between January 2014 and June 2017 were analysed retrospectively. Blood, urine, bronchoalveolar lavage, tracheal aspirate culture (TAC), cerebrospinal fluid, pleural fluid, peritoneal fluid, drainage fluid, and wound site samples were cultured. Cerebrospinal fluid, pleural fluid, peritoneal fluid, drainage fluid, and wound site samples were analysed within the category of 'others' because they were fewer in number. The study included only patients aged 18 years or older who were treated in ICUs. For patients with multiple isolates, only the first strain isolated was included in the analysis.

Clinical samples received by the microbiology laboratory were inoculated on 5% sheep blood agar (RTA, Turkey) and EMB agar (RTA, Turkey) and incubated at 37 °C for 18-24 hours. Colonies showing Gram-negative bacilli in Gram staining and were identified as oxidase negative, lactose positive, and mucoid producing on culture medium were suspended at a turbidity of 0.5 McFarland. Identification and antibiotic susceptibility tests were done in accordance with "European Committee on Antimicrobial Susceptibility Testing" (EUCAST) recommendations using a Phoenix 100 (Becton Dickinson, USA) system. Extended-spectrum beta-lactamase-producing organisms were identified based on susceptibility to aztreonam, third and fourth generation cephalosporins (cefpodoxime 8 µg/mL, ceftazidime 8 µg/mL) alone and/or in the presence of beta-lactamase inhibitors (ceftriaxone/clavulanic acid 2 µg/mL, cefotaxime/clavulanic acid 2 µg/mL, ceftazidime/clavulanic acid 2 µg/mL). Imipenem, meropenem, and ertapenem minimum inhibitor concentration values were tested and metallo-beta-lactamase producing strains were considered carbapenem-resistant.

Statistical Analysis

SPSS v.17.0 software package (SPSS Inc, Chicago, Illinois, USA) was used in statistical analyses of the data obtained from the study. Continuous data were summarized as mean and standard deviation, while categorical data were expressed as number and percentage. Student's t-test was used in comparisons of continuous variables between independent groups. The chi-square (χ^2) test was used when comparing categorical values between independent groups. Statistical significance level was accepted as $p<0.05$.

Results

The mean age of the 443 patients was 66.0±20.2 years (minimum-maximum, 19-102 years); 56.9% (n=252) were male and 43.1% (191) were female.

Of the samples from which *Klebsiella* was isolated, 31.8% (n=141) were TAC, 23.7% (n=105) were blood, 23.3% (n=103) were urine, 9.0% (n=40) were sputum, and 12.2% (n=54) were other sample types.

The three most common units where *Klebsiella*-positive cultures were performed were the Anesthesia ICU with 56.9% (n=252), the Internal Medicine ICU with 16.9% (n=75), and the Neurology ICU with 10.4% (n=46). Data pertaining to all units are summarized in Table 1.

In terms of the distribution of *Klebsiella* species, *Klebsiella pneumoniae* accounted for the large majority of cases (89.7%, n=397). This was followed by *K. oxytoca* (7%, n=31), *K. ozaenae* (2.9%, n=13), *K. granulomatis* (0.2%, n=1), and *K. ornithinolytica* (0.2%, n=1).

Extended-spectrum beta-lactamase-positive strains accounted for 54.4% (n=241) of the cases, while 45.6% (n=202) were ESBL-negative.

The antibiotic susceptibility rates of the *K. pneumoniae* and *K. oxytoca* strains are presented in Table 2.

The mean duration of hospital stay was 47.04±40.7 days (minimum-maximum, 1-220 days). Hospital stays were slightly longer in ESBL-positive cases (47.65±39.6 days) compared to ESBL-negative cases (46.31±42.0 days), but the difference was not statistically significant (p=0.729).

The mortality rate was 54.4% while the remaining 45.6% of the patients were discharged with full recovery. All deaths occurred at the hospital, on day 42.3±34.7 of hospitalization. The mortality rate was 60.2% among patients with ESBL-positive *Klebsiella* versus 47.5% among patients with ESBL-negative *Klebsiella* (χ^2, p=0.008). In addition, the mortality rate was 55.7% among patients with carbapenem-resistant *Klebsiella* and 53.8% among patients with non-carbapenem-resistant *Klebsiella* (χ^2, p=0.717). The association between culture types and patient mortality is shown in Table 3.

Discussion

Drug resistance in Gram-negative bacteria is a serious global concern. Extended-spectrum beta-lactamases are most often produced by *Escherichia coli* and *Klebsiella* spp., which are members of *Enterobacteriaceae* family[7,8]. Extended-spectrum beta-lactamase-producing bacteria are not only resistant to penicillin, but to many cephalosporins and monobactams as well. They may also develop resistance to other drug groups such as quinolones, tetracyclines, aminoglycosides, and carbapenems[9-11].

While the prevalence of ESBL-producing *Klebsiella* is increasing in Turkey and eastern Europe, it is on a downward trend in

Table 1. Distribution of *Klebsiella* isolates according to hospital unit and sample type [n (%)]

	Blood	Urine	TAC	Sputum	Other*	Total
Anesthesia ICU	77 (30.6)	34 (13.5)	93 (36.9)	27 (10.7)	21 (8.3)	252 (100)
Internal medicine ICU	11 (14.7)	42 (56.0)	6 (8.0)	4 (5.3)	12 (16.0)	75 (100)
General surgery ICU	3 (16.7)	2 (11.1)	1 (5.6)	2 (11.1)	10 (55.6)	18 (100)
Neurology ICU	4 (8.7)	17 (37)	18 (39.1)	1 (2.2)	6 (13.0)	46 (100)
Pulmonary ICU	1 (4.0)	2 (8.0)	18 (72.0)	2 (8.0)	2 (8.0)	25 (100)
Neurosurgery ICU	7 (41.2)	4 (23.5)	4 (23.5)	0 (0)	2 (11.8)	17 (100)
Cardiovascular surgery ICU	0 (0)	0 (0)	1 (50.0)	1 (50.0)	0 (0)	2 (100)
Coronary ICU	2 (25.0)	2 (25.0)	0 (0)	3 (37.5)	1 (12.5)	8 (100)
Total (n)	105	103	141	40	54	443

*Includes cerebrospinal fluid, pleural fluid, peritoneal fluid, drainage fluid, and wound site samples.
TAC: Tracheal aspirate culture, ICU: Intensive care unit

Table 2. Antibiotic susceptibility rates of *K. pneumoniae* and *K. oxytoca* strains

Antibiotic	*K. pneumoniae* [n (%)] n=397			*K. oxytoca* [n (%)] n=31		
	ESBL (+) n=226	ESBL (-) n=171	p*	ESBL (+) n=8	ESBL (-) n=23	p*
Piperacillin/tazobactam	144 (63.7)	80 (46.8)	0.001	5 (62.5)	6 (26.1)	0.064
Ceftriaxone	226 (100)	85 (49.7)	0.000	8 (100)	7 (30.4)	0.001
Cefepime	226 (100)	78 (45.6)	0.000	8 (100)	7 (30.4)	0.001
Ceftazidime	226 (100)	83 (48.5)	0.000	8 (100)	5 (21.7)	0.000
Gentamicin	125 (55.3)	70 (40.9)	0.005	1 (12.5)	5 (21.7)	0.569
Amikacin	43 (19.0)	32 (18.7)	0.937	0 (0)	2 (8.7)	0.389
Ciprofloxacin	167 (73.9)	74 (43.3)	0.000	3 (37.5)	4 (17.4)	0.241
Ertapenem	91 (40.3)	53 (31.0)	0.057	1 (12.5)	4 (17.4)	0.746
Imipenem	67 (29.7)	44 (25.7)	0.389	0 (0)	3 (13.0)	0.282
Meropenem	69 (30.5)	43 (25.1)	0.238	0 (0)	3 (13.0)	0.282
TMP-SMX	173 (76.5)	85 (49.7)	0.000	7 (87.5)	5 (21.7)	0.001
Tigecycline	68 (30.1)	18 (10.5)	0.000	0 (0)	1 (4.3)	0.549
Colistin	21 (9.3)	9 (5.30)	0.133	0 (0)	0 (0)	-

*Chi-square test was used for intergroup comparisons. ESBL: Extended-spectrum beta-lactamase, TMP-SMX: Trimetoprim-sulfamethoxazole, p<0.05 was considered significant

Table 3. The relationship between culture type and mortality of cases [n (%)]

Culture type	Outcome		Total
	Discharged	Death	
Blood	42 (40.0)	63 (60.0)	105 (100)
Urine	58 (56.3)	45 (43.7)	103 (100)
Tracheal aspirate culture	58 (41.1)	83 (58.9)	141 (100)
Sputum	16 (40.0)	24 (60.0)	40 (100)
Other*	28 (51.9)	26 (48.1)	54 (100)

*Includes cerebrospinal fluid, pleural fluid, peritoneal fluid, drainage fluid, and wound site samples

western Europe. Antimicrobial resistance patterns may vary between regions, hospitals, and even units within the same hospital. Therefore, each hospital must know its specific antimicrobial resistance profile. Rates of ESBL-producing *Klebsiella* vary widely in the literature, too. Temiz et al.[12] detected ESBL-producing *Klebsiella* at rates of 65.1% in samples obtained from ICUs, inpatient units, and outpatient units (68.3% in *K. pneumoniae* isolates and 10.7% in *K. oxytoca* isolates). Parlak et al.[13] reported ESBL-positive *K. pneumoniae* in 67% of samples obtained from inpatient units and the ICU. Güdücüoğlu et al.[14] reported this rate to be 49%. In the HITIT-2 study involving 6 centers in Turkey, the prevalence of ESBL-producing *K. pneumoniae* was 32.3%, with only 16.2% in ICUs[15]. The International Nosocomial Infection Control Consortium report for Turkey summarized data from 19 hospitals between 2003 and 2012[16]. It was determined in the study that ceftriaxone- and ceftazidime-resistant *K. pneumoniae* strains accounted for 55.7% of central catheter-related bloodstream infections, 46.3% of ventilator-associated pneumonia, and 50.0% of catheter-related urinary tract infections in the ICU. The ESBL-positive *Klebsiella* ratio in our study was 54.4%.

Beta-lactam/beta-lactamase inhibitors may be preferred for infections caused by ESBL-producing bacteria. In a study by Kuzucu et al.[17], 68% of ESBL-producing *K. pneumoniae* isolates were found to be piperacillin/tazobactam resistant. This rate was 32% in another study[18], and was 22.3% in the HITIT-2 study[15]. The results of our study were similar to those of Kuzucu et al.[17]. Resistance to beta-lactam/beta-lactamase inhibitors is increasing.

In severe/systemic infections caused by ESBL-producing *Klebsiella* spp., drugs should be chosen based on susceptibility patterns. In their 2005-2006 analysis, Güdücüoğlu et al.[14] observed no carbapenem resistance among ESBL-positive *K. pneumoniae* isolates. There was also no resistance to carbapenem in three of the centers (Akdeniz, Hacettepe, and Dokuz Eylül Universities) involved in the multicenter HITIT-2 study conducted in 2004-2005. However, carbapenem resistance was detected at a rate of 1.3% in the other three centers[15]. More recently, a study by Saygılı Pekintürk and Akgüneş[19] reported imipenem resistance rates of 2%, 7%, 0%, 38%, and 50% respectively in the years 2011-2015. Although numerous previous studies demonstrated carbapenem susceptibility of ESBL-positive *Klebsiella* isolates, current evidence shows that carbapenem resistance is becoming more prevalent among ESBL-positive *Klebsiella* isolates. We also found high resistance to carbapenems in the ESBL-positive *K. pneumoniae* strains in our study, with rates of 40.3% for ertapenem, 30.5% for meropenem, and 29.7% for imipenem.

In ESBL-positive infections, drugs in the quinolone group may be used as an alternative to beta-lactam/beta-lactamase inhibitors or carbapenems[20]. However, previous studies have generally reported high quinolone resistance rates. Parlak et al.[13] determined ciprofloxacin resistance rates of 11%, 8%, 13%, 35%, and 36% in ESBL-positive *K. pneumoniae* isolates between 2006 and 2010. In another study, the average ciprofloxacin resistance in the years 2011-2015 was 46% (no data for 2011; 48%, 24%, 52%, and 58% respectively for the remaining years)[19]. In another study by Nepal et al.[21], ciprofloxacin resistance of ESBL-positive *K. pneumoniae* isolates was 46.2%. In our study, the rate of ciprofloxacin resistance in ESBL-positive *K. pneumoniae* isolates was much higher than the rates reported in the literature.

We detected higher rates of antibiotic resistance in the ESBL-positive *Klebsiella* isolates in our study compared to resistance rates in the literature. This may be attributed to the fact that all of the patients included in this study were ICU patients.

Conclusion

In order to overcome the problem of resistance in ESBL-positive *Klebsiella* spp., each hospital should be aware of its specific resistance rates and the infection control committee should conduct regular surveillance. Units with high resistance rates should be evaluated for deficiencies, and remedial measures and training should be implemented. Furthermore, cultures and antibiotic susceptibility tests should be utilized more diligently before initiating antibiotics. Policies for the rational use of antibiotics should be established in light of this information in order to reduce resistance rates.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.N., S.A., Design: S.N., S.A., A.R.Ş., Data Collection or Processing: B.T., S.N., Analysis or Interpretation: S.N., A.R.Ş.,

Literature Search: S.N., A.R.Ş., Writing: S.N., S.A.

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