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Original Article

Evaluation of antibiotic resistance patterns of Klebsiella isolates: Five-year observation

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Abstract

Aim: *Klebsiella spp.* is a gram-negative rod, having many virulence factors such as capsule polysaccharides, adhesins, and determinants for iron acquisition. In this study, we aimed to determine the sub-species of *Klebsiella spp.* and their antibiotic resistance profiles isolated from a tertiary hospital in a five-year period.

Material and Methods: The antibiotic resistance profiles of *Klebsiella spp.* isolated from various clinical specimens of patients between January 2014 and December 2018 were retrospectively reviewed.

Results: In a total of 4506 isolates were investigated. Among those isolates, 2,254 were obtained from females and 2.252 were obtained from males. The mean age of the patients was 47.71±29.56 while the median age was 56 years. On the other hand, 2.150 (47.7%) of the isolates were obtained from hospitalized patients, while 2356 (52.3%) were obtained from outpatients. Among those isolates, 1.859 (41.3%) were ESBL positive and along with ESBL positive isolates, 802 were obtained from females and 1,057 were obtained from males and ESBL positivity was significantly more common in males (p:0.001). Moreover, ESBL positivity was significantly more common in patients older than 18 years of age compared with the patients younger than 18 years of age. Ciprofloxacin resistance was reaching 67.4% and Ertapenem resistance was as high as 39.1% in ESBL positive Klebsiella spp.

Conclusion: In conclusion, ESBL positive and carbapenem resistant *Klebsiella spp.* strains are increasing. Multidrug resistant *Klebsiella spp.* strains may cause severe infections increasing mortality. In that aspect, the antibiotic resistance profile should be identified clearly and further studies regarding the preventive measures should be planned.

Keywords: *Klebsiella*; ESBL; antibiotic resistance; carbapenem.

INTRODUCTION

Klebsiella spp. is a gram-negative rod, having many virulence factors such as capsule polysaccharides, adhesins, and determinants for iron acquisition. Although *Klebsiella spp.* is a well-known opportunistic pathogen, it may cause infections in immunocompromised patients (1). Elevated resistance rates and therefore complicated treatment responses have been reported regarding the *Klebsiella spp.* infections, in all over the world (2,3). There are many antibiotic resistance mechanisms defined for *Klebsiella spp.,* including the production of Extended-spectrum beta-lactamases (ESBL) and acquisition of carbapenemases (4-6).

Especially carbapenem-resistant Klebsiella pneumoniae creates a severe risk factor for hospitalized patients increasing mortality, since the treatment alternatives are limited (7). Moreover, increased resistance rates have been shown to be associated with increased mortality (8).

In this study, we aimed to determine the sub-species of Klebsiella spp. and their antibiotic resistance profiles isolated from a tertiary hospital in a five-year period

MATERIAL and METHODS

This study was performed in Health Sciences University Okmeydanı Education and Research Hospital, Medical Microbiology Department. The antibiotic resistance profiles of *Klebsiella spp.* isolated from various clinical specimens of patients between January 2014 and December 2018 were retrospectively reviewed. Only one strain of patients with reproduction in more than one sample was included in the study. Repeated samples were

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excluded from the study and different samples of the same patient were not included in determining susceptibility rates. Demographic features of the infected patients were also investigated.

Blood cultures were assayed on a fully automated blood culture device, BACTEC 9240 (Becton Dickinson, Diagnostic Instrument System, Sparks, USA). The passage of the detected vials in the automated blood culture device to the MacConkey, chocolate and 5% sheep blood agar was performed. Cultures of urine, tissue-abscess, tracheal aspirate, catheter tip, sterile fluids were evaluated according to the material and using standard microbiological techniques according to the procedure (9).

The Phoenix ™ 100 identified Colonies thought to be effective, especially for inpatients, at the species level (Becton Dickinson, Diagnostic Instrument System, Sparks, USA) automated system and antibiotic susceptibilities were studied. Antibiotic susceptibilities of isolated Klebsiella spp. were determined by Kirby-Bauer disc diffusion method. Antibiotic susceptibilities were evaluated in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI) in January 2014-December 2015 (10), and of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in January 2016- December 2018 (9).

Statistical Analyses

Statistical analyses were performed with SPSS 19.0 (IBM Company, Chicago, IL) software. The conformity of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov test. Descriptive statistics (number, percentage, mean and median) were performed. Comparison of descriptive data between groups was performed with cross tables and chi square test. One-way ANOVA test was used to compare the antibiotic resistance rates of different *Klebsiella spp.* Results with P-value < 0.05 were considered statistically significant.

RESULTS

In a total of 4,506 isolates were investigated. Among those isolates, 2,254 were obtained from females and 2252 were obtained from males. The mean age of the patients was 47.71±29.56 while the median age was 56 (range:0-119) years. On the other hand, 2.150 (47.7%) of the isolates were obtained from hospitalized patients, while 2.356 (52.3%) were obtained from outpatients.

Table 1. *Types of Klebsiella spp.* **determined in isolates in time**

Years	*K. oxytoca (n:188)*	*K.pneumoniae (n:3024)*	*Klebsiella spp. (n:1294)*	Total
2014	24(3.6%)	361 (54.9%)	273 (41.5%)	658
2015	14 (1.7%)	346 (42.2%)	462 (56.1%)	822
2016	32 (3.6%)	535 (60.0%)	324 (36.4%)	891
2017	58 (5.7%)	803 (79.0%)	155 (15.3%)	1.016
2018	60 (5.4%)	979 (87.6%)	80 (7.1%)	1.119

Table 2. Types of *Klebsiella spp.* determined in isolates of different materials

Sample type	*K. oxytoca (n:188)*	*K. pneumoniae (n:3024)*	*Klebsiella spp. (n:1294)*	Total
Urine	117	1.761	1.226	3.105
Blood	22	649	17	688
Rectal swap	1	177	0	178
Wound swap	21	124	33	177
Trachealaspirate	4	94	0	98
Abscess	0	40	5	45
Sputum	1	24	1	26
Pharyngeal swap	2	9	0	11
CSF	0	8	0	8
Tissue	5	39	3	47
Catheter	3	68	2	73
Others	12	31	7	50

CSF: Cerebrospinal fluid

Table 3. Distribution of ESBL positivity among different genders, hospitalized patients and outpatients, and among Klebsiella spp

	ESBL (+)	ESBL (-)	p
Female (n:2.254)	802 (35.6%)	1.452 (64.4%)	0.001
Male (n:2.252)	1.057 (46.9%)	1.195 (53.1%)	
Age ≤18 years (n:1.137)	3.76 (33.1%)	761 (66.9%)	0.001
Age > 18 years (n:3.456)	1.483 (42.9%)	1.886 (54.6%)	
Hospitalized (n:2.150)	1.060 (49.3%)	1.090 (50.7%)	0.001
Outpatient (n:2.356)	799 (33.9%)	1.557 (66.1%)	
K. oxytoca (n:188)	51 (27.1%)	137 (72.9%)	0.001
K. pneumoniae (3.024)	1.386 (45.8%)	1.639 (54.2%)	
Klebsiella spp. (n:1.294)	422 (32.6%)	871 (67.4%)	

Types of *Klebsiella spp.* determined in time are summarized in Table 1. Regarding these findings, there were significant increases in *Klebsiella pneumonia* isolates in time.

Klebsiella spp. were most commonly producing urinary tract infections followed by blood stream infections (Table 2).

Among those isolates, 1.859 (41.3%) were ESBL positive and along with ESBL positive isolates, 802 were obtained

Table 4. Antibiotic resistance profile

	K. oxytoca (n:188)	*K. pneumoniae* (n:3024)	*Klebsiella spp.* (n:1294)	p
Amikacin	13 (6.9%)	413 (13.7%)	55 (4.3%)	0.001
Gentamicin	38 (20.2%)	1.280 (42.3%)	303 (23.4%)	0.001
Amoxicillin/ Clavulanic Acid	82 (43.6 %)	1.737 (57.5%)	307 (23.8%)	0.001
Piperacillin-Tazobactam	60 (31.9%)	1.592 (52.6%)	203 (15.7%)	0.001
Cefotaxime	81 (43.0%)	2.161 (77.0%)	559 (43.1%)	0.001
Ceftriaxone	81 (43.0%)	2.161 (77.0%)	559 (43.1%)	0.001
Ceftazidime	56 (29.8%)	2.024 (66.9%)	498 (38.5%)	0.001
Cefepime	51 (29.8%)	1.851 (61.2%)	373 (28.8%)	0.001
Ciprofloxacin	45 (23.9%)	1.738 (57.5%)	389 (30.1%)	0.001
Levofloxacin	39 (20.7%)	1.572 (52.0%)	318 (24.5%)	0.001
Ertapenem	51 (27.1%)	1.386 (45.8%)	88 (6.8%)	0.001
Meropenem	6 (3.2%)	828 (27.4%)	16 (1.2%)	0.001
Imipenem	4 (2.1%)	822 (27.2%)	13 (1.0%)	0.001
Trimethoprime-Sulfamethoxazole	50 (26.6%)	1.702 (56.3%)	450 (34.8%)	0.001
Fosfomisin	21 (11.2%)	290 (9.6%)	141 (11.4%)	0.001
Colistin	15 (8.0%)	620 (20.5%)	11 (0.9%)	0.001
Nitrofurantoin	3 (1.6%)	141 (4.7%)	78 (6.0%)	0.001
Tigecycline	6 (3.2%)	138 (4.6%)	2 (0.2%)	0.001

from females and 1.057 were obtained from males and ESBL positivity was significantly more common in males (p:0.001). The distribution of isolates obtained from hospitalized patients or from outpatients, regarding their ESBL positivity is summarized in Table 3. Approximately half of the isolates obtained from the hospitalized patients were ESBL positive, while in outpatient clinics, about 1/3 of the isolates were ESBL positive. Moreover, ESBL positivity was significantly more common in patients older than 18 years of age compared with the patients younger than 18 years of age.

ESBL positivity was investigated in time. In 2014, the resistance rate was 28.0%, while in 2015, 2016 and 2017 ESBL positivity was 33.3%, 37.8% and 44.0%, respectively and in 2018 ESBL positivity was 55.2%. There was a significant increase in time, regarding the ESBL positivity (p<0.001; Figure 1).

Table 5. Carbapenem resistance in time

	Ertapenem	Imipenem	Meropenem
2014 (n:658)	180 (27.4%)	116 (17.6%)	116 (17.6%)
2015 (n:822)	241 (29.3%)	161 (19.6%)	161 (19.6%)
2016 (n: 891)	329 (36.9%)	190 (21.3%)	194 (21.8%)
2017 (n: 1016)	382 (37.6%)	197 (19.4%)	201 (19.8%)
2018 (n: 1118)	393 (35.2%)	175 (15.6%)	178 (15.9%)
p	0.001	0.224	0.221

Table 6. Carbapenem and Quinolone resistance in ESBL positive Klebsiella spp.

Antibiotic	Resistance rate in ESBL(+) *Klebsiella spp.*
Ertapenem	39.1%
Imipenem	14.3%
Meropenem	19.8%
Ciprofloxacin	67.4%
Levofloxacin	43.0%

Antibiotic resistance profile of different *Klebsiella spp.* are summarized in Table 4. Amoxicillin-Clavulonate, Cefepime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Trimethoprime -Sulfamethoxazole and Piperacillin- Tazobactam resistances were very high in *K. pneumoniae.*

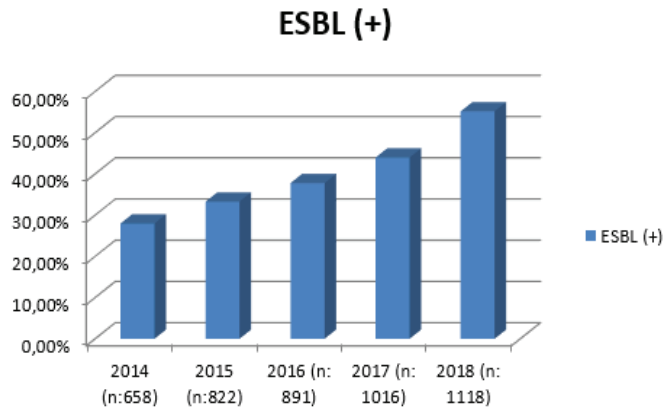

Figure 1. ESBL positivity in time

Third generation cephalosporin resistance was common in all three groups; the resistance rates in *K. pneumonia, Klebsiella spp.,* and *K. oxytoca* were 77%, 43,1%, 43%, respectively. The colistin resistance was highest in *K. pneumoniae* with a rate of 20%. The sensitivity of amikacin, from the aminoglycoside group, was higher in all pathogen groups compared to other antibiotic groups. 68.9% of the materials examined were urine samples. Therefore, the resistance rates of nitrofurantoin used in the treatment of urinary tract infections were 4.7%, 6.0%, 1.6% in K. pneumoniae *Klebsiella spp.,* and K. oxytoca, respectively; while Phosphomycin resistance rates were 9.6%, 11.4%, 11.2% in *K. pneumoniae, Klebsiella spp.*, and *K. oxytoca,* respectively. While the resistant isolates were

not detected in 2014 and 2015; in 2016, 2017 and 2018, it was found 32, 36 and 38 respectively.

Carbapenem resistance in these 5 years of period is summarized in Table 5 and Figure 2. There was an increase in Ertapenem resistance in time but not in Imipenem or Meropenem resistance rates. Imipenem and Meropenem resistance rates were very similar with each other.

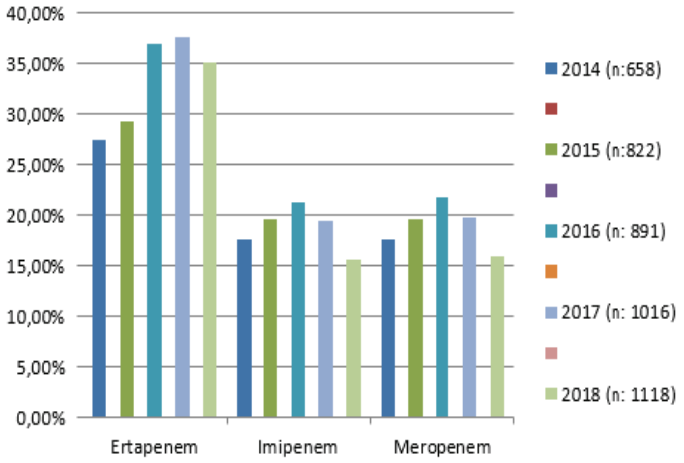

Figure 2. Carbapenem resistance in time

In Table 6, Carbapenem and Quinolone resistance rates in ESBL positive Klebsiella spp. are summarized. Ciprofloxacin resistance was reaching 67.4% and Ertapenem resistance was as high as 39.1% in this group.

DISCUSSION

In this study, we analyzed the epidemiologic features of *Klebsiella spp*. isolates in a tertiary center in a time period of approximately 5 years and we determined that; 1) there was an increase in *K. pnomoniae* subspecies in time; 2) ESBL positivity was also increasing in time, 3) ESBL positivity was more common in males, in hospitalized patients and in patients older than 18 years of age; 4) More than half of the *K. pnomoniae* isolates were resistant to many antibiotics including cephalosporins, Ciprofloxacin, Trimethoprime -Sulfamethoxazole and Piperacillin- Tazobactam; 5) There was an increase in Ertapenem resistance in time reaching 35%; 6) Ertapenem (39%) and Ciprofloxacin (67%) resistances were very high in ESBL positive *Klebsiella spp.*. 7) Nearly the only option for the treatment of carbapenem-resistant K. pneumoniae is colistin which has 20% of resistance.

Empiric treatment may be required in many infections of hospitalized patients and outpatients. *Klebsiella spp.* is an important family causing many diverse infections. In that aspect updates antibiotic resistance profile of these microorganisms should be known clearly by the clinicians (11,12). Zanichelli et al (13) reported the co-trimoxazole and quinolone resistance as about 11-12% in *K. pneumonia* but nitrofurantoin and fosfomycin resistances were higher. However, Fosfomycin resistance decreased in time but quinolone resistance increased.

In this study, Amoxicillin-Clavulonate, Cefepime, Ceftazidime, Ceftriaxone, Cefotaxime Ciprofloxacin, Trimethoprime -Sulfamethoxazole and Piperacillin-Tazobactam resistances were very high (exceeding 50%) in *K. pnomoniae*. The most common resistance rates in *K. oxytoca* were found in Amoxicillin/ Clavulanic Acid, Ceftriaxone, and Cefotaxime To be high level of the third generation cephalosporin resistance in all *klebsiella* species, it indicates that the bacteria develops resistance by different mechanisms except ESBL production. Co-trimaxazole resistance was about 56.3% in *K. pneumoniae,* and 34.8% in *Klebsiella sp*p. Ciprofloxacin resistance was as high as 57.5% in *K. pneumoniae.* The reason of the low resistance of colistin and carbapenem in *Klebsiella spp.* may be due to the higher number of outpatients in this group.

ESBLs are the important pathogenic mechanisms of *Klebsiella* family. ESBLs cause resistance to penicillins, cephalosporins and aztreonam. These enzymes are plasmid-encoded and if present, may result in severe issues in especially nosocomially-acquired infections (14). Different prevalence rates of ESBL-producing strains of *K. pneumoniae* ranging between 23% and 85% are reported in previous literature (15,16). Gajdacs et al (17) reported the ESBL positivity ratio as 23.22-34.22% from outpatient and 10.89-36.06% from inpatient samples for *Klebsiella spp.*, respectively. Koksal et al (18) reported ESBL positivity in approximately 47% of *Klebsiella spp.* in patients with community-acquired urinary tract infections. Being over the age of sixty, history of urinary tract surgery or catheterization, hospitalizations in last 1 year and antibiotic usage in the last 3 months were defined as the risk factors for the ESBL positivity. We determined the ESBL positivity as 41.3% that was significantly more common in males, in hospitalized patients and in patients older than 18 years of age. Moreover, we also determined that in ESBL positive *Klebsiella* isolates, Ciprofloxacin resistance was reaching 67.4% and Ertapenem resistance was as high as 39.1% in this group.

Due to the increased ESBL prevalence, increase in carbapenem prescriptions, resulted in the emergence of ertapenem-resistant strains in last decades (19). Recently, in Italy, the European Antimicrobial Resistance Surveillance Network (EARS-Net) reported ESBL positivity as 55.9% in *K. pneumoniae* and carbapenem resistance as 33.5% (20). Carbapenem-resistant *K. pneumoniae* strains were reported to be increased from 4.76% in 2013 to 16.00% in 2017 in intensive care units. We also determined an increase in Ertapenem resistance in time reaching 35% (21).

In all over the world, many studies are still being investigated to overcome the antibiotic resistance issue in *Klebsiella spp.* Vega et al reported that 36.3% (1465/4032) of *K. pneumoniae* isolates, 16.4% (67/409) of *K. oxytoca* isolates were extended-spectrum β-lactamase (ESBL) producers and among these isolates susceptibility was highest to tigecycline and meropenem (22). In carbapenem resistant *Klebsiella spp.,* the best choice was reported as tigecycline (23). We also determined the tigecycline

resistance as 4.6% in *K. pneumoniae* that was not high.

The most commonly isolated agent in carbapenem-resistant bacterial infections is *K. pneumoniae*. According to the global resistance report published by the World Health Organization (WHO) in 2014, carbapenem-resistant K. pneumoniae isolates were reported to be over 50% and this rate was emphasized to be very critical (24). According to the report of WHO CAESAR in 2018; in Turkey, ertapenem resistance in *K. pneumoniae* isolates isolated in blood and cerebrospinal fluid sample was 43%, and imipenem/meropenem resistance was reported as 38% (25). Because of the rapid increase of carbapenem-resistant enteric bacteria in recent years, the use of colistin in these infections has again come into question as to the only treatment choice (26). In a study by Rojas et al. (27), the colistin resistance in 246 patients infected or colonized with *K. pneumoniae* between 2011 and 2014 was detected as 13% and colistin-resistant *K. pneumoniae* infections were associated with high mortality. Arabacı et al. (28) found 60% colistin resistance in 57 carbapenem-resistant *K. pneumoniae* isolates. In this present study, it was found 20% colistin resistance in *K. pneumoniae* isolates. This result may show that treatment options in carbapenem-resistant isolates are further reduced.

The main power of this study was the high number of isolates. There are also some limitations that should be discussed. This is a retrospective study reporting the results of a single study. Secondly, we did not analyze the genotypic alterations in these isolates in time associated with antibiotic resistance.

CONCLUSION

In conclusion, ESBL positive and carbapenem resistant *Klebsiella spp.* strains are increasing. Multidrug resistant *Klebsiella spp.* strains may cause severe infections increasing mortality. In that aspect, the antibiotic resistance profile should be identified clearly and further studies regarding the preventive measures should be planned.

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