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Antimicrobial resistance profiles of Enterobacter cloacae and Klebsiella aerogenes a tertiary hospital in Turkey: A five-years study

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ABSTRACT

Objective: Enterobacter cloacae and *Klebsiella aerogenes* species have multiple drug resistance and antibiotic resistance is a growing problem regarding to treating infections.

Objective: The aim of this study was to determine and evaluate the antimicrobial resistance profiles of E. cloacae and K. aerogenes isolated from various clinical samples in our laboratory, retrospectively.

Material and Methods: Totally 223 patients who applied to Karabuk University Training and Research Hospital microbiology laboratory between October2016-December2020 were included in this study. Conventional methods and automated systems were used for the identification and antibiotic susceptibilities of strains. Antibiotic susceptibility results were evaluated as per the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.

Results: Total of 223 clinical samples (urine 68.6%, blood 12.6%, endotracheal aspirate 7.2%, wound 4.9%, sputum 3.6%, bronchoalveolar lavage fluid 2.7%, and ear fluid 0.4%) obtained from 223 patients; 119 (53%) females and 104 (47%) females, were analysed. The identified species were E. cloacae (132 strains, 59.2%) and *K. aerogenes* (91 strains, 40.8%). The *Enterobacter cloacae* and *Klebsiella aerogenes* positivity was detected as 30(13.4%) and 20(9.0%) in the samples. The highest resistance was found against cefixime at a rate of 60%; the lowest resistance was against amikacin, meropenem and imipenem ranged between 3% and 4% in both *E. cloacae* and *K. aerogenes* strains.

Conclusions: Amikacin, imipenem and meropenem were the most effective antibiotics against E. cloacae and K. aerogenes. We may prefer TMP-SMX and ciprofloxacin, as oral antibiotic agents in the treatment of E. cloacae/K. aerogenes infections. Amikacin, gentamicin and carbapenems may be the first choice for parenteral antibiotics therapy.

Keywords: Antibiotic resistance, *Enterobacter cloacae*, ESKAPE pathogen, *Klebsiella aerogenes*

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INTRODUCTION

Enterobacter cloacae and *Klebsiella aerogenes* (formerly described Enterobacter aerogenes) are a facultative anaerobe, gram-negative rods, which include to the Enterobacterales family. In recently, twenty-two species have been in the Enterobacter genus (*E. aerogenes, E. amnigenus, E. asburiae, E. arachidis, E. carcinogenus, E. cloacae, E. cowanii, E. dissolvans, E. gergoviae, E. helveticus, E. hormaechei, E. kobei, E. ludwigii, E. mori, E. nimipressuralis, E. oryzae, E. pulveris, E. pyrinus, E. radicincitans, E. soli, E. taylorae, and E. turicensis*). Among these species, seven are called as "E. cloacae complex" (*E. cloacae, E. asburiae, E. hormaechei, E. kobei, E. ludwigii, E. mori, and E. nimipressuralis*) (**1,2**). Currently, whole genome sequence based comparative bacterial phylogenetic analyses of *E. aerogenes* demonstrated that *E. aerogenes* is more closely related to *Klebsiella* pneumoniae than to the Enterobacter species. Then, these bacteria formerly named as *E. aerogenes* was called as *Klebsiella aerogenes* (**3**).

E. cloacae and K. aerogenes are members of the respiratory tract and gastrointestinal microbiota of humans and often isolates as opportunistic pathogens in nosocomial infections, especially in neonates, immunocompromised patients and hospitalized in intensive care units (**1,3**).

Enterobacter cloacae cause neonatal meningitis, bacteraemia, lower respiratory tract infections, skin and soft tissue infections, and urinary tract infections. Enterobacter species are members of the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species*), which are described as the leading cause of resistant nosocomial infections (**1, 2**). *E. cloacae* and *K. aerogenes* associated with the contaminations caused by blood products, intravenous injection fluids, probes, catheters, respiratory therapy equipment, and colonized hands of healthcare workers. Invasive procedures, such as catheterization and intubation and a long-term duration of hospitalization which are frequently found in an intensive care unit (ICU), represent a main source of Enterobacter infection (**3-5**).

Antibiotic resistance is a growing problem regarding to treating Enterobacter infections. Enterobacter species (spp.) have multidrug resistance by means of porine loss, efflux system activation, AmpC cephalosporinase and metallo-beta-lactamase enzyme systems (**6**). The main mechanism of antimicrobial resistance in Enterobacter species is presence of beta-lactamases. They can hydrolyze the beta-lactam ring of penicillin and cephalosporins (**6**). Carbapenems are to be the most effective agent to treatments of multidrug-resistant Enterobacter infections. However, carbapenem-resistant Enterobacter species (CRE) and Extended-Spectrum beta-lactamase (ESBL) have been reported to cause serious nosocomial outbreaks in different countries with a high mortality rate (**7-10**)..

The World Health Organization announced a list of antibiotic-resistant bacteria in 2017, CRE was in the critical priority group for an urgent need to develop new antibiotics (**4**). Though bacterial comparative phylogenetics has demonstrated that K. aerogenes and Enterobacter species belong to different phylogenetic groups, the clinical impact of these genetic differences is unknown. The prevalence, clinical risk factors, antibiotic susceptibility patterns, and patient outcomes have not yet been determined since renaming K. aerogenes.

The aim of this study was to determine and evaluate the antimicrobial resistance profiles of *E. cloacae* and *K. aerogenes* isolated from various clinical samples in our laboratory between 2016-2020 retrospectively.

MATERIAL and METHODS

In this cross-sectional study, antibiotic susceptibility results of 132 E. cloacae and 91 K. aerogenes strains obtained from outpatient or inpatient treated in Karabuk University Training and Research Hospital between January 2016- December 2020, five years period, were included. These results were obtained from the laboratory information system. The other bacteria's antibiotic susceptibility test results and repeated patient results were excluded from this study.

The identification and antibiotic susceptibility of strains were determined with the BD-Phoenix 100 (Becton-Dickinson, Sparks, MD, USA) fully automated system. Antibiotic susceptibility test results were interpreted as per the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (**11**).

Escherichia coli ATCC 25922 strains were used for quality control. The production of the extended-spectrum beta-lactamase (ESBL) enzyme was detected using the combined disk diffusion method (**11**).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS for IBM-PC, release 20.0; SPSS Inc., USA). The descriptive statistics were stated as the number, percentage, and median value. The Colmogorov- Smirnov test was used as normality test. The Mann – Whitney U test and Fisher's exact test were used to evaluate the data, and P-value $\leqslant$ 0.05 was considered statistically significant.

Ethical Review of the Proposal and the Consent: The ethics approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Karabuk University (No: 2021/502).

RESULTS

Among 223 patients, 119 (53%) were female and 104 (47%) were males. The median age of the patients was 57 (0-96) years. The numbers and age ranges of patients included in the study are shown in Table 1.

In our study, a total of 223 clinical specimens were examined over five years' time (2016-2020). The most common samples were urine (153 samples, 68.6%), blood (28 samples, 12.6%), ETA (16 samples, 7.2%). Wound (11 samples, 4.9%), sputum (8 samples, 3.6%), BAL (6 samples, 2.7%) and one ear fluid swab (0.4%) were also analyzed. The 132 of 223 (59.2%) strains were *E. cloacae* whereas 91 of them (40.8 %) were *K. aerogenes*. The distribution of the samples according to the *E. cloacae* and *K. aerogenes* positivity is shown in Table 2.

About 52% (n=116) of the strains were isolated from outpatients while 48% (n=107) were isolated from clinical or intensive care patients. Among outpatients, *E. cloacae* and *K. aerogenes* positivity were 53.4% (62/116) and 46.6% (54/116), respectively. Among clinics, intensive care patients *E. cloacae* and *K. aerogenes* positivity were 65.4% (70/107) and 34.6% (37/107), respectively. When the distribution of the *E. cloacae* and *K. aerogenes* positivity was examined according to clinics (outpatients or clinical or intensive care units), *E. cloacae* positivity was higher but there was not statistically significant (p>0.05).

Enterobacter cloacae and *K. aerogenes* positivity rates are evaluated according to the clinics, where the samples were sent. The most frequently *E. cloacae* and *K. aerogenes* positivity was detected in 30 (13.4%) and 20 (9.0%) of the samples from the pediatric services, in 35 (15.7%) and 23 (10.3%) from an intensive care unit, in 25 (11.2%) and 25 (11.2%) of the samples from urology service, respectively.

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When the distribution of the *E. cloacae* and *K. aerogenes* positivity was examined according to clinics, there was no statistically significant (P >0.05). The distribution of samples according to clinics is shown in Table 3.

Antibiotic susceptibility test was performed on all the samples with *E. cloacae* and *K. aerogenes* growth. Amikacin was found to be the most effective antibiotic against E. cloacae and K. aerogenes.

The highest resistance was found against cefixime as 60% and the lowest resistance was against amikacin, meropenem and imipenem ranged between 3% and 4% in both *E. cloacae* and *K. aerogenes* strains. Fosfomycin resistance rates were 27% among *E. cloacae* and 16% among *K. aerogenes* (P <0.05). The production of ESBL in *E. cloacae* strains was higher than *K. aerogenes* strains. ESBL rates were 26% among *E. cloacae* and 15% among *K. aerogenes*. It was statistically significant (P =0.03). Antibiotic susceptibility test results of *E. cloacae* and *K. aerogenes* strains are shown in Table 4.

Table 1: The gender and age of the patients

	Number of Patients	Median (Min.-Max)	Mean±SD
Female	119	51 (0-96)	47.8±33.0
Male	104	58 (0-95)	46.5±33.2
TOTAL	223	57 (0-96)	47.2±33.0

SD: Standart deviation Min: Minimum, Max: Maximum

Table 2: The distribution of the samples according to the E. cloacae and K. aerogenes positivity

Sample	*Enterobacter cloacae* n (%)	*Klebsiella aerogenes* n (%)	Total n (%)
Urine	86 (38.6%)	67 (30%)	153 (68.6%)
Blood	18 (8.0%)	10 (4.5%)	28 (12.6%)
ETA	9 (4.0%)	7 (3.1%)	16 (7.2%)
Wound	8 (3.6%)	3 (1.4%)	11 (4.9%)
Sputum	5 (2.3%)	3 (1.4%)	8 (3.6%)
BAL	5 (2.3%)	1 (0.4%)	6 (2.7%)
Ear fluid	1 (0.4%)	-	1 (0.4%)
TOTAL	132 (59.2%)	91 (40.8%)	223 (100%)

Table 3: The distribution of samples according to clinics

Clinics	*E. cloacae* n (%)	*K. aerogenes* n (%)	Total n (%)
Intensive care	35 (15.7%)	23 (10.3%)	58 (26.0%)
Pediatric	33 (14.7%)	22 (9.9%)	55 (24.6%)
Urology	25 (11.2%)	25 (11.2%)	50 (22.4%)
Internal medicine	11 (4.9%)	9 (4.0%)	20 (9.0%)
Chest diseases	6 (2.7%)	2 (0.9%)	8 (3.6%)
Palliative care	5 (2.2%)	3 (1.3%)	8 (3.6%)
Gyneacology	4 (4.0%)	3 3 (1.3%)	7 (3.1%)
Neurology	4 (4.0%)	-	4 (4.0%)
Infectious diseases	3 (1.3%)	2 (0.9%)	5 (2.2%)
Neurosurgery	2 (0.9%)	-	2 (0.9%)
Oncology	1 (0.4%)	1 (0.4%)	2 (0.9%)
General surgery	1 (0.4%)	1 (0.4%)	2 (0.9%)
Cardiovascular surgery	1 (0.4%)	-	1 (0.4%)
Otorhinolaryngology	1 (0.4%)	-	1 (0.4%)
TOTAL	132 (59.2%)	91 (40.8%)	223 (100%)

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Table 4: Antibiotic susceptibilities of E. cloacae and K. aerogenes strains [(resistance rate %) number of resistant strains/ numbers of total strains]

Antibiotics	Enterobacter cloacae n (%)	Klebsiella aerogenes n (%)	Total n (%)	P value
CFM	60 (63/104)	61 (48/80)	60 (111/184)	0.81
CAZ	29 (39/132)	22 (20/91)	26 (59/223)	0.61
FOS	**27 (23/86)**	**16 (10/62)**	**29 (43/148)**	**0.03***
ESBL	**26 (34/132)**	**15 (14/91)**	**22 (48/223)**	**0.03***
TZP	26 (34/132)	23 (21/91)	25 (55/223)	0.56
CIP	20 (26/128)	13 (11/87)	17 (37/215)	0.71
TMP-SMX	14 (18/132)	22 (20/91)	17 (38/223)	0.79
GN	7 (9/132)	10 (9/91)	9 (19/223)	0.56
IPM	4 (4/89)	3 (2/62)	4 (6/151)	0.82
MEM	4 (4/89)	3 (2/62)	4 (6/151)	0.82
AK	4 (5/122)	0 (0/88)	2 (5/210)	NA

FOS: Fosfomycin, AMP: ampicillin, AMC: amoxicillin-clavulanic acid, CFM: cefixime , TMP-SMX: trimethoprim/sulfamethoxazole, GN: gentamicin, AK: amikacin, CIP: ciprofloxacin, CAZ: ceftazidime, IPM: imipenem, MEM: meropenem, TZP: tazobactam, ESBL: Extended spectrum beta-lactamase, NA: not applicable.*p<0.05

DISCUSSION

Increasing antibiotic resistance emerges as an important health problem worldwide. Antimicrobial resistance is widespread in Enterobacterales family, especially *E. coli*, *Klebsiella* and Enterobacter species. In 2009, the Infectious Disease Society of America (IDSA) included these three genera into ESKAPE pathogens (12).

Enterobacter species are intrinsic resistant to aminopenicillins, first and second-generation cephalosporins because they can produce chromosomally derived AmpC beta-lactamase (7). On the other hand, ESBL-producing Enterobacter species emerged due to the overuse of third-generation cephalosporins (13). Since ESBL-producing isolates can hydrolyze penicillin, cephalosporins, and monobactams, treatment options are limited. In this study, we found the rate of ESBL in Enterobacter species to be 22%. This ratio was significantly higher in *E. cloacae* strains than *K. aerogenes* and was 26% and 17%, respectively (P = 0.03). The ESBL rates are highly versatile among countries. For instance, it has been reported as 7.5% (14) in the Netherlands and 72.7% (15) from Bosnia. This may be due to the difference in antibiotic using strategies among countries and the isolates' collection date. The treatment options of ESBL-producing Enterobacter infections are limited. Carbapenems are often the first choice. However, as a result of the overuse of carbapenem, carbapenem-resistant Enterobacter isolates have emerged. Carbapenem resistance has been reported between 0%-35.1% in Enterobacter isolates globally (13,15-17). One hundred-thirty Enterobacter spp. isolated in India, MBL was detected in 36.9% of the strains and it has been reported that they carry VIM-2, VIM-6, and NDM-1. Also, Omp 35 and Omp 36 porin loss were found associated with carbapenem resistance (18).

This study detected 4% resistance to imipenem and meropenem in *E. cloacae* and *K. aerogenes* strains. Yazıcı et al. (19) reported 2.4% in 2004, Aksaray et al. (20) found a resistance rate of 4% in 2006, whereas Ozcan et al. (21) reported 11.4% carbapenem resistance among Enterobacter spp. in 2020. Accordingly, the carbapenem resistance rate is low in our study. However, it is noteworthy that all seven carbapenem-resistant strains were isolated in 2020.

In a China study, carbapenem resistance in *E. cloacae* strains was 1% in 2007, whereas this rate was reported as 6.8% in 2017 (22). On the other hand, Nedjaci et al. from Algeria have reported no carbapenem resistance in *E. cloacae* strains in 2013 (13). Besides, Cui et al. (16) 11.5% from China, Uzunovic et al. (15) 7.1% from Bosnia, and Ghanavati et al. reported as 35.1% resistance rate in Iran (17).

Aminoglycoside antibiotics are good therapeutic options for both carbapenem-resistant and ESBL-producing isolates. It has been reported that aminoglycoside resistance develops through aminoglycoside-modifying enzymes in Enterobacter species (7). In this study, we have found 4% resistance to gentamicin and 2% to amikacin. Gentamicin resistance was reported ranging from 21.1%-44% in Turkey (20,21,23). However, its highly variable ranging from 9.4%-85.9% worldwide (15,16,22,24,25). Therefore, we should determine empirical antibiotic treatment protocols according to regional antibiotic resistance rates and follow.

Cefixime is an oral third-generation cephalosporin frequently prescribed in children and pregnant women. In this study, we found 60% resistance to cefixime. In 2014, Khosravi et al. have reported 71% resistance to cefixime in urinary Enterobacter strains in Iran (26). On the other hand, we found resistance at a rate of 17% to TMP-SMX and ciprofloxacin, which are oral antibiotics commonly used in the treatment of urinary infections. In 2020, Ozcan et al. from Turkey has reported a resistance rate of 27.3% to ciprofloxacin and 19.3% to TMP-SMX (21). In previous studies, ciprofloxacin resistance is reported between 2.4-% 8% (19,20) in Turkey. It has reported ranging from 13.3%-78.6% worldwide (15-17). TMP-SMX resistance is between 18.9% and 79.7% in studies reported from China (16,22,24).

Although fosfomycin was found in 1960, it was discontinued over time. However, it has become popular today as it is effective against most multidrug-resistant bacteria. It can be used both oral and intravenously. In this study, we found resistance to fosfomycin at a rate of 27% in *E. cloacae* isolates and 16% in *K. aerogenes* strains. Demir et al. (27) from Turkey have reported the fosfomycin resistance rate as

44% in urinary Enterobacter isolates and Fajfi et al. reported at a rate of 74.4% from the Czech Republic (28). The IDSA does not recommend antibiotics with a resistance rate of more than 20% in empirical antibiotic therapy (29). Accordingly, TMP-SMX and ciprofloxacin may be preferred instead of cefixime and fosfomycin in the empirical treatment of Enterobacter infections in our region.

This study has some limitations. It is a retrospective, single-center study based on laboratory data. Also, we did not include the patients' clinical features, diagnosis, and treatment protocols.

CONCLUSION

Enterobacter cloacae and *K. aerogenes* have many intrinsic and acquired resistance determinants. Besides, it was observed that antibiotic resistance gradually increases over time. In our region, TMP-SMX and ciprofloxacin may be preferred for urinary infections caused by these species. Aminoglycoside antibiotics and carbapenems can be the first choice to treat systemic infections. Apart from determining antibiotic resistance profiles, it should be monitored regularly.

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Ethical issues: All authors declare originality of research.

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