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Original Article

The Frequency of Integrons and OXA Genes in Uropathogenic Isolates of *Klebsiella pneumoniae*

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Abstract

Background and Aim: One of the most critical concerns in *Klebsiella pneumoniae* isolated from nosocomial infections is antibiotic resistance due to transferable resistance genes. This study aims to investigate the relationship and role of integrons in the transport of OXA-type genes in the production of carbapenem-resistant isolates.

Methods: In this study, 270 isolates of *K. pneumoniae* were isolated from patients with urinary tract infection symptoms hospitalized at Milad hospital of Tehran during 2017-2018. The biochemical methods confirmed *K. pneumoniae* isolates. Also, antimicrobial susceptibility testing was performed using an E-test method. Carbapenem-resistant isolates were confirmed using an automated antimicrobial susceptibility testing system (Phenix BD USA). The presence of OXA genes, integron, and its class were determined by PCR method.

Results: According to our findings, the most effective antibiotics against uropathogenic *K. pneumoniae* isolates were piperacillin-tazobactam and meropenem, respectively. *Out of the 270 isolates, 27 (10%)* were detected as carbapenem-resistant *K. pneumoniae* isolates. Moreover, 47.2%, 40.1%, 39.2%, and 36.4% of *K. pneumoniae* isolates were resistant to ceftriaxone, ceftazidime, trimethoprim-sulfamethoxazole, and amoxicillin/clavulanate, respectively. A significant proportion of isolates had class I integron. Meaningful differences in OXA-51, 58, and 24 genes were found in carbapenem-resistant and carbapenem-susceptible *K. pneumoniae* isolates. No significant relationship was observed between class 1 and 2 integrons and other studied gene determinants of antimicrobial resistance.

Conclusion: According to the observed results, OXA-23, OXA-24, OXA-58, and OXA-51-like groups were the most prevalent genes in carbapenem-resistant *K. pneumoniae* isolates, respectively. Also, 97.9% of carbapenem-susceptible *K. pneumoniae* isolates had class 1 integron.

Keywords: *Klebsiella pneumoniae*; Urinary Tract Infection; Integron; Antimicrobial Susceptibility; Carbapenem.

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Introduction

Klebsiella species are highly prevalent as a group of Gram-negative bacilli that can be detected in different parts of the body as normal flora and the environment (1). The most important cause of hospital-acquired infections, meningitis, pneumonia, bacteremia, wound infections, and urinary tract infections are *K. pneumoniae* which is one of the major bacteria of *Klebsiella* species. (2, 3). *K. pneumoniae* producing β-lactamases enzymes exhibit resistance to β-lactams and their derivatives such as the third generation of cephalosporins (4). Carbapenem resistance among gram-negative strains has become a global challenge because of their fast spread and the shortage of efficient antimicrobial drugs (5, 6). The carbapenem-resistant isolates expand resistance to other antibiotics such as aminoglycosides, tetracyclines, and sulfonamides. The resistance to carbapenems in Gram-negative bacteria has become a considerable public health concern over the last decade. The

principal reason for hospital-acquired and nosocomial infections, moreover, is the main Gram-negative multidrug-resistant bacteria, including the mentioned genes (7-9). Almost all b-lactam antibiotics, including carbapenems have been inhibited by carbapenemases, and have now been seen mainly in *Enterobacteriaceae*, *A. baumannii*, and *P. aeruginosa* (10). The identification and distribution of plasmid-encoded carbapenemases have recently changed our view of the problem in Gram-negative bacteria by reporting the dramatic increase in global dissemination of carbapenem-resistant bacteria carrying the KPC-type, VIM-type, NDM-type and OXA-type carbapenemases (6, 11, 12).

Class 1 integrons are the most common integrons among gram-negative bacteria whose protected region contains genes that are resistant to quaternary ammonium compounds and sulfonamides. Class 2 integrons are found in transposon 7 and its derivatives (13). Class 3 integrons appear to be much less common and so are less involved in the spread of multidrug resistance. The researchers used two regions as target regions for identification in bacteria to detect the class of integrons (14). One of these regions is the gene encoding the integrase enzyme, which is a good target to identify the class of integrons. Another area used is the variable region between the two protected regions in the structure of integrons (13). In this research, the patterns of resistance against commonly used antibiotics in various lineages of *K. pneumoniae* clinical isolates were discovered and the role of integrons to expand antimicrobial resistance was detected.

Methods

Two hundred and seventy of *K. pneumoniae* isolates were isolated from patients with UTI symptoms hospitalized at Milad hospital of Tehran during 2017-2018. All isolates were confirmed using standard biochemical tests (15). All isolates were stored at -80°C in tryptic soy broth with 15% glycerol for future molecular studies.

E-test MIC standard methods were used for antimicrobial susceptibility testing (Liofilchem® MIC *Test Strips*). The MIC was determined for antibiotics including ceftazidime (CAZ), ceftriaxone (CRO), meropenem (MEM), ciprofloxacin (CIP), piperacillin/tazobactam (TZP), gentamicin (GEN), amoxicillin-clavulanate (AMC), and trimethoprim/sulfamethoxazole (SXT) for all isolates, using E-test standard methods. The result was reported as resistant, intermediate, and susceptible according to M100-CLSI 2019 guidelines (16).

Carbapenem resistance confirmation: A selection of isolates has also been tested for carbapenemase activity with Carba-NP as defined by CLSI. The recommended QC strains were set up with each day of testing. Briefly, one inoculation loop (10 µl) of the isolate, recovered from Mueller-Hinton Agar (BD Ltd, USA), was re-suspended in 200 µl of 0.02% acetyl trimethyl ammonium bromide (CTAB) (Merck, Germany); then 100 µl of the bacterial suspension was added to 100 µl of diluted phenol red (Merck, Germany) solution containing 0.1 mM ZnSO4 (Merck, Germany) (pH = 7.5) supplemented with 6 mg/ml of imipenem (SciENcelab, Inc.). The phenol red solution, with no antibiotic, was used as a control tube for each isolate. Both tubes were vortexed and incubated at 37 °C for a maximum of two hours. The color of the test tube changed to full yellow or orange, indicating carbapenemase-producing isolate while the control tube remained red (17).

Detection of OXA group genes and the class of integrons: The high pure PCR template preparation kit (Roche, Germany) was used for genomic DNA extraction. The OXA-group genes were detected using previously published specific primer sets (Metabion, Germany) (Table 1) (18). DNA amplification was performed by Peqlab PCR thermal cycler and PCR Master Mix (Ampliqon Inc., Denmark). The PCR reactions were performed in a total volume of 25 µl including 12 µl of Master Mix Red (Ampliqon Inc., Denmark) and 1 µl of the target DNA. Forward and Reverse primers were added according to table 1. Initial denaturation set at 94 °C for 5 min, was followed by 30 cycles of 95°C for 25 seconds, the optimal annealing temperature for each gene for 40 sec, and 72°C for 50 sec. Then, a final extension step was carried out

at 72°C for 5 min. PCR products were resolved in 1.5% w⁄v agarose gels.

PCR reaction was performed to determine the class of integrons using primers shown in Table 1. These primers have been selected to identify *IntI*, *IntII*, and *IntIII* genes. PCR with a final volume of 25 µl was performed. Each reaction consists of 14 microliters of Mastermix Red (Ampliqon Inc., Denmark), 0.5 microliters of each primer (10 pm/ μl), and one microliter of template DNA. The temperature. The PCR product was checked by electrophoresis on 2 % agarose gel in TBE buffer (19, 20).

Statistical analysis: SPSS v.22 (SPSS Inc., Chicago, IL, USA) was used for data analysis. We used the Chi-squared test to assess the correlation of the variables between OXA-type gene determinants and integrons. P-value < 0.05 was considered statistically significant.

Table 1. Primer sequences were used in this study

Target gene	Primer	Annealing Temperature (°C)	Product size	Reference
Oxa-51-like	TAATGCTTTGATCGGCCTTG	58	392	(18)
	TGGATTGCACTTCATCTTGG			
Oxa-23-like	GATCGGATTGGAGAACCAGA	58	465	
	ATTTCTGACCGCATTTCCAT			
Oxa-24-like	GGTTAGTTGGCCCCCTTAAA	58	668	
	AGTTGAGCGAAAAGGGGATT			
Oxa-58-like	AAGTATTGGGGCTTGTGCTG	58	404	
	CCCCTCTGCGCTCTACATAC			
intI	CAG TGG ACA TAA GCC TGT TC	59	160	(19)
	CCC GAG GCA TAG ACT GTA			
intII	GTA GCA AAC GAG TGA CGA AAT G	59	788	
	CAC GGA TAT GCG ACA AAA AGG T			
intIII	GCC TCC GGC AGC GAC TTT CAG	62	979	
	ACG GAT CTG CCA AAC CTG ACT			

Results

Isolates and antimicrobial susceptibility

Among 270 uropathogenic *K. pneumoniae* isolates, 81 specimens were from men, while 189 were collected from women. The patients' age was from one to 94 years.

In this research, *out of the 270 isolates, 27 (10%) isolates* were detected as carbapenem-resistant *K. pneumoniae*. Also, the results of the antimicrobial susceptibility test showed that 47.2%, 40.1%, 39.2%, and 36.4% of *K. pneumoniae* strains were resistant to CRO, CAZ, SXT, and AMC, respectively. Also, 26.9%, 26.5%, 12.3%, and 10% of *K. pneumoniae* strains were resistant to CIP, GEN, TZP and MEM, respectively (Figure 1). Carbapenem resistance of *K. pneumoniae* strains was affirmed by the carba-NP test.

OXA-group genes and the class of integrons

In this study, out of all isolated *K. pneumoniae*, 81 (30%) isolates carried a gene encoding β-lactamase of the OXA-23-like group including 74 susceptible isolate and 7 resistant isolates. OXA-24, OXA-40, and OXA-58-like were not observed in *susceptible* strains. Also, 7(2.6%) carbapenem-susceptible isolates had a gene encoding OXA-51-like enzymes.

Our findings of the OXA-group genes in carbapenem-resistant *K. pneumoniae* show that 7 (26%) of carbapenem-resistant *K. pneumoniae* isolates had a gene encoding β-lactamase belonging to the OXA-23-like group. Also, 5 (18.5%) and 3 (11.1%) of the carbapenem-resistant *K. pneumoniae* isolates carried a gene encoding an OXA-24-like and an OXA-51-like enzyme, respectively. OXA-

40-like carbapenemase was not observed in both groups of *K. pneumoniae* isolates. Moreover, 4(14.8%) of carbapenem resistant *K. pneumoniae* isolates had a gene encoding a β-lactamase of the OXA-58-like group. Co-existence of OXA-23 and OXA-51-like, OXA-23 and OXA-58-like, and OXA-23 and OXA-24-like were observed among 3 (11.1%) of *K. pneumoniae* isolates (table 2).

Our study on *intI*, *intII*, and *intIII* genes showed that 27 (100%) of carbapenem-resistant isolates and 238 (97.9%) carbapenem-susceptible isolates had class 1 integron. And only five carbapenem-susceptible isolates had class 2 integron. Data analysis did not show any significant relationship between the presence of class 1 integron and OXA-58 and OXA-51(P >0.05). Also, our findings showed that there was no the relationship between class 1 integron and resistance to all tested antibiotics (P>0.05).

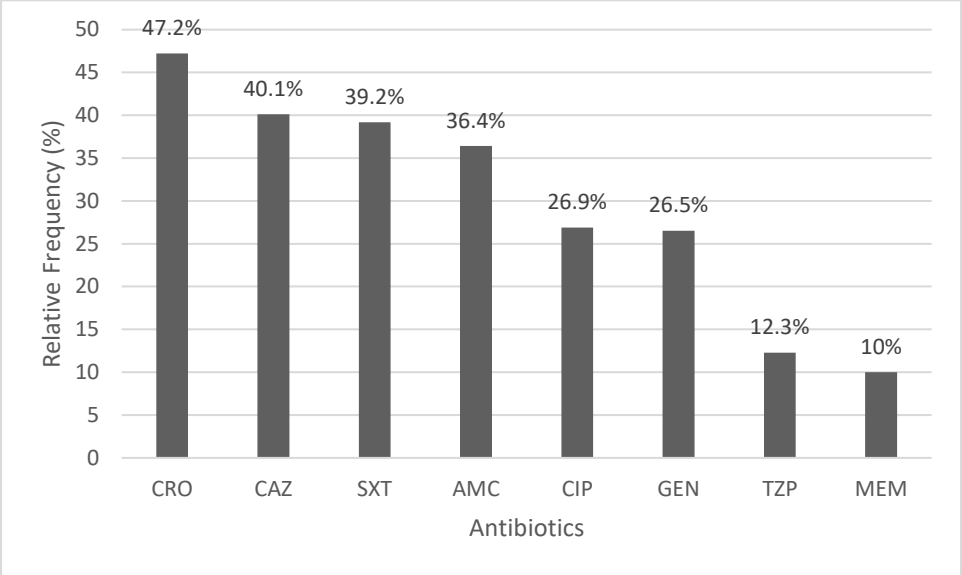

Figure 1. Antibiotic resistance pattern among *K. pneumoniae* isolates. CRO: Ceftriaxone; CAZ: Ceftazidime; SXT: Trimethoprim-Sulfamethoxazole; AMC: Amoxicillin/clavulanate; CIP: Ciprofloxacin; GEN: Gentamicin; MEM: Meropenem; TZP: Piperacillin-Tazobactam

Table 2. The frequency of OXA-type genes in carbapenem resistant and susceptible *K. pneumonia* isolates.

Genes	*K. pneumoniae*	
	Carbapenem-resistant n=27	**Carbapenem-susceptible n=243**
OXA-23	7	74
OXA-24	5	0
OXA-40	0	0
OXA-51	3	7
OXA-58	4	0

Discussion

In this study, out of 270 *K. pneumoniae*, 27 isolates were carbapenem-resistant. *Klebsiella pneumoniae* was the most prevalent isolate in 40-49 years patients. This is probably because most members of this group go to hospitals for treatment.

Moini et al. detected the high resistance rates to ampicillin (100%) and trimethoprim-sulfamethoxazole (93%) during their research on positive urine cultures for *K. pneumoniae* (17).

Moreover, 87% and 93% of isolates were susceptible to imipenem and meropenem, respectively (21). In the present study, the susceptibility rates to trimethoprim-sulfamethoxazole (60.8%) and meropenem (83.1%) were observed. According to our study, the susceptibility to carbapenems and trimethoprim-sulfamethoxazole is decreasing and their administration should be done with caution.

Also, 85% of *K. pneumoniae* isolates were multidrug-resistant in Lina's study (22). Moreover, resistance to ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole, and gentamycin antibiotics was 100%, 54%, 54%, and 27% respectively. Also, 100% of studied isolates were susceptible to imipenem (22). In our study, 47.2%, 40.1%, 39.2%, 36.4%, 26.9%, and 26.5% of *K. pneumoniae* isolates were resistant to ceftriaxone, ceftazidime, trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, ciprofloxacin, and gentamycin, respectively. As our findings indicate, all carbapenem-resistant isolates were ESBL-producing and meropenem as a representative of carbapenems was seen susceptible in 90% of *K. pneumoniae* isolates. Also, 87.3% of *K. pneumoniae* isolates were susceptible to piperacillin-tazobactam.

Comparing our findings with the previous studies showed different antibiotic resistance rates in developing countries, that may be dependent on major elements such as unsuitable use of antibiotics, geographical locations and social factors, different patients' features, and sampling biases. Carbapenem resistance has appeared as the most general concern among *K. pneumoniae* isolates in Iran. Due to the expanded resistance to other tested antibiotics, the treatment of various urinary tract infections caused by *K. pneumoniae* has become difficult.

In this research, the status of OXA-23-like, OXA-24-like, OXA-40-like, OXA-51- like, and OXA-58-like genes in collected *K. pneumoniae* isolates in Tehran were examined. Some chromosomally encoded OXA β-lactamases could be transferred among *A. baumannii* isolates and they formed the basis of transferable carbapenem resistance in this species. In some cases, OXA β-lactamases have migrated into the *Enterobacteriaceae* and become a significant cause of carbapenem resistance (5, 23). The carbapenem hydrolyzing class D β-lactamases such as OXA-23 and OXA-51 in *K. pneumoniae* are key factors in carbapenem resistance (24, 25). Few studies have been performed on OXA-group genes in *K. pneumoniae*.

Although OXA-51 and OXA-23 had the weak capability to hydrolyze carbapenem antibiotics, it has been shown OXA-51/23-like gene declined the level of susceptibility to carbapenems in *Enterobacteriacae* (26, 27). Budak et al. in 2013, has found the presence of OXA-51-like gene in *K. pneumoniae* isolated from clinical specimens in Turkey (26). In the research performed by El-bedawy et al. in 2019, 14 (73.68%), 2 (10.53%), and 4 (21.05%) of carbapenem-resistant *K. pneumoniae* isolate from Egyptian clinical samples were positive for *OXA-48*, *OXA-51*, and *OXA-181*, respectively (28). In our study, a significant association was observed between OXA-51, OXA-58, and OXA-24 genes and carbapenem-resistant *K. pneumoniae* isolates ($P<0.05$).

The worldwide investigation of class 1 and 2 integrons in clinical isolates of *K. pneumoniae* shows the prevalence of class 1 integron and class 2 integron. Derakhshan et al. have indicated the class 1 integron in *K.pneumoniae* and also its correlation with the high level of resistance to amoxicillin-clavulanic acid, ceftriaxone, ciprofloxacin, gentamicin, and ceftazidime (29). Also, Derakhshan et al. in other research showed the most ESBL-producing *K. pneumoniae* isolates included class 1 integron (30). In this study, the rates for class 1 integron were more than the rate of class 2 integron in clinical *K. pneumoniae* isolates, like some other studies from Iran. The significant relation of class 1 integrons with resistance to other studied antibiotics such as ciprofloxacin, piperacillin/tazobactam, gentamicin, amoxicillin-clavulanate, and trimethoprim/ sulfamethoxazole has been found among isolated pathogens. Liao et al. have also shown that class 1 integron had a positive correlation with aminoglycoside resistance in the nosocomial *K. pneumoniae* infection. In addition, Malek Jamshidi et al. indicated class 1 integron was dramatically associated with resistance to

quinolones, and aminoglycoside (31). No correlation between class 1 integron and antibiotic resistance in burn isolates of MDR *A. baumannii* was not observed by Rastegar-Lari et al. (32). Sedighi et al. (33) showed that the plasmids harboring multi-drug resistance genes had a co-carriage of β-lactamase genes and antibiotic resistance integrons. In the present research, it was shown that the susceptible and resistant isolates against used antimicrobials had class 1 integrons. Despite the observation of class 2 integrons in 5 carbapenem-sensitive isolates, no significant relationship was observed between class 2 integrons and antimicrobial resistance and oxa-type genes.

This study has limitations that, if removed, will result in clearer results. Sometimes, some genes may appear as gene cassettes while not found in the variable region. This reason could be described by the limitation of PCR or loss of 5′ and 3′ conserved segments of integrons.

Conclusion

OXA-23, OXA-24, OXA-58, and OXA-51-like groups were the most prevalent genes in carbapenem-resistant *K. pneumoniae* isolates, respectively. OXA-23-like was found in both carbapenem-susceptible and carbapenem-resistant *K. pneumoniae* isolates. Also, 97.9% of carbapenem-susceptible *K. pneumoniae* isolates had class 1 integron.

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Conflict of Interest

The authors declared that they have no conflict of interest associated with this study.

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Ethics

This study and all procedures performed were approved by the Ethics Committee of Islamic Azad University of IRAN (registration number IR.IAU. PS.REC.1399.178).

Author’s contribution

Conceptualization, E.P., and R.H.; methodology, E.P., and R.H.; validation, E.P., and R.H.; formal analysis, E.P.; investigation, E.P.; resources, E.P.; data curation, E.P., and R.H.; writing—original draft preparation, E.P.; writing—review and editing, R.H.; visualization, R.H.; supervision, R.H., M. R. and M. F. ; project administration, E.P.; funding acquisition, E.P.”.

References

1. Spagnolo AM, Orlando P, Panatto D, Perdelli F, Cristina ML. An overview of carbapenem-resistant Klebsiella pneumoniae: epidemiology and control measures. Reviews in Medical Microbiology. 2014;25(1):7-14.

2. Bahramian A, Shariati A, Azimi T, Sharahi JY ,Bostanghadiri N, Gachkar L, et al. First report of New Delhi metallo-β-lactamase-6 (NDM-6) among Klebsiella pneumoniae ST147 strains isolated from dialysis patients in Iran. Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2019;69:142-5.

3. Al-Badr A, Al-Shaikh G. Recurrent Urinary Tract Infections Management in Women: A review. Sultan Qaboos Univ Med J. 2013;13:359-67.

4. Murphy CN, Clegg S. Klebsiella pneumoniae and type 3 fimbriae :nosocomial infection, regulation and biofilm formation. Future microbiology. 2012;7(8):991-1002.

5. Martin RM, Bachman MA. Colonization, Infection, and the Accessory Genome of Klebsiella pneumoniae. Frontiers in cellular and infection microbiology. 2018.۸:۴;

6. Dortet L, Poirel L, Al Yaqoubi F, Nordmann P. NDM-1, OXA-48 and OXA-181 carbapenemase-producing Enterobacteriaceae in Sultanate of Oman. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2012;18(5):E144-8.

7. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary

tract infections: a review. Journal of chemotherapy (Florence, Italy). 2017;29(sup1):2-9.

8. Bonnet R. Growing group of extended-spectrum beta-lactamases: the CTX-M enzymes. Antimicrobial agents and chemotherapy. 2004;48(1):1-14.

9. Cantón R, Coque TM. The CTX-M beta-lactamase pandemic. Current opinion in microbiology. 2006;9(5):466-75.

10. Morosini MI, García-Castillo M, Coque TM, Valverde A, Novais A, Loza E, et al. Antibiotic coresistance in extended-spectrum-beta-lactamase-producing Enterobacteriaceae and in vitro activity of tigecycline. Antimicrobial agents and chemotherapy. 2006;50(8):2695-9.

11. Nordmann P ,Poirel L. Emergence of plasmid-mediated resistance to quinolones in Enterobacteriaceae. The Journal of antimicrobial chemotherapy. 2005;56(3):463-9.

12. Jacoby GA, Walsh KE, Mills DM, Walker VJ, Oh H, Robicsek A, et al. qnrB, another plasmid-mediated gene for quinolone resistance. Antimicrobial agents and chemotherapy. 2006;50(4):1178-82.

13. Taherikalani M, Maleki A, Sadeghifard N, Mohammadzadeh D, Soroush S, Asadollahi P, et al. Dissemination of class 1, 2 and 3 integrons among different multidrug resistant isolates of Acinetobacter baumannii in Tehran hospitals, Iran. Polish journal of microbiology. 2011;60(2):169-74.

14. Kargar M, Mohammadalipour Z, Doosti A, Lorzadeh S, Japoni-Nejad A. High Prevalence of Class 1 to 3 Integrons Among Multidrug-Resistant Diarrheagenic Escherichia coli in Southwest of Iran. Osong public health and research perspectives. 2014;5(4):193-8.

15. Connie R. Mahon DCL GM. Textbook of diagnostic microbiology-E-Book: Elsevier Health Sciences. 2014:450-1.

16. Weinstein MP. Performance Standards for Antimicrobial Susceptibility Testing. Thirtieth, editor: CLSI; 2019. 332 p.

17. Rudresh SM, Ravi GS, Sunitha L, Hajira SN, Kalaiarasan E, Harish BN. Simple, rapid, and cost-effective modified Carba NP test for carbapenemase detection among Gram-negative bacteria. Journal of laboratory physicians. 2017;9(4):303-7.

18. Hou C, Yang F. Drug-resistant gene of blaOXA-23, blaOXA-24, blaOXA-51 and blaOXA-58 in Acinetobacter baumannii. International journal of clinical and experimental medicine. 2015;8(8):13859-63.

19. Machado E, Cantón R, Baquero F, Galán JC, Rollán A, Peixe L, et al. Integron content of extended-spectrum-beta-lactamase-producing Escherichia coli strains over 12 years in a single hospital in Madrid, Spain. Antimicrobial agents and chemotherapy. 2005;49(5):1823-9.

20. Karczmarczyk M, Abbott Y, Walsh C, Leonard N, Fanning S. Characterization of multidrug-resistant Escherichia coli isolates from animals presenting at a university veterinary hospital. Applied and environmental microbiology. 2011;77(20):7104-12.

21. Moini AS, Soltani B, Taghavi Ardakani A, Moravveji A, Erami M, Haji Rezaei M, et al. Multidrug-Resistant Escherichia coli and Klebsiella pneumoniae Isolated From Patients in Kashan, Iran. Jundishapur journal of microbiology. 2015;8(10):e27517.

22. Lina T, Rahman S, Gomes D. Multiple-Antibiotic Resistance Mediated by Plasmids and Integrons in Uropathogenic Escherichia coli and Klebsiella pneumoniae. Banglad J Microbiol. 2007;24:19-23.

23. Evans BA, Amyes SG .OXA β-lactamases. Clinical microbiology reviews. 2014;27(2):241-63.

24. Hou C, Yang F. Drug-resistant gene of blaOXA-23, blaOXA-24, blaOXA-51 and blaOXA-58 in Acinetobacter baumannii. Int J Clin Exp Med. 2015;8:13859-63.

25. Alvargonzalez JJC, Hernando AV ,Martín MDR, Casas CM, Iglesias JO, Marín MFB, et al. Sequential outbreaks in a Spanish hospital caused by multiresistant OXA-58-producing Acinetobacter baumannii ST92. Journal of medical microbiology. 2014;63(Pt 8):1093-8.

26. Budak S, Aktaş Z, Oncul O ,Acar A, Ozyurt M, Turhan V, et al. Detection of OXA-51 Carbapenemase Gene in Klebsiella pneumoniae: A Case Report and a New Dimension on Carbapenemase Resistance. Mol Genet Med. 2013(7):17-47.

27. Babakhani S, Shokri S, Baharvand M. Antibiotic resistance pattern of Klebsiella pneumoniae isolated from nosocomial infections in Aleshtar

hospital, Lorestan province. Report of Health Care. 2015;1(2):55-9.

27. El-Badawy MF, El-Far SW, Althobaiti SS, Abou-Elazm FI, Shohayeb MM. The First Egyptian Report Showing the Co-Existence of bla (NDM-25), bla (OXA-23), bla (OXA-181), and bla (GES-1) Among Carbapenem-Resistant K. pneumoniae Clinical Isolates Genotyped by BOX-PCR. Infection and drug resistance. 2020;13:1237-50.

29. Derakhshan S NPS, Fallah F, Bakhshi B, Rahbar M, et al. Detection of Class 1, 2, and 3 Integrons Among Klebsiella pneumoniae Isolated from Children in Tehran Hospitals. Arch Pediatr Infect Dis.2(1):164-8.

30. Derakhshan S, Najar Peerayeh S, Bakhshi B. Association Between Presence of Virulence Genes and Antibiotic Resistance in Clinical Klebsiella Pneumoniae Isolates. Laboratory Medicine. 2016;47(4):306-11.

31. Malek Jamshidi MR, Zandi H, Eftekhar F. Correlation of quinolone-resistance, qnr genes and integron carriage in multidrug-resistant community isolates of Klebsiella spp. Iranian journal of basic medical sciences. 2019;22(12):1387-91.

32. Abdolaziz R-L, Hajar M-B, Mohammad A, Rahim N, Parviz O. Distribution of Class I Integron among Isolates of Acinetobacter baumannii Recoverd from Burn Patients. Journal of Medical Bacteriology. 2015;(2)1-2

33. Sedighi M, Halajzadeh M, Ramazanzadeh R, Amirmozafari N, Heidary M, Pirouzi S. Molecular detection of β-lactamase and integron genes in clinical strains of Klebsiella pneumoniae by multiplex polymerase chain reaction. Revista da Sociedade Brasileira de Medicina Tropical. 2017;50(3):321-8.