ORIGINAL ARTICLE

Co-existence of *blaOXA-48*, *rmtB* and *armA* among *Klebsiella pneumoniae* Isolates Causing Respiratory Tract Infections in Alexandria, Egypt

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ABSTRACT

Background: *Klebsiella pneumoniae is frequently implicated in numerous health-care infections, including respiratory tract infections. Aminoglycosides are among the available options to manage such infections. Hence, resistance to aminoglycosides in K. pneumoniae isolates is a clear source of concern.* ***Objective:*** *The aim of our study was to investigate the presence of 16S rRNA methyltransferases genes among aminoglycoside resistant K. pneumoniae isolates causing respiratory tract infections.* ***Methodology:*** *K. pneumoniae isolates resistant to gentamycin, tobramycin and amikacin were collected from samples obtained from respiratory tract infections from different hospitals in Alexandria, Egypt. Antimicrobial susceptibility testing was performed using disc diffusion method. Genotypically, we investigated the presence of different 16S rRNA methyltransferases encoding genes (armA, rmtA, rmtB, rmtC and rmtD) as well as other genes (aac(6')Ib and blaOXA-48).* ***Results:*** *Thirty K. pneumoniae isolates resistant to aminoglycosides were collected, and they were also resistant to carbapenems. Fourteen out of the 30 (46.67%) isolates harbored armA gene and two of these 30 isolates (6.67%) carried rmtB. However, rmtA, rmtC and rmtD were not detected. Fifteen (50%) of the isolates harbored aac(6')Ib gene. On the other hand, blaOXA-48 gene was present in 29 (96.67%) out of our 30 isolates.* ***Conclusions****: All isolates that were resistant to aminoglycosides were found to be multi-drug resistant (MDR) isolates. Eighteen isolates harbored at least one gene conferring resistance to aminoglycosides. Fourteen of these harbored genes encoding 16S rRNA methyltransferases. The co-occurrence of different resistance genes among many of our isolates represents a clear threat.*

INTRODUCTION

Klebsiella pneumoniae is a remarkable, Gram-negative, bacteria commonly associated with numerous health-care infections, including respiratory tract infections. It has established itself as a notorious infectious agent, due to its growing antimicrobial resistance[1].

Interestingly, aminoglycosides are among the empirically suggested options for suspected hospital associated pneumonia as well as ventilator associated pneumonia[2]. In fact, aminoglycosides are among the effective options that can be used, this is in part due to their synergistic effect when used with other antibacterial agents. However, the wide use of these agents has contributed to the rising aminoglycosides resistance. Different mechanisms contribute to resistance to these agents, however, 16S rRNA methyltransferases are enzymes that play a significant role in aminoglycosides resistance[3, 4]. *rmtA* was first reported in *Pseudomonas aeruginosa*, in 1997, in Japan, while *armA* was first reported in *K. pneumoniae* in Paris. Since their discovery, they have been reported from different places around the world[5-7].

Resistance to aminoglycosides among *K. pneumoniae* isolates is indeed a valid source of concern[8]. The aim of our study was to investigate the presence of 16S rRNA methyltransferases genes among aminoglycoside resistant *K. pneumoniae* isolates causing respiratory tract infections.

METHODOLOGY

K. pneumoniae isolates resistant to gentamycin, tobramycin and amikacin were collected from samples obtained from respiratory tract infections from different hospitals in Alexandria, Egypt. The isolates were collected from March 2021 to August 2021. Susceptibility testing was performed for all samples that

were collected, using disk diffusion method, and it was performed according to the CLSI guidelines[9].

The different antibiotic discs used were: amikacin, gentamicin, tobramycin, ampicillin/sulbactam, cefepime, ceftazidime, imipenem, meropenem, ciprofloxacin, levofloxacin and doxycycline. All discs were from Oxoid (Cambridge, UK).

All collected isolates, were then investigated for the presence of 16S rRNA methyltransferases genes. Then, all isolates that were resistant to carbapenems were investigated for the presence of *blaOXA-48*. The details of the primers used are listed in (table 1). All primers were purchased from Invitrogen. (ThermoFischer, CA, USA).

DNA extraction was done using boiling method, as described before by Yang et *al*[10]. PCR was performed on a total volume of 20 µl, on BioRad T100™ Thermal Cycler (CA, USA). The amplification plan was as follows: activation was at 95 °C for 5 minutes, then 40 cycles of (denaturation at 95 °C for 30 seconds, annealing and extension at 72 °C for 1 minute) followed by a final extension step at 72 °C for 7 minutes. The annealing temperatures for the different primers are listed in (table 1). After that, the PCR products were separated by gel electrophoresis on BioRad PowerPac Basic (CA, USA), on (2%) agarose gel with 0.5 µg/ml ethidium bromide The PCR master mix used was Cosmo PCR Red Master Mix (Willowfort, Birmingham, UK).

Table 1: The primers used in our study

Primer	Nucleotide Sequence (5'–3')	Amplicon size	Annealing temperature	Reference
armA (F)	AAAGTACAATCAGGGGCAGTT	269 bp	52 °C	[5]
armA (R)	TCGTCGTCTTTAACTTCCCAA			
rmtA (F)	CTAGCGTCCATCCTTTCCTC	634 bp	52 °C	[11]
rmtA (R)	TTGCTTCCATGCCCTTGCC			
rmtB (F)	GCTTTCTGCGGGCGATGTAA	173 bp	56 °C	[11]
rmtB (R)	ATGCAATGCCGCGCTCGTAT			
rmtC (F)	CGAAGAAGTAACAGCCAAAG	711 bp	49.5 °C	[11]
rmtC (R)	ATCCCAACATCTCTCCCACT			
rmtD (F)	CGGCACGCGATTGGGAAGC	401 bp	53 °C	[11]
rmtD (R)	CGGAAACGATGCGACGAT			
aac(6')Ib (F)	CAAAGTTAGGCATCACA	540 bp	55 °C	[12]
aac(6')Ib (R)	ACCTGTACAGGATGGAC			
blaOXA-48 (F)	AAATCACAGGGCGTAGTTGTG	555 bp	52 °C	[13]
blaOXA-48 (R)	GACCCACCAGCCAATCTTAG			

RESULTS

Thirty *K. pneumoniae* isolates resistant to gentamycin, tobramycin and amikacin were collected from respiratory tract infections from different hospitals in Alexandria, Egypt. These isolates were obtained from different sample sources including sputum, endotracheal tube (ETT), bronchioalveolar lavage (BAL) and (MiniBAL). The details are shown in (Figure 1).

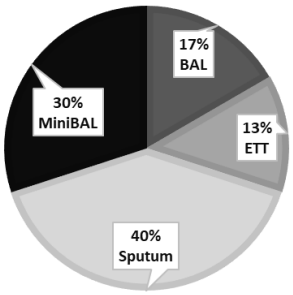

Fig. 1: The different respiratory tract samples from which the thirty *K. pneumoniae* were recovered.

The susceptibility testing of the thirty *K. pneumoniae* isolates showed that all the isolates that were resistant to the three aminoglycosides (gentamicin, tobramycin, and amikacin) were also resistant to carbapenems (imipenem and meropenem), and to the other beta-lactam agents tested (ampicillin/sulbactam, ceftazidime and cefepime). The results of the susceptibility testing were described (table 2).

Table 2: Susceptibility patterns of the thirty *K. pneumoniae* isolates

Antimicrobial agent	Resistant	Intermediate	Sensitive
Gentamicin	30 (100%)	0 (0%)	0 (0%)
Tobramycin	30 (100%)	0 (0%)	0 (0%)
Amikacin	30 (100%)	0 (0%)	0 (0%)
Ampicillin/Sulbactam	30 (100%)	0 (0%)	0 (0%)
Ceftazidime	30 (100%)	0 (0%)	0 (0%)
Cefepime	30 (100%)	0 (0%)	0 (0%)
Imipenem	30 (100%)	0 (0%)	0 (0%)
Meropenem	30 (100%)	0 (0%)	0 (0%)
Ciprofloxacin	30 (100%)	0 (0%)	0 (0%)
Levofloxacin	29 (96.67%)	1 (3.33%)	0 (0%)
Doxycycline	30 (100%)	0 (0%)	0 (0%)

For the 16S rRNA methyltransferases genes, fourteen out of the thirty isolates harbored *armA* gene and two of these thirty isolates harbored *rmtB*. However, *rmtA*, *rmtC* and *rmtD* were not detected among the thirty isolates. Fifteen of the isolates harbored *aac(6')Ib* gene. On the other hand, twenty-nine out of our thirty isolates harbored *blaOXA-48* gene. The details are shown in (Table 3). Examples of the detected bands are shown in Figure (2) and Figure (3). The distribution of different genes among the 30 *K. pneumoniae* isolates that were collected is shown in (Table 4).

Table 3: Results of the investigation of different genes among the 30 *K. pneumoniae* isolates

	Positive		Negative	
	N	**%**	**N**	**%**
armA	14	46.67	16	53.33
rmtA	0	0	0	0
rmtB	2	6.67	28	93.33
rmtC	0	0	0	0
rmtD	0	0	0	0
aac(6')Ib	15	50	15	50
blaOXA-48	29	96.67	1	3.33

Table 4: The distribution of different genes among the 30 *K. pneumoniae* isolates

Number of isolates	Different Genes
1	*blaOXA-48+ aac(6')Ib +armA+rmtB*
1	*blaOXA-48+armA+rmtB*
9	*blaOXA-48+armA+ aac(6')Ib*
4	*blaOXA-48+ aac(6')Ib*
2	*blaOXA-48+armA*
1	*armA+ aac(6')Ib*
12	*blaOXA-48*

A: Examples of *blaOXA-48* bands **B: Examples of *aac(6')Ib* bands**

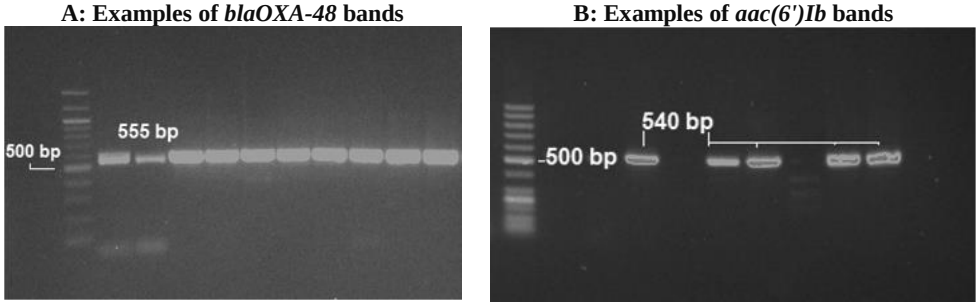

Fig. 2: Examples for the bands of *blaOXA-48* (A), and *aac(6')Ib* gene (B).

A: Examples of *armA* bands **B: *RmtB* bands**

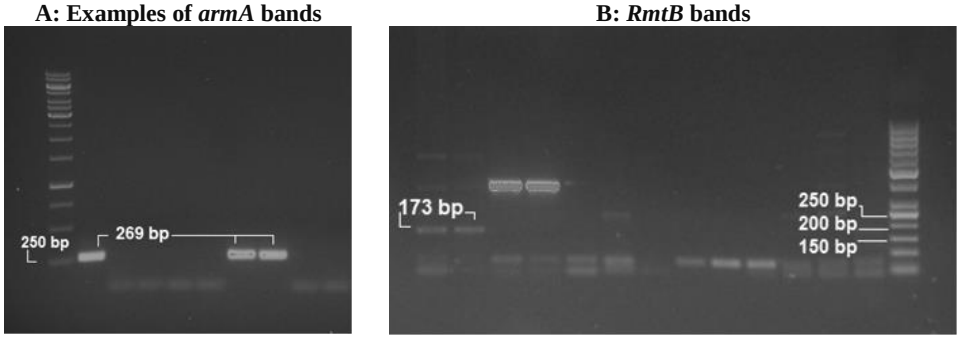

Fig. 3: Examples for the bands of the detected 16S rRNA methyltransferases genes *armA* gene (A), and *rmtB* gene (B).

DISCUSSION

Klebsiella pneumoniae is frequently associated with numerous health-care infections, including respiratory tract infections[1]. Aminoglycosides are among the effective options that can be used to manage infections caused by challenging Gram-negative bacteria, due to their broad spectrum and due to their synergistic effect when used with other antibacterial agents. So, resistance to aminoglycosides among *K. pneumoniae* isolates is an eminent source of concern [3, 8].

Thirty *K. pneumoniae* isolates resistant to gentamycin, tobramycin and amikacin were collected over a six-month period. All the isolates that were resistant to these three antibacterial agents, were also resistant to cefepime, ceftazidime, imipenem, meropenem, ciprofloxacin and doxycycline. Hence, all the isolates were found to be multidrug resistant (MDR) *K. pneumoniae*. In fact, MDR *K. pneumoniae* isolates, impose an eminent threat, as they cause infections that are hard to treat, leading to elevated risks of mortality, and this is accompanied with soaring health-care costs[14].

Carbapenems are considered one of the pillars of treatments of infections caused by MDR bacteria. However, due to the prominent use of these agents, resistance soon emerged[15]. *Klebsiella pneumoniae* is one of the most common carbapenem resistant pathogens encountered in health-care settings[16]. In our study, all our isolates were resistant to carbapenems. Here, 29 (96.67%) out of the 30 carbapenem resistant *K. pneumoniae* isolates were found to possess *blaOXA-48* gene. Karakonstantis *et al*[17]., stated that OXA-48-like carbapenemases are predominant in the Mediterranean Basin region. In Egypt, El-Kholy et *al*[18]., reported that *blaOXA-48* gene was found in (40.6%) of the carbapenem resistant *K. pneumoniae* isolates, while, Elshamy et *al*[19]., reported that *blaOXA-48* gene was present in (77.4%) of their *K. pneumoniae* isolates In Saudi Arabia, similar results were found by Al-Abdely et *al*[15]., where (71.2%) of their CRE positive *K. pneumoniae* carried *blaOXA-48*.

Regimens containing aminoglycosides, are among the few remaining therapeutic options for carbapenem-resistant *K. pneumoniae* [20]. In our work, we focused on investigating the presence of 16S rRNA methyltransferases. We investigated the presence of *armA*, *rmtA*, *rmtB*, *rmtC* and *rmtD*. We found fourteen (46.67%) of the thirty isolates harbored genes encoding 16S rRNA methyltransferase enzymes. All the fourteen isolates harbored *armA* gene, while two of these co-harbored *armA* and *rmtB* genes.

armA gene is considered one of the most encountered 16S rRNA methyltransferase genes[21]. In this study, *armA* was the most abundantly present gene encoding 16S rRNA methyltransferases. *armA* was found in almost half of the isolates; (46.67%) of the thirty aminoglycoside-resistant *K. pneumoniae* isolates. Also, in a Chinese study, Liao *et al*[22]., reported that *armA* was the most prevalent 16S rRNA methylase gene (42.3%) among their tested isolates, while Ahmed et *al*[8]., stated that *armA* gene was found in (21.6%) of their isolates in Saudia Arabia. On the other hand, Roch et *al*[23]., did not find *armA* gene among their isolates.

By comparison to *armA* gene, *rmtA* is infrequently encountered, with few reports from Japan and Korea[21]. Here, we did not find any *rmtA* genes among the thirty aminoglycoside-resistant *K. pneumoniae* isolates. Similarly, Roch et *al*[23]., could not find any *rmtA* gene among their isolates. Ahmed et *al*[8]., reported that only (11.8%) of their isolates harbored *rmtA* gene.

rmtB was first described, in Japan, from a *Serratia marcescens* clinical strain, which was isolated in 2002[24]. In our study, only two isolates harbored *rmtB*. Ahmed et *al*[8]., reported that *rmtB* was present in (29.4%) of their isolates harbored *rmtB* gene, while Roch et *al*[23]., found *rmtB* gene in (30%) of their isolates. Liao et *al*[22]., found that (30.8%) of their isolated carried *rmtB* gene.

rmtC was also first described, in Japan, from a *Proteus mirabilis* clinical strain, isolated in 2003[25]. In the present study, *rmtC* was not detected among any of our isolates. Erdem et *al*[26]., reported the presence of *rmtC* in three out of the ten isolates.

rmtD was first described from a *P. aeruginosa* isolate; in Brazil[27]. In our study, we did not find *rmtD* gene among our isolates. However, in a recent study in Saudi Arabia, *rmtD* was the most detected 16S rRNA methyltransferase gene among their isolates[8]. Erdem et *al*[26]., reported the presence of rmtD in (50%) of their isolates.

In the present study, *aac(6')Ib* was found in 15 (50%) of the 30 *K. pneumoniae* isolates. Similar results were reported by Tohamy et *al*[28]., who found that 14 of the 24 MDR *K. pneumoniae*, harbored *aac(6')Ib* and Ahmed et *al*[8]., who found this gene in (45.1%) of their *K. pneumoniae* isolates. On the other hand, Kashefieh et *al*[29]., reported that (32%) of their isolates harbored *aac(6')Ib* gene and Abo-State et *al*[30]., also found ,*aac(6')-Ib* in (30%) of their isolates.

In our study, all the isolates harbored at least one resistance gene. Fourteen of the isolates harbored 16S rRNA methyltransferases genes. Two isolates co-harbored two different 16S rRNA methyltransferases genes. Interestingly, the isolates that harbored *rmtB* also harbored *armA*. The same was reported by Liao et *al*[22]., who reported the co-occurrence of *rmtB* with *armA* in (26.9%) of their isolates. Only one isolate co-harbored 4 different genes; *blaOXA*-48, *aac(6')Ib*, *armA* and *rmtB*. Interestingly, the isolates that harbored *rmtB* also harbored *armA*.

CONCLUSION

We investigated the presence of 16S rRNA methyltransferase encoding genes among aminoglycoside-resistant *K. pneumoniae* isolates. Eighteen isolates harbored at least one gene conferring resistance to aminoglycosides. Fourteen of these harbored genes encoding 16S rRNA methyltransferases. All isolates that were resistant to three of the aminoglycosides were found to be MDR isolates. The co-occurrence of different genes among many of our isolates is considered a clear threat. Newer antimicrobial agents and different combinations are urgently needed, because the wide spread of MDR *K. pneumoniae* isolates threatens to render one of the greatest advances in the twentieth century (antibiotics), useless.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

REFERENCES

1. Paczosa MK, Mecsas J. Klebsiella pneumoniae: Going on the Offense with a Strong Defense. Microbiol Mol Biol Rev. 2016;80(3):629-61.
2. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):575-82.
3. Gopalakrishnan S, Kamalanathan A, Rajan S, Bhagat VM, Ali MKS. Emergence of armA and rmtB genes among VIM, NDM, and IMP metallo-beta-lactamase-producing multidrug-resistant Gram-negative pathogens. Acta Microbiol Immunol Hung. 2018;65(1):107-18.
4. Cirit OS, Fernandez-Martinez M, Yayla B, Martinez-Martinez L. Aminoglycoside resistance determinants in multiresistant Escherichia coli and Klebsiella pneumoniae clinical isolates from Turkish and Syrian patients. Acta Microbiol Immunol Hung. 2019;66(3):327-35.
5. Taylor E, Sriskandan S, Woodford N, Hopkins KL. High prevalence of 16S rRNA methyltransferases among carbapenemase-producing Enterobacteriaceae in the UK and Ireland. Int J Antimicrob Agents. 2018;52(2):278-82.
6. Galimand M, Courvalin P, Lambert T. Plasmid-mediated high-level resistance to aminoglycosides in Enterobacteriaceae due to 16S rRNA methylation. Antimicrob Agents Chemother. 2003;47(8):2565-71.
7. Yokoyama K, Doi Y, Yamane K, Kurokawa H, Shibata N, Shibayama K, et al. Acquisition of 16S rRNA methylase gene in Pseudomonas aeruginosa. Lancet. 2003;362(9399):1888-93.
8. Ahmed OB, Asghar AH, Bahwerth FS. Increasing frequency of Aminoglycoside-Resistant Klebsiella pneumoniae during the era of pandemic COVID-19. Mater Today Proc. 2021.
9. Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing, 31th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute, Wayne, PA. 2021.
10. Yang JL, Wang MS, Cheng AC, Pan KC, Li CF, Deng SX. A simple and rapid method for extracting bacterial DNA from intestinal microflora for ERIC-PCR detection. World J Gastroenterol. 2008;14(18):2872-6.
11. Wu Q, Zhang Y, Han L, Sun J, Ni Y. Plasmid-mediated 16S rRNA methylases in aminoglycoside-resistant Enterobacteriaceae isolates in Shanghai, China. Antimicrob Agents Chemother. 2009;53(1):271-2.
12. Miro E, Grunbaum F, Gomez L, Rivera A, Mirelis B, Coll P, et al. Characterization of aminoglycoside-modifying enzymes in enterobacteriaceae clinical strains and characterization of the plasmids implicated in their diffusion. Microb Drug Resist. 2013;19(2):94-9.
13. Grobner S, Linke D, Schutz W, Fladerer C, Madlung J, Autenrieth IB, et al. Emergence of carbapenem-non-susceptible extended-spectrum beta-lactamase-producing Klebsiella pneumoniae isolates at the university hospital of Tubingen, Germany. J Med Microbiol. 2009;58(Pt 7):912-22.
14. Petrosillo N, Taglietti F, Granata G. Treatment Options for Colistin Resistant Klebsiella pneumoniae: Present and Future. J Clin Med. 2019;8(7).
15. Al-Abdely H, AlHababi R, Dada HM, Roushdy H, Alanazi MM, Alessa AA, et al. Molecular characterization of carbapenem-resistant Enterobacterales in thirteen tertiary care hospitals in Saudi Arabia. Ann Saudi Med. 2021;41(2):63-70.
16. Zhan Q, Xu Y, Wang B, Yu J, Shen X, Liu L, et al. Distribution of fluoroquinolone resistance determinants in Carbapenem-resistant Klebsiella

pneumoniae clinical isolates associated with bloodstream infections in China. BMC Microbiol. 2021;21(1):164.

17. Karakonstantis S, Kritsotakis EI, Gikas A. Treatment options for K. pneumoniae, P. aeruginosa and A. baumannii co-resistant to carbapenems, aminoglycosides, polymyxins and tigecycline: an approach based on the mechanisms of resistance to carbapenems. Infection. 2020;48(6):835-51.
18. El-Kholy AA, Girgis SA, Shetta MAF, Abdel-Hamid DH, Elmanakhly AR. Molecular characterization of multidrug-resistant Gram-negative pathogens in three tertiary hospitals in Cairo, Egypt. Eur J Clin Microbiol Infect Dis. 2020;39(5):987-92.
19. Elshamy AA, Saleh SE, Alshahrani MY, Aboshanab KM, Aboulwafa MM, Hassouna NA. OXA-48 Carbapenemase-Encoding Transferable Plasmids of Klebsiella pneumoniae Recovered from Egyptian Patients Suffering from Complicated Urinary Tract Infections. Biology (Basel). 2021;10(9).
20. Huang Y, Rana AP, Wenzler E, Ozer EA, Krapp F, Bulitta JB, et al. Aminoglycoside-resistance gene signatures are predictive of aminoglycoside MICs for carbapenem-resistant Klebsiella pneumoniae. J Antimicrob Chemother. 2021.
21. Doi Y, Wachino JI, Arakawa Y. Aminoglycoside Resistance: The Emergence of Acquired 16S Ribosomal RNA Methyltransferases. Infect Dis Clin North Am. 2016;30(2):523-37.
22. Liao W, De Wang L, Li D, Du FL, Long D, Liu Y, et al. High Prevalence of 16s rRNA Methylase Genes Among Carbapenem-Resistant Hypervirulent Klebsiella pneumoniae Isolates in a Chinese Tertiary Hospital. Microb Drug Resist. 2021;27(1):44-52.
23. Roch M, Sierra R, Sands K, Martins W, Schrenzel J, Walsh TR, et al. Vertical and horizontal dissemination of an IncC plasmid harbouring rmtB 16S rRNA methylase gene, conferring resistance to plazomicin, among invasive ST258 and ST16 KPC-producing Klebsiella pneumoniae. J Glob Antimicrob Resist. 2021;24:183-9.
24. Doi Y, Yokoyama K, Yamane K, Wachino J, Shibata N, Yagi T, et al. Plasmid-mediated 16S rRNA methylase in Serratia marcescens conferring high-level resistance to aminoglycosides. Antimicrob Agents Chemother. 2004;48(2):491-6.
25. Wachino J, Yamane K, Shibayama K, Kurokawa H, Shibata N, Suzuki S, et al. Novel plasmid-mediated 16S rRNA methylase, RmtC, found in a proteus mirabilis isolate demonstrating extraordinary high-level resistance against various aminoglycosides. Antimicrob Agents Chemother. 2006;50(1):178-84.
26. Erdem F, Abulaila A, Aktas Z, Oncul O. In vitro evaluation of double carbapenem and colistin combinations against OXA-48, NDM carbapenemase-producing colistin-resistant Klebsiella pneumoniae strains. Antimicrob Resist Infect Control. 2020;9(1):70.
27. Doi Y, de Oliveira Garcia D, Adams J, Paterson DL. Coproduction of novel 16S rRNA methylase RmtD and metallo-beta-lactamase SPM-1 in a panresistant Pseudomonas aeruginosa isolate from Brazil. Antimicrob Agents Chemother. 2007;51(3):852-6.
28. Tohamy ST, Aboshanab KM, El-Mahallawy HA, El-Ansary MR, Afifi SS. Prevalence of multidrug-resistant Gram-negative pathogens isolated from febrile neutropenic cancer patients with bloodstream infections in Egypt and new synergistic antibiotic combinations. Infect Drug Resist. 2018;11:791-803.
29. Kashefieh M, Hosainzadegan H, Baghbanijavid S, Ghotaslou R. The Molecular Epidemiology of Resistance to Antibiotics among Klebsiella pneumoniae Isolates in Azerbaijan, Iran. J Trop Med. 2021;2021:9195184.
30. Abo-State MAM, Saleh YE-S, Ghareeb HM. Prevalence and sequence of aminoglycosides modifying enzymes genes among E. coli and Klebsiella species isolated from Egyptian hospitals. Journal of radiation research and applied sciences. 2018;11(4):408-15.