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RESEARCH ARTICLE

INVESTIGATION OF ANTIBIOTIC AND ANTISEPTIC RESISTANCE GENES IN METHICILLIN-RESISTANT AND METHICILLIN-SUSCEPTIBLE *STAPHYLOCOCCUS AUREUS* ISOLATES

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ABSTRACT: Aim: This study aimed to determine the antibiotic susceptibility of *Staphylococcus aureus* isolated from different clinical materials sent to the Microbiology Laboratory of Hatay Mustafa Kemal University Hospital, to investigate the mechanisms mediating antibiotic and antiseptic resistance, to determine the SCC*mec* type of methicillin-resistant isolates. Materials and Method: Overall, 187 *S. aureus* were included in the study. Antibiotic susceptibilities of the isolates were performed by the disc diffusion method and evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Antibiotic resistance, antiseptic resistance, and Staphylococcal Cassette Chromosome *mec* (SCC*mec*) types in MRSA strains were investigated using polymerase chain reaction (PCR). Results: While all of the isolates were found to be susceptible to linezolid and vancomycin; various rates of resistance for penicillin (87.1%), cefoxitin (49.93%), erythromycin (19.79%), ciprofloxacin (13.37%), tetracycline (11.23%), clindamycin (10.16%), trimethoprim-sulfamethoxazole (8.02%), gentamicin (17.82%), fusidic acid (64.2%) and rifampin (1.07%) were determined. A statistically significant difference was found between MRSA and MSSA strains in terms of MDR phenotype rates (p=0.001). Among *S. aureus* isolates, single resistance genes or various combinations of resistance genes were detected. SCC*mec* type III (52.4%) was the most common SCC*mec* type. Conclusions: The results of this study indicated that current control strategies should be revised to minimize antibiotic resistance and periodic surveillance studies must be carried out.

KEYWORD: *Staphylococcus aureus*, antibiotic resistance, antiseptic resistance, SCC*mec* typing

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INTRODUCTION:

The rise of antibiotic resistance (AMR) has become a global public health concern as it threatens its ability to treat infectious diseases [1]. Worldwide, *S. aureus* is among the opportunistic pathogens that cause a wide range of clinical cases, from superficial skin lesions to deeply located abscesses and life-threatening sepsis, in both community and healthcare settings [2]. The pathogenesis of *S. aureus* infections is to great extent related to the virulence repertoire of the infecting agent, antibiotic resistance especially multidrug resistance (MDR) further complicated staphylococcal infections [3]. Following the discovery of penicillin by Sir Alexander Fleming, the "antibiotic age" began and deadly infections became curable. However, in the mid-1940s, only a few years later with its introduction into clinical practice, penicillin resistance has been encountered; this was followed by the emergence of methicillin-resistant *S. aureus* (MRSA) strains in 1961 [4]. In the following year, infections caused by antibiotic-resistant *S. aureus* strains, particularly MRSA strains that are generally associated with an MDR profile, have reached epidemic proportions [5].

Different mechanisms are responsible for antibiotic resistance among *S. aureus* isolates including (i) modification or degradation of antibiotic, (ii) efflux of antibiotic, (iii) sequestration of antibiotic, and (iv) target modification/bypass/protection mechanisms [6]. Due to the life-threatening consequences of infections caused by *S. aureus* strains, appropriate management of such cases is essential. Therefore, it is of importance for clinicians to know and understand the resistance mechanisms used by pathogens to prescribe the appropriate antibiotic, especially when the pathogen is known but the antibiogram result is still pending [7].

Quaternary ammonium compounds (QAC), such as chlorhexidine digluconate (CHDG) and benzalkonium chloride (BAC), are widely used antiseptics in healthcare settings to prevent nosocomial infections. However, widespread use of QAC gave rise to the emergence of *Staphylococcus* spp. having low susceptibility to QAC [8]. QAC resistance is mediated by multiple drug efflux pumps encoded by plasmids. So far, six different Qac efflux pumps (QacA, QacB, QacC, QacG, QacH, and QacJ) have been identified in the *Staphylococcus* species. Of these, QacA and QacB belong to the Major Facilitator (MF) Superfamily, while QacC, QacG, QacH, and QacJ belong to the Small Multidrug Resistance (SMR) family [9].

The objectives of the study were to (i) determine the antibiotic susceptibility of *S. aureus* isolated from clinical materials sent to the Microbiology Laboratory of Hatay Mustafa Kemal University Hospital, to (ii) investigate the mechanisms mediating antibiotic and antiseptic resistance, and to (iii) determine the SCC*mec* type of MRSA isolates.

MATERIALS AND METHODS:

A total of 187 *S. aureus* (86 MRSA and 101 MSSA), previously isolated from clinical specimens submitted to the Microbiology Laboratory of the Hatay Mustafa Kemal University Hospital from January to September 2020, were included in the study.
Antibiotic susceptibilities of the isolates were evaluated by disc diffusion method according to guidelines recommended by European Committee on Antimicrobial Susceptibility Testing [10], and the following antibiotic discs were used: penicillin (10 U), cefoxitin (30 µg), vancomycin (30 µg), rifampin (5 µg), tetracycline (30 µg), fusidic acid (10 µg), ciprofloxacin (5 µg), clindamycin (2 µg), gentamicin (10 µg), linezolid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), and erythromycin (15 µg). *S. aureus* ATCC 29213 was used as quality control. The isolates that have resistance to at least one antibiotic in three or more antibiotic classes were classified as multi-drug resistant (MDR) [11].
Genomic DNA from *S. aureus* isolates was extracted using DNeasy Blood and Tissue kit (Qiagen, Hilden, Germany). Before extraction, 15 µl of lysozyme (10 mg/ml) and 10 µl of lysostaphin (10 mg/ml) were

added to the bacterial suspension for lysis of the cell wall of the isolates and incubated at 37 ºC for 45 minutes [12].

PCR amplification for beta-lactam resistance gene (*bla*Z), aminoglycoside resistance genes [*aac(6')-aph(2''), aph(3')-IIIa and ant(4)-Ia*], tetracycline resistance genes (*tet*K and *tet*M), macrolide resistance genes (*erm*A and *erm*C), lincosamide resistance gene (*lnu*A), fusidic acid genes (*fus*B and *fus*C) and antiseptic resistance genes (*qac*A/B, *smr*, *qac*G, *qac*H, and *qac*J) were carried out using primers as reported in previous studies [13-19].

Staphylococcal Cassette Chromosome *mec* (SCC*mec*) types in MRSA isolates were searched as previously reported by Kondo et al. [20].

The statistical analyses were performed using SPSS v.16 (SPSS Inc., Chicago, IL, USA). The frequencies of the variables were given as numbers and percentages. A p-value less than 0.05 was considered statistically significant.

RESULTS:

Antibiotic Susceptibility Testing

The antibiotic susceptibility testing revealed to resistance rates of 87.1% for penicillin (163/187, 95% CI: 82.23-91.96), 49.93% for cefoxitin (96/187, 95% CI: 41.92-56.93), 8.02% for trimethoprim-sulfamethaxazole (15/187, 95% CI: 4.09-11.95) 11.23% for tetracycline (21/187, 95% CI: 6.66-15.80), 6.42% for fusidic acid (12/187, 95% CI: 2.87-9.96), % 10.16 for clindamycin (19/187, 95% CI: 5.79-14.53), 19.79% for erythromycin (37/187, 95% CI: 14.02-25.55), 17.82% for gentamicin (13/187, 95% CI:12.07-23.56), 13.37% for ciprofloxacin (25/187, 95% CI: 8.45-18.29), respectively. A statistically significant difference was found between MRSA and MSSA strains in terms of MDR phenotype rates [25.8% vs 74.2%, OR:4.244 (95% CI: 1.786-10.087), p=0.001]. The antibiotic test results observed in MRSA and MSSA isolates were given in Table 1.

Table 1. Antibiotic susceptibility test results detected in MRSA and MSSA isolates

Antibiotic	MRSA (n=86)		MSSA (n=101)		P-value
	Susceptible n (%)	Resistant n (%)	Susceptible n (%)	Resistant n (%)	
Penicillin	0 (0)	86 (100)	94 (23.8)	77 (76.2)	0.000
Cefoxitin	0 (0)	86 (100)	91 (90,1)	10 (9.9)	0.000
Erythromycin	63 (73.3)	23 (26.7)	87 (6.1)	14 (13.9)	0.028
Tetracycline	68 (79.1)	18 (20.9)	98 (97)	3 (3)	0.000
Clindamycin	72 (3.7)	14 (16.3)	96 (95)	5 (5)	0.011
Trimethoprim-sulfamethoxazole	75 (87.2)	11 (12.8)	97 (96)	4 (4)	0.027
Gentamicin	76 (88.4)	10 (11.6)	98 (97)	3 (3)	0.020
Ciprofloxacin	77 (89.5)	9 (10.5)	85 (84)	16 (16)	0.282
Fusidic Acid	77 (89.5)	9 (10.5)	98 (97)	3 (3)	0.037
Rifampin	85 (97.7)	2 (2.3)	0	0	0.210
Linezolid	86 (100)	0	101 (100)	0	-
Vancomycin	86 (100)	0	101 (100)	0	-

Distribution of antibiotic and antiseptic resistance genes

Of 163 penicillin-resistant isolates, 154 (94.5%) had *bla*Z (Figure 1). Among 35 erythromycin-resistant isolates, 24 (68.6%) were found to carry *erm* genes that *erm*C and *erm*A were detected in 45.7% (n=16) and 22.9% (n=8) of the isolates, respectively (Figure 2). Out of 19 clindamycin-resistant isolates, 9 harbored the *Inu*A gene (Figure 3). Of the 21 tetracycline-resistant isolates, 12 possessed *tet*M and 4 had *tet*K, while two had both *tet*K and *tet*M (Figure 4). Gentamicin resistance was found to be associated with *aac(6')-Ie-aph(2'')-Ia* gene alone or in combination with *aph(3')-IIIa* and *ant(4')-Ia* genes in 9 isolates, however; 2 isolates did not show any association (Figure 5). While the *smr* gene was detected in one isolate (Figure 6), *fus*B and *fus*C were detected in 4 and 2 isolates in 12 fusidic acid-resistant isolates, respectively (Figure 7).

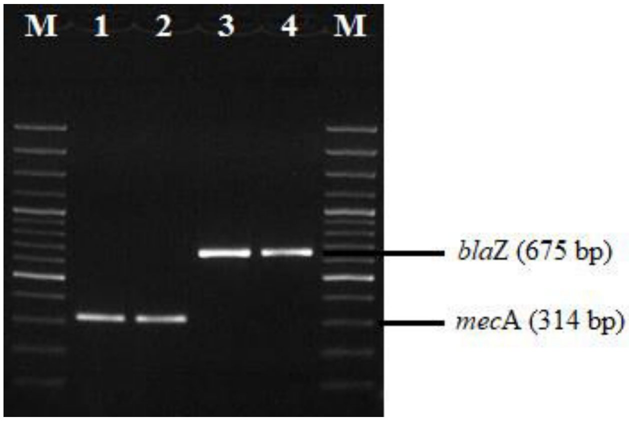

Figure 1. Agarose gel electrophoresis of *bla*Z and *mec*A genes

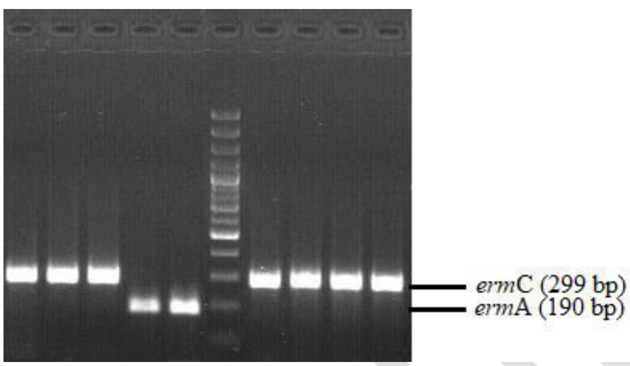

Figure 2. Agarose gel electrophoresis of *erm*A ve *erm*C genes

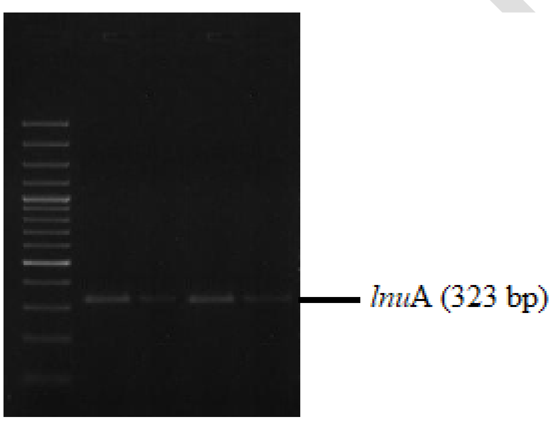

Figure 3. Agarose gel electrophoresis of *lnu*A

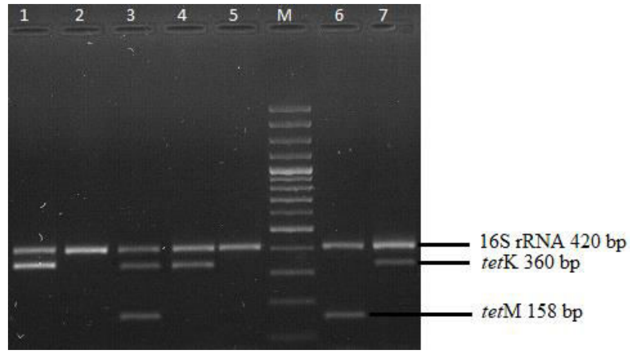

Figure 4. Agarose gel electrophoresis of *tet*K, *tet*M ve 16S rRNA genes

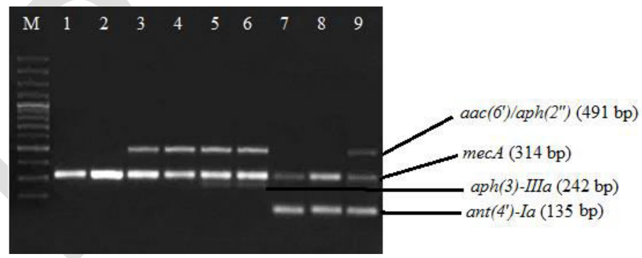

Figure 5. Agarose gel electrophoresis of AMEs and *mec*A genes

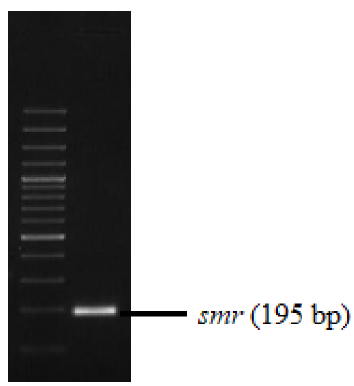

Figure 6. Agarose gel electrophoresis of *smr* gene

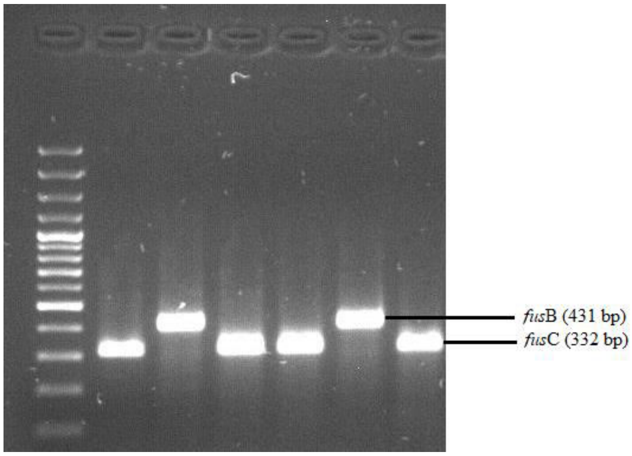

Figure 7. Agarose gel electrophoresis of *fus*B *and fus*C genes

SCC*mec* typing

Among MRSA isolates, the most common SCC*mec* type was SCC*mec* type III (n=45, 52.4%), followed by SCC*mec* type IV (n=18, 20.9%), SCC*mec* type II (n=9, 10.5%), and SCC*mec* V (n=5, 5.8%), respectively (Figure 8, 9). Nine (10.5%) of the isolates could not be typed by this method.

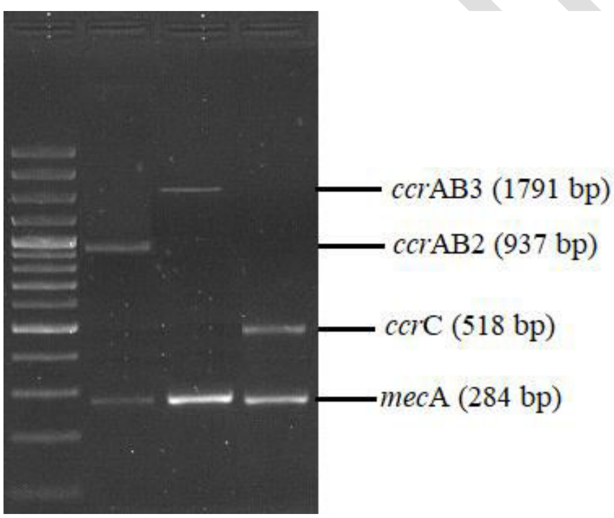

Figure 8. Agarose gel electrophoresis of *ccr* gene complexes determined by mPCR I

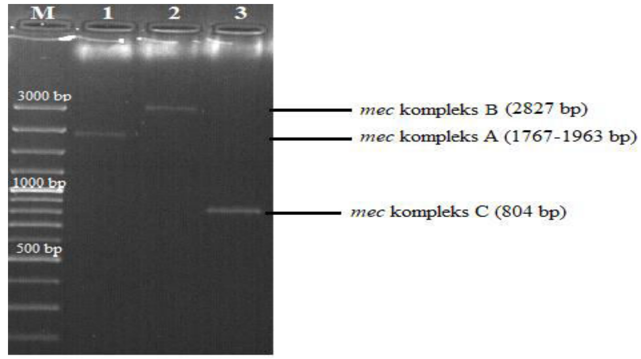

Figure 9. Agarose gel electrophoresis of *mec* gene complexes determined by mPCR II.

DISCUSSION:

S. aureus is one of the pathogens of the ESKAPE, which is a common cause of deadly or life-threatening infections, particularly in children, critically ill, and immunocompromised patients due to its potential MDR mechanisms and virulence [21].

In contrast to the findings of most of the national studies, the prevalence of MRSA isolates was found to be higher in this study [22-24]. This variation in MRSA prevalence rates may be due to selective pressure exerted by the use of antibiotics and/or the spread of resistant bacteria, and infection control measures in hospitals and regions.

The MRSA strains have been reported to show much more MDR phenotype in comparison with MSSA strains. Similarly, MRSA strains exhibited a higher prevalence rate of MDR phenotype. Ventola suggested that the overuse and/or misuse of antibiotics was a driving force in the evolution of resistance [25]. In addition, statistically significant resistance rates for antibiotics used in the study were observed between MRSA and MSSA strains, except ciprofloxacin and rifampin.

The main resistance mechanism to penicillin is the enzymatic hydrolysis of the ring of β-lactam antibiotics by β-lactamase encoded by *bla*Z [13]. In the current study, *bla*Z gene was found in 94.5% (n=154) of the isolates. In earlier studies, all penicillin-resistant isolates were found to carry *bla*Z gene [26, 27].

Ribosomal methylation of 23 rRNA by methylases encoded by *erm* (erythromycin ribosome methylation) genes is the most encountered resistance mechanism to macrolides in *S. aureus* [28]. In the current study, *erm*C was the most common gene detected in 45.7% (n=16) of erythromycin-resistant isolates (n=35), followed by *erm*A, which was found in 22.9% of the isolates. In previous studies conducted in Turkey, various frequencies of *erm* genes have been reported in erythromycin-resistant isolates. Previously, similar observations were also reported by Yılmaz and Aslantaş [26] and Yıldız et al. [29]. In the former study, the distribution of *erm*A, *erm*B and *erm*C genes were found to be 19.4%, 6.5%, and 91.9%, of the isolates, respectively. Yıldız et al. found the frequencies of these genes as 21.3%, 8.9%, and 56.9% among the MRSA isolates, respectively [29]. In contrast to our findings, Duran et al. reported *erm*A as the most common genotype followed by *erm*C (28.6%) and *erm*B (9.5%) [27].

Aminoglycoside modifying enzymes (AMEs) are the main mechanism of resistance for aminoglycoside resistance. Among staphylococci, 6'-N-acetyltransferase-2"-O-phosphotransferase, encoded by the *aac(6')-Ie-aph(2")* gene, is the most common AME (31). In this study, gentamicin resistance was found to be associated with *aac(6')-Ie-aph(2")-Ia* gene alone or in combination with *aph(3')-IIIa* and *ant(4')-Ia* genes in 9 isolates, however; 2 gentamicin isolates did not carry any gene investigated. The previous studies conducted in Turkey have also shown that *aac(6')-Ie-aph(2")* was the most common gene among staphylococci together with other AME genes [26, 27, 29].

In this study, resistance to tetracycline was mainly associated with ribosomal protection proteins, mediated by *tet*M gene (57.1%), followed by *tet*K (19%) encoding active efflux pump, and both *tet*K and *tet*M (9.5%). This finding is consistent with previous studies on *S. aureus* in Turkey [26, 27, 29]. Therefore, it can be stated that the *tet*M gene plays an important role in tetracycline resistance.

Apart from constitutive resistance to macrolide–lincosamide–streptogramin B (cMLSb), another mechanism of resistance for lincosamides is enzymatic inactivation of the antibiotic. The lincosamide nucleotidyl transferases encoded by *lnu* genes (*lnu*A and *lnu*B genes) are responsible for resistance to lincosamides in staphylococci [31]. In this study, the *lnu*A gene was detected in 47.4% (n=9) of 19 clindamycin-resistant isolates.

Fusidic acid exerts its antibacterial activity through the blockade of elongation factor G (EF-G), which is required for bacterial protein synthesis [17, 32]. In this study, the resistance rates for fusidic acid were found as 10.5% and 3% for MRSA and MSSA isolates, respectively. Nergiz et al. compared fusidic acid resistance rates in MSSA and MRSA strains isolated at an interval of ten years (2001-2011) and found that fusidic acid resistance rates for MSSA and MRSA strains varied between 4.2% and 5.7% in 2001, and between 18.9% and 22.2% in 2011, respectively [33]. A comparable resistance rate for fusidic acid was reported by Yiğit et al., who found 14.2% of MRSA and 14.3% of MSSA isolates as fusidic acid-resistant, respectively [34]. However, a lower or no resistance rate for fusidic acid resistance in both MSSA strains and MRSA strains was reported by Azap et al. The authors reported that all of the MSSA strains were susceptible to fusidic acid, and 0.8% of MRSA strains were resistant to fusidic acid [35].

SCC*mec* typing has epidemiological importance. Considering the genetic features, SCC*mec* type I-II-III is typically restricted to HA-MRSA strains, SCC*mec* type IV is mainly associated with CA-MRSA strains [20]. Based on SCC*mec* typing results, SCC*mec* Type III (52.4%) was the most common SCC*mec* type, followed by SCC*mec* type IV

(20.9%), SCC*mec* type II (10.5%), and SCC*mec* V (5.8%), respectively. Similar results were also reported in previous studies conducted in Turkey. In a multicenter study, the distribution of SCC*mec* type I, II, III, and IV were reported to be 1.1%, 1.5%, 91.1%, and 5.2%, respectively [36]. In another multicenter study, SCC*mec* type III (91.4%) was detected as the most common SCC*mec* type, followed by SCC*mec* type 7.6% (38). Interestingly, in a recent study, the presence of livestock-related MRSA (LA-MRSA) ST398 clones has also been reported from human infections in Turkey [38].

QACs are disinfectants used to control and prevent nosocomial infections. Widespread use of QAC led emergence and spread of *qac* genes mediating efflux-based resistance among clinical *Staphylococcus* strains [9]. The carriage of *qac* genes on plasmids facilitated the rapid spread of *qac* resistance, and the presence of several plasmid-mediated antiseptic resistance genes such as *qac*A/B, *smr*, *qac*G, *qac*H, and *qac*J, which have been reported as a result of the reduced susceptibility to antiseptic agents [9, 19, 39].

In this study, while the *smr* gene was detected in only one of MRSA isolates, other *qac* genes were not found in the remaining isolates. In contrast to our study, higher prevalence rates of *qac* genes have been reported in previous studies carried out in Turkey. Iğnak et al. reported that 15 (51.7%) of 29 *S. aureus* isolates had at least one *qac* gene. In this study, frequency of *qac*A/B, *smr*, *qac*G, *qac*H, *and qac*J genes were 10%, 10%, 70%, 0.0%, and 4 (40%) in MRSA (n=10) isolates and 10.5%, 15.8%, 21.1%, 0.0%, and 15.8% in MSSA (n=19) isolates, respectively [39]. Nakipoğlu et al. detected the *smr* gene in only 36% of *MRSA* isolates, whereas the qacA/B gene in only 4.0% of MSSA strains [41]. On the other hand, Duran et al. found the frequency of qacA/B and *smr* genes to be 47.4% and 28.9% in MRSA isolates (n=38) and 19.4% and 6.5% in MSSA (n=31) isolates [42].

CONCLUSION:

In the current study, linezolid and vancomycin were found to be the most effective antibiotics. On the other hand, the high prevalence of MRSA strains with MDR phenotype emphasizes re-defining current control strategies to control the emergence and spread of antibiotic resistance. This study also highlighted the importance of periodic surveillance studies in healthcare settings to achieve effective control strategies of MDR infections and reduce antibiotic resistance rates.

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