Distribution of *erm* and *msr* Genes Encoding Resistance to Macrolide, Lincosamide and Streptogramin B Antibiotics in Clinical *Staphylococcus* Isolates

Klinik *Staphylococcus* İzolatlarında Makrolid, Linkozamid ve Streptogramin B Grubu Antibiyotiklere Direnç Gelişimine Neden Olan *erm* ve *msr* Genlerinin Araştırılması

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ABSTRACT Objective: Cross-resistance is an important issue for macrolide, lincosamide and streptogramin B (MLS_B) antibiotics. The *erm* genes alter their ribosomal binding site by encoding ribosomal methylases. Phenotypic presentation of *erm*-mediated resistance can be inducible ($iMLS_B$) or constitutive ($cMLS_B$). Expression of *msr* genes which encode active efflux pumps confers the MS_B phenotype. In this study, we investigated the frequency of MLS_B resistance phenotypes and the presence of *erm* and *msr* genes in clinical *Staphylococcus* isolates. **Material and Methods:** The frequency of MLS_B resistance phenotypes were investigated using D-zone test in 731 clinical *Staphylococcus* strains. The presence of *erm* and *msr* genes was investigated by polymerase chain reaction in macrolide-resistant strains. **Results:** Of the investigated isolates, 37.3% had $iMLS_B$, 35.8% had cMLSB, and 26.9% had MS_B phenotypes. Among studied, 45.9% of the strains carried *ermC*, 15.5% carried *ermA*, and 4.2% carried *ermA* and *ermC* genes. Phenotypic presentation of 51.4% of the *erm* gene carriers were $iMLS_B$ and 48.6% were $cMLS_B$. Of the MS_B phenotype strains, 73.3% carried the *msrA+msrB* gene combination and 3.3% carried *msrB* alone. Various *erm* and *msr* gene combinations were determined in 13.7% of the isolates of which 54.3% expressed $iMLS_B$ or $cMLS_B$ phenotypes and 45.7% expressed the MS_B phenotype. MS_B phenotype and gene combination frequencies were more in coagulase-negative staphylococci (CoNS). **Conclusion:** Investigating genes conferring resistance to lincosamides is important for reducing the risk of treatment failure especially for erythromycin resistant, clindamycin susceptible strains. Due to the increasing resistance problem in staphylococcal infections, clinicians must be aware of resistance development while prescribing MLS_B antibiotics.

Key Words: Staphylococcus; drug resistance, microbial; polymerase chain reaction

ÖZET Amaç: Makrolid-linkozamid-streptogramin B (MLS_B) grubu antibiyotikler için çapraz direnç önemli bir sorundur. *erm* genlerinin kodladığı ribozomal metilazlar, bu antibiyotiklerin hedefi olan ribozomları değiştirir. *erm* geni aracılı direncin fenotipik görünümü indüklenebilir ($iMLS_B$) veya yapısal ($cMLS_B$) olabilir. Aktif atım pompalarını kodlayan *msr* genlerinin ekspresyonu, MS_B fenotipini ortaya çıkartır. Bu çalışmada, klinik *Staphylococcus* izolatında MLS_B direnç fenotiplerinin sıklığı ve dirençli izolatlarda *erm* ve *msr* genlerinin araştırılması amaçlanmıştır. **Gereç ve Yöntemler:** MLS_B direnç fenotiplerinin sıklığı 731 klinik *Staphylococcus* izolatında D-zon testi ile araştırılmış ve makrolid direnci bulunan suşlarda *erm* ve *msr* genleri polimeriz zincir reaksiyonu ile belirlenmiştir. **Bulgular:** Araştırılan izolatların %37,3'ünde $iMLS_B$, %35,8'inde $cMLS_B$, %26,9'unda ise MS_B fenotipi gözlenmiştir. Suşların %45,9'unda *ermC*, %15,5'inde *ermA* geni tespit edilirken, %4,2'sinin *ermA* ve *ermC* genlerini birlikte taşıdığı belirlenmiştir. *erm* geni taşıyan suşların %51,4'ünde fenotipik görünüm indüklenebilir, %48,6'sında ise yapısal özellikte bulunmuştur. MS_B fenotipli suşların %73,3'ünde *msrA+msrB* gen kombinasyonu, %3,3'ünde ise tek başına *msrB* geni tespit edilmiştir. İzolatların %13,7'sinin çeşitli *erm* ve *msr* gen kombinasyonları taşıdığı, bunların %54,3'ünün indüklenebilir veya yapısal MLS_B direnç fenotipine sahip olduğu, %45,7'sinin ise MS_B fenotipi eksprese ettiği belirlenmiştir. MS_B fenotipi ve gen kombinasyon sıklığı koagülaz negatif stafilokoklarda daha yüksek bulunmuştur. **Sonuç:** Eritromisin dirençli fakat klindamisin duyarlı suşlarda linkozamid direnç geni varlığının araştırılması klindamisin tedavi başarısızlığı riskinin azaltılması açısından önemlidir. Stafilokok enfeksiyonlarında artan direnç sorunu nedeniyle, MLS_B grubu antibiyotikler reçete edilirken direnç gelişimi açısından dikkatli olunması gereklidir.

Anahtar Kelimeler: Stafilokok; ilaç direnci, mikrobiyal; polimeraz zincir reaksiyonu

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Staphylococci are among the leading causes of hospital-as well as community-onset infections throughout the world. The incidence of staphylococcal infections is increasing despite the use of powerful antimicrobial agents and stringent infection-control procedures.[1]

Macrolide, lincosamide, and streptogramin B (MLS_B) groups of antibiotics are widely used in the treatment of staphylococcal infections. These chemically distinct compounds act by binding to the 50S subunit of the ribosomes and inhibiting the protein synthesis in susceptible bacteria.[2,3] Due to their common binding site on the ribosomes, cross-resistance is an important issue for this group of antibiotics. Resistance can develop by three mechanisms: (i) through target site alteration by methylation or mutation, (ii) through efflux of the antibiotic, (iii) by inactivation of the drug.[2,4,5] A number of genes have been identified responsible for these resistance mechanisms. Three related determinants, *ermA, ermB* and *ermC* genes encode ribosomal methylases and confer resistance to MLS_B antibiotics by altering the binding site on the ribosome. The phenotypic presentation of this type of MLS_B resistance may be either inducible ($iMLS_B$; strains are resistant to 14- and 15-membered ring macrolides and susceptible to 16-membered ring MLS_B) or constitutive ($cMLS_B$; resistance includes 16-membered ring MLS_B). The *msrA* and *msrB* genes which encode active efflux pumps belonging to the ABC transporter family, are responsible for the MS_B phenotype. These isolates are inducibly resistant to 14- and 15-membered ring macrolides and to streptogramin B after induction with erythromycin, but remain susceptible to lincosamides and 16-membered ring macrolides even after induction.[4,6]

Understanding the underlying mechanisms of antimicrobial resistance is important for establishing appropriate antimicrobial therapy regimens and taking necessary precautions for infection control. The frequency of MLS_B resistance differs extensively among different study populations. In this study, we aimed to investigate the distribution of MLS_B resistance genes among macrolide-resistant staphylococcal isolates.

MATERIAL AND METHODS

STAPHYLOCOCCUS ISOLATES

During the study period (November 2004-September 2007) a total of 731 *Staphylococcus* strains were isolated as the causative agents of various infections of different patients hospitalized in different clinics of Ankara Numune Education and Research Hospital, which is one of the biggest tertiary state hospitals in Turkey. Among these strains, 335 macrolide-resistant *Staphylococcus* isolates were evaluated for the presence of resistance genes. These 335 strains were isolated from various clinical specimens including blood (n=258, 77.0%), surgical wound (n=53, 15.8%), sterile body fluids such as pleural, pericardial, peritoneal and cerebrospinal fluids (n=19, 5.7%), and endotracheal aspirate (n=5, 1.5%). Identification of *Staphylococcus aureus* or coagulase-negative staphylococci (CoNS) was based on conventional microbiological methods (colony and Gram stain morphology, catalase and coagulase tests) and confirmed by using the Vitek system (bioMe'rieux-France). Strains were stored in brain-heart broth containing 30% glycerol at -20°C.

ANTIMICROBIAL SUSCEPTIBILITIES

Antimicrobial resistance patterns of the isolates were determined by using the VITEK2 system AST P535 card (bioMérieux-France). In order to display the MLS_B resistance phenotypes, double disk diffusion method (D-zone test) was performed according to the Clinical and Laboratory Standards Institute (CLSI) instructions.[7] *S. aureus* ATCC 25 923 strain was used as the control strain in antimicrobial susceptibility tests. *Staphylococcus* strains with minimum inhibitory concentration (MIC) values ≥8 μg/mL and ≥4 μg/mL were considered as resistant to erythromycin and clindamycin, respectively. Stains with MIC values ≤0.5 μg/mL were considered as susceptible to both antibiotics.

POLYMERASE CHAIN REACTION (PCR) AMPLIFICATION OF *erm* AND *msr* GENES

Genomic DNA was extracted from staphylococcal cultures by phenol-chlorophorm extraction method.[8] PCR amplification of *ermA, ermB, ermC,*

msrA and *msrB* genes were performed by using the method of Lina et al.[5] *S. aureus* HM290-1, *S. aureus* CR5 80, *S. aureus* HM1055, and *S. aureus* RN4220 strains were used as positive controls for the amplification of *ermA, ermB, ermC* and *msrA/*msrB genes, respectively.

RESULTS

STAPHYLOCOCCUS ISOLATES

Of 731 *Staphylococcus* strains, 254 (34.7%) were *S. aureus* and 477 (65.3%) were CoNS. Of the macrolide-resistant 335 isolates (45.8%), 63 (18.8%) were *S. aureus* and 272 (81.2%) were CoNS. Macrolide-resistance was observed in 24.8% of *S. aureus* and 57% of CoNS strains.

ANTIMICROBIAL SUSCEPTIBILITES

Fifty-four (85.7%) of the *S. aureus* strains and 198 (72.8%) of the CoNS strains were methicillin-resistant. With VITEK 2 system, 63 *S. aureus* and 272 CoNS strains were found to be resistant to macrolides (MIC values ≥8 μg/mL). Of these macrolide resistant strains, 120 were also resistant to clindamycin (MIC values ≥4 μg/mL). MLS_B resistance phenotypes of these strains determined by the D-zone test are given in Table 1.

DISTRIBUTION OF *erm* AND *msr* GENES

Macrolide-resistant 335 isolates were investigated for the presence of *ermA, ermB, ermC, msrA* and *msrB* genes by PCR. Distribution of the resistance genes in *Staphylococcus* strains is shown in Table 2. *erm* genes were more frequent among $iMLS_B$ and $cMLS_B$ resistance phenotypes, as expected. Among the resistant strains, *ermC* gene was the most frequent one in CoNS isolates. None of the strains carried the *ermB* gene alone. Of MLS_B resistant CoNS strains, 139 (51.1%) carried the *ermC* gene alone, and 46 (16.9%) CoNS strains carried *ermC* gene in combination with other resistance genes. On the other hand, *ermA* gene was more frequently found among *S.aureus* strains: 36 (57.1%) carried the *ermA* gene as the only resistance determinant, and 6 (9.5%) in combination with other resistance genes. All MS_B phenotype isolates carried at least one *msr* gene encoding efflux pumps. None of the strains carried *msrA* gene alone. All MS_B phenotyped *S. aureus* strains (n=5) carried *msrA+msrB* combination. The genetic background of MS_B phenotype CoNS strains were more complex: Of 85 MS_B phenotype CoNS strains, 61 (71.8%) carried *msrA+msrB* genes. Three (3.5%) methicillin sensitive CoNS (MS-CoNS) strains carried *msrB* gene alone. In 21 (24.7%) MS_B phenotype CoNS strains, *msr* genes were found in combination with *erm* genes. In 2 *S. aureus* isolates and 44 CoNS strains, *erm* and *msr* genes were found in various combinations. Of these 46 strains, 12 (26.1%) displayed the $iMLS_B$ phenotype, 13 (28.3%) displayed the $cMLS_B$ phenotype and 21 displayed (45.6%) MS_B phenotype. Phenotypic and genotypic correlations of the isolates are shown in Table 3.

DISCUSSION

The frequency of MLS_B resistance among staphylococci shows great variation in different geographical regions and patient groups.[9-13] In Turkey,

TABLE 1: MLS_B resistance phenotypes determined by D-zone test.

	S. aureus (n=63)		CoNS (n=272)		
	MRSA	MSSA	MR-CoNS	MS-CoNS	Total
Resistance phenotype	n (%)	n (%)	n (%)	n (%)	n (%)
$iMLS_B$	34 (62.9)	6 (66.7)	68 (34.3)	17 (22.9)	125 (37.3)
$cMLS_B$	17 (31.5)	1 (11.1)	87 (43.9)	15 (20.3)	120 (35.8)
MS_B	3 (5.6)	2 (22.2)	43 (21.7)	42 (56.8)	90 (26.9)
Total	54	9	198	74	335

MRSA: Meticilline resistant *Staphylococcus aureus*; MSSA: Meticilline sensitive *Staphylococcus aureus*; MR-CoNS: Meticilline resistant coagulase-negative staphylococci; MS-CoNS: Meticilline sensitive coagulase-negative staphylococci; $iMLS_B$: Inducible MLS_B resistance phenotype; $cMLS_B$: Constitutive MLS_B resistance phenotype; MS_B: MS_B resistance phenotype

TABLE 2: Distribution of the resistance genes.

	MRSA (n=54)			MSSA (n=9)			MR-CoNS (n=198)			MS-CoNS (n=74)			
Gene	**$iMLS_B$**	**$cMLS_B$**	**MS_B**	**$iMLS_B$**	**$cMLS_B$**	**MS_B**	**$iMLS_B$**	**$cMLS_B$**	**MS_B**	**$iMLS_B$**	**$cMLS_B$**	**MS_B**	**Total**
ermA	30	3	-	3	-	-	3	10	-	-	3	-	52
ermC	2	10	-	2	1	-	55	65	-	13	6	-	154
msrB	-	-	-	-	-	-	-	-	-	-	-	3	3
ermA+ermC	-	4	-	1	-	-	2	4	-	2	1	-	14
msrA+msrB	-	-	3	-	-	2	-	-	34	-	-	27	66
ermC+msrB	-	-	-	-	-	-	-	-	-	-	1	1	2
ermA+msrA+msrB	1	-	-	-	-	-	-	2	1	-	-	3	7
ermB+msrA+msrB	-	-	-	-	-	-	-	-	1	-	-	-	1
ermC+msrA+msrB	1	-	-	-	-	-	5	6	6	1	4	7	30
ermA+ermC+msrA+msrB	-	-	-	-	-	-	3	-	-	1	-	1	5
ermB+ermC+msrA+msrB	-	-	-	-	-	-	-	-	1	-	-	-	1
Total	34	17	3	6	1	2	68	87	43	17	15	42	335

MRSA: Meticilline resistant *Staphylococcus aureus*; MSSA: Meticilline sensitive *Staphylococcus aureus*; MR-CoNS: Meticilline resistant coagulase-negative staphylococci; MS-CoNS: Meticilline sensitive coagulase-negative staphylococci; $iMLS_B$: Inducible MLS_B resistance phenotype; $cMLS_B$: Constitutive MLS_B resistance phenotype; MS_B: MS_B resistance phenotype.

a number of investigators have studied the frequencies of the resistance phenotypes among *Staphyloccus* isolates, and striking variations were observed in the frequencies of $iMLS_B$ (7.8-20.8% in *S. aureus* and 24.3-58.3% in CoNS), $cMLS_B$ (24.3-58.3% in *S. aureus* and 40.2-57.8% in CoNS), and MS_B (0-20.8% in *S. aureus* and 0-21.6% in CoNS) phenotypes among *S. aureus* and CoNS strains.[14-17] In our study, $iMLS_B$ phenotype was more frequent among macrolide resistant *S. aureus* isolates (63.5% versus 31.3% in CoNS), while macrolide resistant CoNS strains were most frequently expressing the $cMLS_B$ phenotype (37.5% versus 28.6% in *S. aureus*). The MS_B phenotype was observed in 31.3% of the CoNS and 7.9% of *S. aureus* isolates.

The genes conferring resistance to MLS_B antibiotics were also investigated by multiplex PCR analysis by Aktas et al. in 102 erythromycin resistant staphylococci.[14] Of 78 CoNS isolates, %78.2 were found to carry the *ermC* gene, 8.9% carried the *ermA* gene, 6.4% carried the *ermB* gene and 11.5% carried the *msrA* gene. Among 24 *S .aureus* isolates, the frequencies of strains carrying the *ermA, ermC* and *ermA+ermC* genes were found to be 50%, 62.5%, and 37.5%, respectively. *ermC*-related macrolide resistance was more prevalent among both CoNS and *S. aureus*.[14] In our study, 36 (57.1%) of the 63 macrolide resistant *S. aureus* strains carried the *ermA* gene, while *ermC* gene was the most frequently found resistance gene among CoNS isolates (51.1%). This result is consistent with the findings of several previous studies.[1,6,18,19]

TABLE 3: Phenotype-genotype correlations of the *Staphylococcus* strains.

		Genotype		
Study strains	**Phenotype**	***erm* (+)**	***msr* (+)**	**Both *erm* and *msr* (+)**
S. aureus	$iMLS_B$	38	-	2
	$cMLS_B$	18	-	-
	MS_B	-	5	-
CoNS	$iMLS_B$	75	-	10
	$cMLS_B$	89	-	13
	MS_B	-	64	21

CoNS: Coagulase-negative staphylococci;
$iMLS_B$: Inducible MLS_B resistance phenotype;
$cMLS_B$: Constitutive MLS_B resistance phenotype; MS_B: MS_B resistance phenotype.

The *ermB* gene, which was initially found in *S. pyogenes* and *E. faecalis*, is not highly prevalent among *Staphylococcus* isolates.[6,20,21] The prevalence of *ermB* gene has been reported to be between 0 and 2.4% for *S. aureus* and 0 and 0.7% for CoNS in different studies.[6,22,23] In our study, none of the *Staphylococcus* isolates were found to carry the *ermB* gene as the only resistance determinant. Only 2 (0.7%) CoNS strains expressing the MS_B

phenotype were found to carry the *ermB* gene in combination with other resistance genes (*msrA, msrB* and *ermC*).

The underlying mechanism of the MS_B phenotype is the active efflux of erythromycin and streptogramin B antibiotics via transporters encoded by the *msr* genes. These strains remain susceptible to lincosamides and 16-membered ring macrolides.[4-6,21] Steward et al. have found the *msrA* gene alone in all MS_B phenotype isolates while *msrA* gene positivity rate of MS_B phenotype isolates has been found as 2.1% in *S. aureus* and 11.3% in CoNS strains in the study of Lina et al.[6,20] In our study, none of the isolates carried the *msrA* gene alone. All *msrA*-positive *Staphylococcus* strains (n=110), also carried the *msrB* gene. Only four MS-CoNS strains expressing the MS_B phenotype carried the *msrB* gene, either alone (n=3), or in combination with the *ermC* gene (n=1). All (n=90, 100%) of the MS_B phenotype *Staphylococcus* strains were *msrA* and/or *msrB* positive.

For the strains carrying both *msr* and *erm* genes (n=46), 21 (45.7%) expressed MS_B, 12 (26.1%) expressed $iMLS_B$, and 13 (28.3%) expressed $cMLS_B$ phenotypes. The genetic background was more directly correlated with the resistance phenotype in *S. aureus* strains. On the other hand, *erm* and *msr* gene combinations were more frequent in our CoNS strains. Two of 54 (3.7%) MRSA, 25 of 198 (12.6%) MR-CoNS and 19 of 74 (25.7%) MS-CoNS strains carried a combination of *erm* and *msr* genes, *ermC*+*msrA*+*msrB* being the most frequent (n=30). The expressed phenotype was either $iMLS_B$ or $cMLS_B$ in 17 (56.7%) of these strains. As expected, the presence of either of the *erm* genes masks the MS_B phenotype since *erm* genes confer a higher level of resistance to a wider range of antibiotics.[4] For the MS_B strains carrying both *erm* and *msr* genes, this presentation may probably be due to our inability to differentiate the MS_B phenotype strains from $iMLS_B$ phenotypes by D-zone test. Although the CLSI method suggests placing the disks 15-20 mm apart for *S. aureus* and 20-26 mm apart for CoNS,[7] and there are studies highlighting the working of distances up to 28 mm in the literature; there are also studies suggesting the use of closer distances between 10-15 mm for obtaining more discriminating results in the D-zone test.[5,7,9,24,25] In our study, we did not perform the D-zone test with closer distances for every strain, but we believe that, at least for some of the isolates, the distance between the clindamycin and erythromycin disks were too far for observing the D shaped zone, and misled us for determining these probable $iMLS_B$ strains as MS_B phenotypes. It is important to distinguish the $iMLS_B$ phenotype from the MS_B phenotype, as the former ones may become resistant when lincosamides are used to treat the infection, thus they must be reported as lincosamide resistant. On the other hand, isolates with the MS_B phenotype remain susceptible to lincosamides and must be reported as susceptible. Our result underlines the importance of determining the optimal spacing between the disks used in the D-zone test, or performing molecular tests for determining the presence of resistance genes.

CONCLUSION

In order to decrease treatment failure risk, resistance profiles in clinically important bacteria must be correctly identified in the clinical microbiology laboratory. Usually, determination of the resistance profiles are based on routine antimicrobial susceptibility tests. In order to obtain reliable results, antimicrobial testing must be performed according to the universally accepted methods, and results must be interpreted carefully. Despite these, phenotypic methods may not always reflect the genetic basis of the resistant microorganism.

Macrolides are among the most frequently prescribed antibiotics in Turkey, especially for upper respiratory tract and skin and soft tissue infections of the pediatric age group.[26,27] Resistance to MLS_B antibiotics is reported from many countries, as well as many regions from Turkey. During our study period, 57% of the CoNS and 24.8% of the *S. aureus* clinical isolates were found to express a MLS_B resistance phenotype. Interpreting phenotypic methods may be problematic, especially for discriminating MS_B phenotype strains from $iMLS_B$ phenotypes. Investigating genes conferring resistance to MLS_B antibiotics is important for reducing

the risk of treatment failure especially for erythromycin resistant, clindamycin susceptible strains. Due to the increasing resistance problem in staphylococcal infections, clinicians must be aware of the risk of resistance development while prescribing MLS_B group of antibiotics.

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