

**ANTIBACTERIAL SUSCEPTIBILITY PATTERNS AND CROSS-RESISTANCE OF METHICILLIN RESISTANT AND SENSITIVE STAPHYLOCCUS AUREUS ISOLATED FROM THE HOSPITALIZED PATIENTS IN SHIRAZ, IRAN**

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**ABSTRACT**

Nosocomial infections caused by methicillin-resistant staphylococci (MRSA) pose a serious problem in many countries. This study aimed to determine the antibacterial susceptibility patterns of methicillin sensitive and resistant *Staphylococcus aureus* isolates from the hospitalized patients. Totally 356 isolates of *Staphylococcus aureus* (*S. aureus*) including 200, 137 and 19 corresponding to MSSA, MRSA, and intermediate MRSA strains, respectively were isolated. Antibacterial susceptibility patterns of the isolates to 14 antibiotics were examined using Kirby-Bauer method. MICs of 15 antibiotics to 156 MRSA isolates were determined by E test method. Cross-resistances of MRSA isolates (137+19) to the other tested antibiotics were also determined. *S.aureus* with high frequencies were isolated from the blood, sputum and deep wound samples. All of 200 MSSA isolates were sensitive to oxacillin, vancomycin, tecoplanin, rifampin, linezolid, quinupristin/dalfopristin, mupirocin and fusidic acid. A gradient of reduced susceptibility of MSSA to cephalexin, co-trimoxazole, ciprofloxacin, clindamycin, tetracycline, erythromycin and gentamicin were evident. MRSA isolates were sensitive to vancomycin, tecoplanin, linezolid, quinupristin/dalfopristin, mupirocin and fusidic acid, while reduced susceptibility of them to rifampin, co-trimoxazole, clindamycin, cephalexin, tetracycline, ciprofloxacin, erythromycin and gentamicin were observed. MRSA isolates exhibited a high range of cross-resistance to the eight tested antibiotics. Overall, co-trimoxazole, ciprofloxacin, clindamycin, tetracycline, erythromycin and gentamicin showed low activity against MSSA and MRSA isolates which may indicate they are not suitable to be used in clinical practices. To preserve the effectiveness of antibiotics, rational prescription and concomitant application of preventive measures against the spread of MRSA are recommended.

**Key words:** MRSA; minimum inhibitory concentration; empirical therapy

**INTRODUCTION**

*Staphylococcus aureus* is a major nosocomial pathogen that causes a range of diseases such as endocarditis, osteomyelitis, toxic-shock syndrome, food poisoning,

carbuncles, and boils (21). With the discovery of  $\beta$ -lactam antibiotics in the late 1930s, remarkable hope for the treatment of infectious disease appeared. However, in the early 1950s, acquisition and spread of  $\beta$ -lactamase producing plasmids thwarted the effectiveness of penicillin for treating *S. aureus*

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infections. In 1959, methicillin, the synthetic penicillin, was introduced while by 1960, methicillin-resistant *S. aureus* strains were identified. It was the direct result of *S. aureus* acquiring the *mecA* gene, which encodes for an altered penicillin binding protein gene (PBP2a) (2). By the early 1960s, European hospitals were reporting outbreaks of MRSA infections, and subsequently MRSA clones spread to health-care institutions around the world (27). In the United States, MRSA is responsible for approximately 25% of nosocomial infections, and reports of community acquired MRSA infections are increasing (28). The multidrug resistant phenotypes of MRSA strains and their intrinsic  $\beta$ -lactam resistance make them difficult and costly to treat (5, 24). In some medical institutions such as New York city hospitals, MRSA accounts for approximately 29% of the nosocomial infections and 50% of the associated deaths (25). Similarly, the high prevalence of MRSA in Shiraz and other parts of Iran have been reported previously (8, 12, 20). Controlling MRSA remains a primary focus of the most hospital infection control programs (3). Unfortunately, the clinical management of the MRSA infected patients has been complicated by the increasing proportion of infections, a problem that was initially limited to the hospital-acquired strains but has now extended to the community-associated strains (24,28). Attributable mortality rates for *S. aureus* bacteraemia (SAB) in the developed world have risen up to 30% (7,10,15), and the costs of treating nosocomial infections, screening for MRSA carriage, and changes in prescribing practice to include the coverage for MRSA are considerable. The availability of over-the-counter antibiotics in many developing countries is likely to be a major driver of drug resistance.

This study seeks to determine the prevalence of MRSA, MSSA and to analyze qualitative and quantitative aspects of antibiotics susceptibility patterns of the isolated bacteria in hospitalized patients. Furthermore, the cross-resistance of MRSA isolates to the tested antibiotics will be determined. Availability of such data have clinical implications for selecting suitable empirical antibiotic therapy, reducing length of stay in the hospital, as well as reducing the

mortality/morbidity rates in the patients with infectious diseases. Furthermore, findings of the above regional studies could be comparatively developed to other parts of the world.

## MATERIALS AND METHODS

### Isolation of staphylococci

Totally 356 consecutive non-duplicate *Staphylococcus aureus* were isolated from the blood, urine, sputum, deep wound, nasal washing, skin lesion, nose swab, abscess, CSF, joint fluids, eye discharge, pleural fluid, toe web and ascitic fluid of patients from May 2006 to March 2007 in Nemazee hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. This hospital is tertiary setting facilities with one thousand beds. The isolates were identified as staphylococci based on gram stain, morphology, catalase, bacitracin disc sensitivity, coagulase and DNase activities using commercial media and reagent (catalase test with hydrogen peroxidase 3%:coagulase test with fresh rabbit plasma; bacitracin sensitivity with Mast antibiotic disc; UK and DNase activity with DNase test agar supply from Merck company, Germany).

### Susceptibility patterns of the isolates

**Qualitative assay:** Qualitative antibacterial susceptibility of 156 MRSA and 200 MSSA isolates were determined according to the standard disk diffusion (Kirby-Bauer) method using Mast Co (Mast Co, Merseyside, UK). *S. aureus* (ATCC 25923) were used as controls for the antibiotic susceptibility determination. Antibacterial susceptibility pattern was interpreted as recommended by Clinical Laboratory Standards Institute (CLSI, 22). Susceptibilities of MRSA and MSSA to the panel of antibiotics including gentamicin (GM; 10 $\mu$ g), cephalexin (CN; 30 $\mu$ g), co-trimoxazole, (SXT; 25 $\mu$ g), rifampin (RF;5 $\mu$ g), ciprofloxacin (CIP;5 $\mu$ g), vancomycin (V;30 $\mu$ g), tecoplanin (TEC;30 $\mu$ g) oxacillin (OX;1 $\mu$ g), erythromycin (E;15 $\mu$ g), quinupristin/dalfopristin (QD;15 $\mu$ g), tetracycline (Te;30 $\mu$ g), clindamycin (CD;2 $\mu$ g), linezolid (LZD;30 $\mu$ g), mupirocin (MUP; 10  $\mu$ g), and fusidic acid (FUS; 10  $\mu$ g) were determined.

**Quantitative assay:** MICs of the above 15 antibiotics to the 156 isolates of MRSA were determined by the E test method (AB Biodisk, Sweden). American Typing Collection (ATCC 25923) of *S. aureus* was used as a control strain in antibacterial susceptibility testing. Following overnight incubation, the MICs breakpoints were interpreted according to the manufacturer's instructions.

#### Cross-resistance profile

To carefully characterize the patterns of antibiotic resistance of MRSA, cross-resistance of the isolates to 8 antibiotics with reduced activities were calculated by SPSS version 11.5 software.

#### RESULTS

*S. aureus* with high frequencies were isolated from the blood, sputum and deep wound samples, while low frequencies of this bacterium were isolated from ascetic fluid and perineal samples (Table 1). All of the 200 MSSA isolates were found sensitive to eight antibiotics and a gradient of reduced susceptibility of the MSSA to seven antibiotics were noticed

(Table 2). Based on MICs determination, all the 156 MRSA were sensitive to vancomycin, tecoplanin, linezolid, quinupristin/dalfopristin, mupirocin and fusidic acid and a reduced gradient of susceptibility of MRSA to the rest of antibiotics were observed (Table 2). To interpret antibiotic resistance patterns of MRSA more precisely, cross-resistance of these isolates to the eight antibiotics with reduced anti-MRSA activities were calculated and presented in Table 3. MRSA isolates showed high range of cross-resistance to the eight tested antibiotics including co-trimoxazole (93-100 %), clindamycin (84-100%), cephalexin (83-100 %), tetracycline (78-100%), rifampin (65-100%), ciprofloxacin (82-99%) erythromycin (76-99%) and gentamicin (70-87%). Similarly, high range of MIC<sub>50</sub> and MIC<sub>90</sub> values for MRSA isolates were noticed. Values of MIC<sub>50</sub> and MIC<sub>90</sub> for the tested antibiotics against the MRSA isolates are collected in Table 4. Co-trimoxazole, ciprofloxacin, clindamycin, tetracycline, erythromycin and gentamicin showed low activities against all the isolates of *S. aureus* (MRSA, MSSA). Antibiotics sensitivity patterns of all MSSA and MRSA isolates were illustrated in Figure 1.

**Table 1.** Source of MRSA and MSSA.

Source	MRSA (%)	MSSA (%)	Total (%)
Blood	54 (15.1)	55(15.3)	109 (30.6)
Sputum	25 (7.0)	25 (7.0)	50 (14.0)
Wound	22 (6.2)	26 (7.3)	48 (13.5)
Urine	8 (2.2)	18( 5.0)	26(7.3)
Nasal swab	10 (2.9)	13 (3.6)	23(6.4)
Skin lesion	6 (1.7)	15 (4.2)	21 (5.9)
Nose discharge	6 (1.7)	13 (3.6)	20(5.6)
Abcess	8 (2.2)	7 (1.9)	15 (4.2)
CSF	8 (2.2)	10 (2.9)	18(5.0)
Joint fluids	4 (1.1)	3 (0.9)	7 (1.9)
Eye discharge	1 (0.3)	4(1.1)	5 (1.4)
Pleural fluid	2 (0.6)	4(1.1)	5 (1.4)
Toe web	1 (0.3)	3 (0.9)	4 (1.1)
Ascitic fluid	1 (0.3)	2 (0.6)	3 (0.9)
Perinea sample	-	2(0.6)	2 (0.6)
<b>Total</b>	<b>156 (43.8)</b>	<b>200(56.2)</b>	<b>356 (100)</b>

**Table 2.** Susceptibility patterns of MSSA and MRSA isolates to antibiotics with reduced sensitivity.

Antibiotics							
	SXT(%)	CN(%)	CIP(%)	CD(%)	TE(%)	E(%)	GM(%)
MSSA	S=188(94)	S=189(94.5)	S=154(77)	S=142(71)	S=140(70)	S=96(48)	S=38(19)
	R=8(4)	R=5(2.5)	R=7(3.5)	R=11(5.5)	R=18(9)	R=14(7)	R=100(50)
	IR=4(2)	IR=6(3)	IR=39(19.5)	IR=47(23.5)	IR=42(21)	IR=90(45)	IR=62(31)
MRSA	RF (%)	SXT (%)	CD (%)	CN (%)	TE (%)	CIP (%)	E (%)
	S=139(89.1)	S=48(30.7)	S=37(23.7)	S=33(21.1)	S=27(17.3)	S=25(16.0)	S=14(10.9)
	R=15(9.6)	R=101(64.8)	R=105(67.3)	R=115(73.7)	R=123(78.8)	R=119(76.2)	R=117(75)
	IR=2(1.3)	IR=7(4.5)	IR=14(9.0)	IR=8(5.2)	IR=6(3.9)	IR=12(7.8)	IR=22(14.1)
							IR=13(8.4)

Abbreviation: SXT; co-trimoxazole, CN cephalxin, CIP; ciprofloxacin, CD; clindamycin, TE; tetracycline, E; erythromycin, GM; gentamicin, RF; rifampin, S sensitive, R; resistant, IR; intermediate resistant.

**Table 3.** Cross-resistance of MRSA to the tested antibiotics.

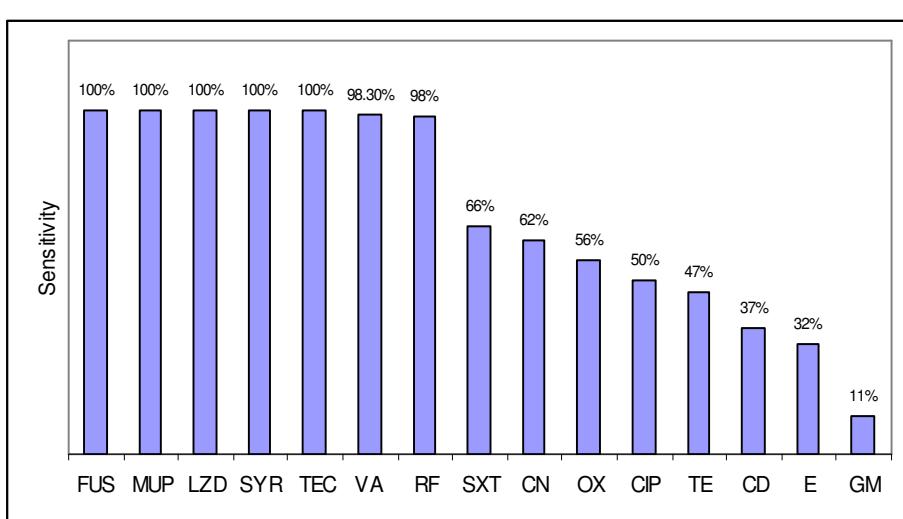
n	Number of isolates and percent (values in parenthesis) resistant to							
	GM	E	CIP	TE	CN	CD	SXT	RF
GM	155		139 (87)	131 (85)	129 (83)	123 (79)	119 (77)	108 (70)
E	139	138 (99)		124 (89)	119 (86)	120 (86)	113 (81)	106 (76)
CIP	131	130 (99)	125 (95)		115 (88)	115 (88)	113 (86)	107(82)
TE	129	129 (100)	119 (93)	114 (88)		113 (88)	106 (82)	101 (78)
CN	123	123 (100)	120 (98)	115 (93)	113 (92)		107 (87)	102 (83)
CD	119	119 (100)	113 (95)	113 (95)	113 (95)	106 (89)		100 (84)
SXT	108	108 (100)	106 (98)	107 (99)	107 (99)	101 (94)	100 (93)	
RF	17	17 (100)	17 (100)	17 (100)	16 (94)	17 (100)	15 (88)	11 (10)

Abbreviation: GM; gentamicin, E; erythromycin, CIP; ciprofloxacin, TE; tetracycline, CN cephalxin, CD; clindamycin, SXT; co-trimoxazole, RF; rifampin

**Table 4.** Range of MIC<sub>50</sub> & MIC<sub>90</sub> values for MRSA isolates to the tested antibiotics.

Antibiotics	OX	VA	TEC	LZD	SYR	MUP	FUS	RF	SXT	CD	CN	CIP	E	GM
MIC 50µg/ml	256	2	0.75	0.75	0.5	0.094	0.125	0.012	32	256	265	32	256	256
MIC 90µg/ml>256		4	1.5	1	0.75	0.125	0.19	4	32	256	>256	32	>256	256

Abbreviations: OX:oxacillin,VA:vancomycin,TEC:tecoplanin,LZD:linezolid,SYR:quinupristin/dalfopristin,MUP mupirocin,FUS: fusidic acid, rifampin, SXT:co-trimoxazole, CD:clindamycin, CN: cephalxin, CIP: ciprofloxacin,E: erythromycin and GM:gentamicin.



**Figure 1.** Sensitivity patterns of 356 isolates of MSSA & MRSA to the 15 tested antibiotics Abbreviations: FUS: fusidic acid, MUP: mupirocin, LZD: linezolid, SYR: quinupristin/dalfopristin, TEC: tecoplanin, VA: vancomycin, R: rifampin, SXT: co-trimoxazole, CN: cephalxin, OX: oxacillin, CIP: ciprofloxacin, TE: tetracycline, CD: clindamycin, E: erythromycin and GM: gentamicin.

## DISCUSSION

Methicillin-resistant strains of *S. aureus* are important nosocomial infections worldwide. Our data indicate that *S. aureus* with high frequency was isolated from the blood samples (30.6 %), of which 50% were MRSA, followed by sputum and deep wound samples with 14 % and 13.5 %, respectively. The high incidence of *S. aureus* bacteremia (SAB), mostly driven by community acquired (CA) infections was also previously reported (7, 10, 14, 15). Studies from various countries revealed that the rates of SAB are rising and the proportion due to methicillin ( $\beta$ -lactam) resistant MRSA is also increasing (7, 15). Wyllie *et al.* (29) reviewed the rates of nosocomial SAB in two Oxfordshire hospitals in England between 1997 and 2004. They showed an increase in the rates of nosocomial SAB, but the incidence of methicillin susceptible *S. aureus* (MSSA) bacteremia was unchanged over the period. However, in the UK, Johnson *et al.* (13) observed a marked rise both in the number of SAB cases and in the proportion due to MRSA reported by hospital laboratories. According to this report, the number of isolated MRSA from 1990 to 2004 ranged between 2 % to 40 %, where the latter value stands at plateau level in recent years. Kaech *et al.* (15) viewed SAB in a Swiss hospital with a low incidence of MRSA. The rate of SAB increased by 23%. This change was related to a 140% increase in community acquired bacteremia, which was in turn attributed largely to intravenous drug use (15). The SCOPE project (6), a prospective surveillance project in the USA, found that 20% of nosocomial bacteremia between 1995 and 2002 were due to *S. aureus*. The proportion of the strains resistant to methicillin rose from 22% in 1995 to 57% in 2001. Collectively, these data lend support to the idea that the increased ratio of MRSA/MSSA especially in patients suffering from bacteremia due to MRSA could be a global issue which demands international cooperation to prevent the potential worldwide crisis.

Relatively high incidence of skin and wound infections (19.5%) was noticed in the present study. The results are consistent with the previous reports on the prevalence of

cutaneous MRSA infections in US emergency room patients (18).

Evaluation of the antibiotic susceptibility patterns of MSSA and MRSA indicates the sensitivity of MRSA isolates were markedly reduced as compared with that of MSSA isolates. Nevertheless, complete sensitivity of MSSA and MRSA to the six tested antibiotics including vancomycin, tecoplanin, linezolid, quinupristin/dalfopristin, mupirocin and fusidic acid could provide relatively more alternative choice of the antibiotics available for treatment. Given the low activities of co-trimoxazole, ciprofloxacin, clindamycin, tetracycline, erythromycin and gentamicin against all the *S. aureus* isolates, we may suggest that they are not suitable for use in clinical practices. Low activities of these antibiotics against *S. aureus* could be due to the selection of resistant isolates resulting from mutations at drug target sites, or from the disturbance of drug accumulation in cytoplasm due to cell wall or cell membrane rearrangement (14, 16, 17, 30). Alternatively, resistance genes could transfer due to mobile genetic elements such as plasmid, transposon and integrons (1, 11, 23, 26). Nevertheless, comparison of MICs values in particular MIC<sub>50</sub> and MIC<sub>90</sub> may suggest that more likely the latter phenomenon could be responsible for the emergence of the majority of isolates with high MIC values. To determine the mechanisms of MRSA resistance in our isolates, precise molecular methods such as staphylococcal cassette chromosome typing (SCC typing) and sequencing of resistant determinants should be initiated. The findings indicate that the minority of resistant isolates could emerge due to the mutation of those with low MIC values. Apparently, continuous antibiotics pressure on sensitive isolates could facilitate the domination of any emerging possible resistant isolates. Unfortunately, most of the tested antibiotics in this study are extensively used in our clinics for prophylactic and treatment purposes. Therefore, comprehensive control measures and prudent application of effective antibiotics should be adopted to overcome this critical situation (9). It is worth mentioning that two points should be considered for clinical use of antibiotics; first of all the cost-effectiveness of the antibiotics and the second is the pharmacological

availability of different types of antibiotics for various clinical purposes. For example, linezolid is an expensive antibiotic as compared to tecoplanin (19). Mupirocin is likely available in the form of topical cream and ointment preparations (4) which limit its systemic application.

It is well known that MRSA characteristically are multi-drug resistant strains (16). High incidence of cross-resistance of MRSA noticed in this survey may indicate that different resistance mechanisms are involved in the resistance of MRSA to different classes of antibiotics. Therefore, every isolate of MRSA should be considered potentially multi-drug resistant with respect to its clonal selection and transferring of the isolates to the other hospitalized patients (9).

In summary, decreased susceptibility of MRSA to the daily consuming antibiotics indicates that special controlling protocol should be adopted in our clinics and hospitals. This program should include direct or indirect promotion of control measures in hospital wards and clinics to prevent the transferring of MRSA from patient to patient. Moreover, rational prescription of sensitive antibiotics and ceasing of the over-the-counter presenting of them are also recommended. The application of this protocol along with periodical surveillance of antibacterial susceptibility patterns of MRSA and MSSA could preserve their sensitivity levels to the antibiotics and alleviate the situation, accordingly.

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