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**Original Article**

# The Detection of Mupirocin Resistance and Nasal Carriage of Methicillin Resistant *Staphylococcus aureus* among Healthcare Workers at University Hospitals of Tehran, Iran

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**Abstract**

**Background:** Nasal mupirocin is found to eradicate effectively methicillin-resistant *Staphylococcus aureus* (MRSA) from colonized patients, but there are concerns about resistant strains. The aim of this study was to detect the mupirocin resistance and nasal carriage of methicillin resistant *S. aureus* among healthcare workers (HCWS) at the university hospitals of Tehran.

**Methods:** Totally 270 nasal swabs were collected and *S. aureus* were identified by confirmatory tests in 2013. Determination of oxacillin and mupirocin resistance was performed by disk diffusion method and the mupirocin MIC assessed using E-test. The *ileS*-2 (*mup*A) and *mec*A genes were detected in DNA extracts by multiplex PCR.

**Results:** The prevalence of *S. aureus* nasal carriage among HCWs was 14.44%. E-test and disk diffusion methods showed 5 and 4 mupirocin resistant isolates, respectively. Statistically significant difference was observed between sex ($P$=0.035), hospitals ($P$=0.0001) and occupation ($P$=0.009) with nasal carriage of *S. aureus*. A significant difference was found between sex ($P$=0.041) and occupation (0.034) with regard to MRSA carriage. All MRSA isolates were susceptible to linezolid, fusidic acid and vancomycin.

**Conclusion:** Since the HCWs play an important role as a reservoir for resistant isolates in the hospital setting, regularly screening should be performed for identification of nasal carriers.

**Keywords:** Methicillin-resistant *Staphylococcus aureus*, Mupirocin, Healthcare workers, Nasal carriers

## Introduction

The global emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) has become a thoughtful problem for public health. MRSA has been identified as one of the major cause of nosocomial infections, which is resistant to various classes of antibiotics (1). Staphylococci could colonize the skin and nasal mucosa (2).

Eradication or inhibition of staphylococcal colonization is still considered as an important strategy to prevent infection and transmission of these strains. Rationale behind such a strategy is that the most staphylococcal infections are caused by endogenous strains; so, carriage of *S. aureus* is a major risk factor for subsequent infections (3). The eradication of this organism in nasal carriers with mupirocin has been shown to reduce the rate of nosocomial infections in hospitalized patients (4).

Mupirocin is available as an antimicrobial agent. Nasal formulation of mupirocin was recommended by the Food and Drug Administration of United States (US FDA) as part of an infection control for using in the eradication of nasal car-

riage of *S. aureus* in adult patients and healthcare workers (HCW) to reduce the risk of infection among high-risk patients for acquisition of MRSA. Using mupirocin is limited for infection control and other prophylactic functions in order to tackle the concerns of the emergence of resistance (5).

There are three groups of susceptibility to mupirocin that include susceptible to mupirocin (MIC≤4µg/ml), low level resistant to mupirocin (MIC to64µg/ml) and high level resistant to mupirocin (MIC≥512 µg/ml) (6). Currently there is no desirable method for interpreting the susceptibility tests of mupirocin. Existing methods based on MIC determination by E-test method and detection of resistance genes by PCR are used (5). Since HCWs are in direct contact by the patients, they have a significant role in dissemination of resistant isolates in the hospital setting.

Therefore, we decided to do present study in order to evaluate the prevalence of MRSAs that are resistant to mupirocin, isolated from HCWs nasal carriers and accomplish molecular techniques and the MIC together for epidemiological purposes. Antibiotic susceptibility pattern of MSSA and MRSA isolates was determined as well. If nasal carriers identified, the therapeutic measures can be proceed to prevent the dispersion of resistant isolates in hospital setting.

## Materials and Methods

### Study design

In this cross sectional survey 270 HCWs nasal swabs were collected from five hospitals affiliated to Tehran University of Medical Sciences (TUMS) in 2013. All participants gave written informed consent.

### Bacterial isolation

After sampling, using sterile swabs, samples immediately transferred to transport medium moved to the Department of Pathobiology, then sub cultured on blood agar and incubated for 24 hours at 37 °C. Identification of *S. aureus* was performed by confirmatory tests [Gram's stain, catalase, coagulase and DNase tests and mannitol fermentation on mannitol salt agar (MSA)].

### Antibiotic susceptibility tests

### Disk diffusion method

The antibiotic susceptibility pattern was determined by the disk diffusion method. The antibiotics used in this study included: amikacin (30 µg), ciprofloxacin (5 µg), erythromycin (30 µg), fusidic acid (5 µg), gentamicin (10 µg) linezolid (30 µg), mupirocin (5 µg), oxacillin (1 µg), rifampin (5 µg), tetracycline (30 µg), tobramycin (10 µg) and vancomycin (30 µg). (MAST Diagnostics, Merseyside, U.K.). This was carried out on Mueller-Hinton agar medium (for oxacillin containing 4% NaCl) and growth inhibition zones were measured and interpreted according to the CLSI guidelines (7). *S. aureus* ATCC29213 was used as control strain.

### Determination of minimal inhibitory concentration (MIC)

The mupirocin MIC assessed using E-test® mupirocin strips (AB Biodisk**,** Solna, Sweden) according to the manufacture's guidelines**.** Strains were considered susceptible if MIC was ≤4 mg/l and levels of mupirocin resistance were defined as low-level with MIC 8–256 mg/l and high-level with MIC ≥512 mg/l.

### DNA extraction

DNA was extracted using a DNeasy kit (Qiagen, Valencia, CA) as recommended by the manufacturer.

### Multiplex PCR

The *ile*S-2 (*mupA* gene**)** and *mec*A genes were detected in DNA extracts by multiplex PCR assay, as described previously (8) with some modifications (Table 1). The genes were amplified on an Eppendorf (Hamburg, Germany) thermocycler with the final volume of 50 µlit containing 24 µlit of Qiagen HotStarTaq master mix (Invitrogen, Carlsbad, CA, contain PCR buffer with 3 mM MgCl2, 400 µM of each dNTP and 2.5 units HotStarTaq DNA Polymerase), 2 µlit of each primer (20 pMol, MecA and Mup), 14 µlit of RNase-free water and 8 µlit of DNA template. Then products were electrophoresed on agarose gel and the presence or absence of resulting bands was evaluated.

### *Statistical analysis*

Data were analyzed using SPSS statistical software, version 16.0. The categorical data were compared using the Chi-square test or Fisher's exact test and quantitative variables were compared by one-way ANOVA. Statistical significance was set at 0.05 levels.

**Table 1:** Multiplex PCR condition and primers used in this study

| Gene | Primers | Relevant produced product | positive control | Negative control | Amplification condition |
|---|---|---|---|---|---|
| *mecA* | MecA1 (5'- GTA GAA ATG ACT GAA CGT CCG ATA A-3')<br>MecA2 (5'-CCA ATT CCA CAT TGT TTC GGT CTAA-3') | 310 bp | Oxacillin-resistant *S. aureus* ATCC 33591 | Oxacillin-susceptible *S. aureus* ATTCC 25923 | Initial denaturation: 94°C, 5 min 35amplification cycles: denaturation :94°C, 35 s annealing: 58°C, 30 s elongation:72°C, 45 s final elongation:72°C, 10 min |
| *ileS*-2 (*mupA* gene ) | MupA (5'-TAT ATT ATGCGA TGG AAG GTT GG-3')<br>MupB (5'-AAT AAAATC AGC TGG AAA GTG TTG-3') | 456 bp | Mupirocin-resistant *S. aureus* HU1A | Mupirocin-susceptible *S. aureus* HU9A | |

## Results

Totally 270 nasal swabs were taken from HCWs (including physicians, nurses, paramedical staff and crewmembers). The mean age of HCWs was 34.21 years (range from 21 to 53 years) and male to female ratio of 0.481(183 female and 87 male). Of 270 samples, 39 *S. aureus* (14.44%) were isolated, among which 17 (43.58%) were resistant to methicillin (Table 2). All these strains were isolated from A, B and C hospitals and there was no *S. aureus* nasal carrier among HCWs of D and E hospitals. Demographic characteristics of the nasal carriers of *S. aureus* are summarized in Table 3.

**Table 2:** Characteristics of collected specimens

| Hospitals | n(%) of collected swabs | n(%) of isolated *S. aureus* | n(%) of isolated methicillin-resistant *S. aureus*(MRSA) | n(%) of isolated mupirocin-resistant *S. aureus*(MuRSA) |
|---|---|---|---|---|
| A | 35(12.97) | 14(35.9) | 7(41.18) | 2(40) |
| B | 43(15.92) | 11(28.2) | 3(17.64) | 1(20) |
| C | 79(29.27) | 14(35.9) | 7(41.18) | 2(40) |
| D | 70(25.92) | 0 | 0 | 0 |
| E | 43(15.92) | 0 | 0 | 0 |
| Total | 270(100) | 39(100) | 17(100) | 5(100) |

**Table 3:** Demographic characteristics of *S. aureus* nasal carriers

| Characteristics | Mean Age (Year) | Work Experience Mean (Year) | Sex (No.) | | Designation |
|---|---|---|---|---|---|
| Hospitals | | | F | M | |
| C | 30 | 6 | 7 | 7 | physician:2/Paramedical staff:3/Nurse:8 crew members:1 |
| B | 37 | 11 | 7 | 4 | Physicien:2/Paramedical staff:2/Nurse:5 crew members:2 |
| A | 38 | 12 | 7 | 7 | Physicien:2/Paramedical staff:1/Nurse:8 crew members:3 |

Using E-test method, 5 isolates were identified as mupirocin resistant *S. aureus* (MuRSA), while disk diffusion method showed four MuRSA. Multiplex PCR assay results showed that two *S. aureus* were positive for *mupA* gene and both of them showed high level resistance to mupirocin (MIC>1024). All MRSA isolates were positive for *mecA* gene. MIC range for all strains studied for mupirocin resistance was between < 4 and > 1024 (Table 4). Furthermore, it is notable that all mupirocin resistant isolates were MRSA and there were no MuRSA among methicillin susceptible *S. aureus* (MSSA). The frequencies of MRSA, MSSA and MuRSA isolates were different (Table 2). Significant difference was observed between the hospitals under studied with nasal carriage of *S. aureus* (Table 5).

**Table 4:** Characteristics of mupirocin-resistant *S. aureus* isolates

| Isolate | *mecA*/*mupA* | Susceptibility to mupirocin by disk diffusion method | Mupirocin MIC(µg/ml) |
|---|---|---|---|
| S2 | +/- | R | 24 |
| S9 | +/- | R | >1024 |
| M9 | +/- | R | 24 |
| SH4 | +/+ | S | >1024 |
| SH10 | +/+ | R | >1024 |

**Table 5:** Statistical analysis for nasal carriage of *S. aureus* among HCWs

| Variable | Nasal carrier (n=39) | | *P*-Value | | Odds ratio | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | MSSA, No. (%) | MRSA, No. (%) | *S. aureus* carrier status | MRSA carrier status | 95% Confidence Interval | | | | | |
| | | | | | Upper | | Lower | | Value | |
| | (n=22) | (n=17) | | | *S. aureus* | MRSA | *S. aureus* | MRSA | *S. aureus*[1)] | MRSA[2)] |
| **Hospital** | | | | | | | | | | |
| A | 7(31.8) | 7(41.18) | (*P*=0.000) | (*P*=0.436) | | | | | | |
| B | 8(36.4) | 3(17.64) | | | | | | | | |
| C | 7(31.8) | 7(41.18) | | | | | | | | |
| D | 0 | 0 | | | | | | | | |
| E | 0 | 0 | | | | | | | | |
| **Sex** | | | (*P*=0.035) | (*P*=0.041) | 4.660 | 0.972 | 1.046 | 0.067 | 2.208 | 0.255 |
| Female | 15(68.2) | 6(35.3) | | | | | | | | |
| Male | 7(31.8) | 11(64.7) | | | | | | | | |
| **Age(years)** | | | | | | | | | | |
| <30 | 6(27.28) | 9(52.94) | (*P*=0.285) | (*P*=0.142) | | | | | | |
| 30-40 | 8(36.36) | 6(35.3) | | | | | | | | |
| >40 | 8(36.36) | 2(11.76) | | | | | | | | |
| **Years of Working** | | | (*P*=0.437) | (*P*=0.103) | | | | | | |
| 0-9 | 9(40.9) | 12(70.6) | | | | | | | | |
| 9-15 | 4(18.2) | 3(17.64) | | | | | | | | |
| 15-29 | 9(40.9) | 2(11.76) | | | | | | | | |
| **Occupation** | | | | | | | | | | |
| Nurse | 8(36.36) | 12(70.6) | (*P*=0.009) | (*P*=0.034) | | | | | | |
| paramedical staff | 6(27.27) | 0 | | | | | | | | |
| crew member | 6(27.27) | 2(11.76) | | | | | | | | |
| Physician | 2(9.1) | 3(17.64) | | | | | | | | |

[1)] : Odds Ratio for *S. aureus* nasal colonization (Negative / Positive)
[2)] : Odds Ratio for MRSA nasal colonization (Negative / Positive)

There was no significant difference between the age and years of working in hospital with regard to nasal carriage of MSSA, MRSA and MuRSA. But statistically significant difference was observed between nursing occupation with nasal carriage of MSSA, MRSA but not with MuRSA (Table 5 and 6). A significant relation was observed between the sexes with regard to the nasal carriage of *S. aureus* (*P*=0.035) and MRSA (*P*=0.041). All MSSA and MRSA strains were susceptible to linezolid, fusidic acid and vancomycin. Antibiotic susceptibility pattern of MRSA and MSSA isolates is presented in Table 7.

**Table 6:** Statistical analysis for nasal carriage of MuRSA among HCWs

| Variable | Nasal carrier (n=39) | | *P*-value | Odds ratio | | |
|---|---|---|---|---|---|---|
| | MuSSA No. (%) (n=34) | MuRSA No. (%) (n=5) | | 95% Confidence Interval Upper | Lower | Value[1)] |
| Age | | | *P* value > 0.05 (*P*=0.950) | | | |
| <30 | 13(38.23) | 2(40) | | | | |
| 30-40 | 12(35.30) | 2(40) | | | | |
| >40 | 9(26.47) | 1(20) | | | | |
| Sex | | | *P* value > 0.05 (*P*=0.162) | 1.737 | 0.018 | 0.175 |
| Female | 20(58.82) | 1(20) | | | | |
| Male | 14(41.18) | 4(80) | | | | |
| Years of Working | | | *P* value > 0.05 (*P*=0.388) | | | |
| 0-9 | 17(50) | 4(80) | | | | |
| 9-15 | 7(20.59) | 0 | | | | |
| 15-29 | 10(29.41) | 1(20) | | | | |
| Occupation | | | *P* value > 0.05 (*P*=0.343) | | | |
| nurse | 16(47.06) | 4(80) | | | | |
| paramedical staff | 6(17.65) | 0 | | | | |
| crew member | 8(23.53) | 0 | | | | |
| Physician | 4(11.76) | 1(20) | | | | |

[1)]: Odds Ratio for Mupirocin (Resistance / sensitive), MuSSA, mupirocin susceptible *S.aureus*

**Table 7:** Antibiotic susceptibility pattern of MRSA and MSSA isolated from HCWs

| Antibiotic | MSSA (N = 22), n (%) | | MRSA (N = 17), n (%) | |
|---|---|---|---|---|
| | S | R | S | R |
| Amikacin | 21(95.45) | 1(4.55) | 5(29.40) | 12(70.60) |
| Ciprofloxacin | 21(95.45) | 1(4.55) | 7(41.2) | 10(58.80) |
| Erythromycin | 21(95.45) | 1(4.55) | 2(11.80) | 15(88.20) |
| Fusidic acid | 22(100) | 0 | 17(100) | 0 |
| Gentamicin | 13(59.10) | 9(40.9) | 3(17.65) | 14(82.35) |
| Linezolid | 22(100) | 0 | 17(100) | 0 |
| Mupirocin | 22(100) | 0 | 12(70.60) | 5(29.40) |
| Oxacillin | 22(100) | 0 | 0 | 17(100) |
| Rifampin | 22(100) | 0 | 16(94.1) | 1(5.9) |
| Tetracycline | 20(90.90) | 2(9.10) | 3(17.65) | 14(82.35) |
| Tobramycin | 22(100) | 0 | 15(88.2) | 2(11.80) |
| Vancomycin | 22(100) | 0 | 17(100) | 0 |

## Discussion

*S. aureus* nasal colonization appears to play a significant role in the epidemiology and pathogenesis of infection (9). Mupirocin is a topical antibiotic agent that interferes with bacterial protein synthesis, which can be used for eradication of staphylococcal nasal colonization and control of MRSA transmission in Health Care Facilities (10). Today, the emergence of MuRSA strains has been reported from many parts of the world. The prevalence of these strains in Korea, India, South Africa and Nigeria has been reported 5%, 14.6%, 7% and 0.5 % respectively (11-14). Currently prevalence of mupirocin resistance in MRSA is increasing in areas where are widely used these antibiotics (15). There are scattered reports and limited number of study conducted to detect staphylococcal nasal colonization in Iran. In a study of hospitalized patients in Kermanshah, on nasal swabs, all isolates were susceptible to mupirocin that reflected the limited use of this antibiotic, especially in that region (16).

In present study the prevalence of *S. aureus* nasal colonization was 14.44% among which 17(43.58%) were MRSA and others were MSSA and 5 (1.85%) isolates found to be mupirocin-resistant. Of MuRSA isolates 3 were high level resistant. Prevalence of nasal carriage of *S. aureus* varied between hospitals and statistical information showed a significant relationship between the hospitals and presence of *S. aureus* nasal carrier as well. This seems to be due to differences in infection prevention and control measures. There were statistically significant relationship between nursing job and nasal carriage of *S. aureus* and MRSA but not with MuRSA carriage. This could be a warning because of the high possibility of nurse-to-patient transmission of these bacteria and dissemination of them in hospital setting. Therefore, practice of sanitary principles along with the routine screening of nasal carriers for the treatment purposes can be very useful in preventing the creation of epidemics in hospital setting. None of the nasal carriers had a history of hospitalization or antibiotic use within the previous three months in our study. A significant relation was found between the sexes and nasal carriage of *S. aureus* ($P$=0.035) and MRSA ($P$=0.041) but not with MuRSA ($P$=0.182). This result is likely due to sample size or gender distribution of HCWs in the hospitals under studied. It is notable that we did not found any significant difference between age and years of working in hospital with regard to the nasal carriage of MSSA, MRSA and MuRSA.

In present study *mupA* gene PCR results were positive for two isolates and both of them were showed high-level resistance (MIC>1024) to mupirocin (isolates SH4, SH10). In addition, both of these two isolates were MRSA. Studies show that almost all of mupirocin resistant MRSA isolates with high resistance to mupirocin have positive PCR result for *mupA* gene (17, 18). Among these studies, there are some exceptions; this means that there are strains with high-level resistance to mupirocin, which are negative for the *mupA* gene. In these strains *mupA* gene, may located on chromosome rather than being on plasmids (19). This may justify and explain our result about strain S9. The results of our study indicated that one of the MRSA isolates (SH4) showed high level resistance to mupirocin by E-test method while was sensitive to mupirocin in disk diffusion method (this test was repeated 3 times), and it is noteworthy that this strain had positive PCR for *mupA* gene. Treatment with mupirocin in the presence of high-level resistance strains is not effective. In addition, there is evidence suggesting that presence of low-level resistant strains may cause failure in treatment (20-22). This emphasizes the importance of identification of both high and low level resistant strains.

So, due to some discrepancy in these two tests (disk diffusion test and E-test) it seems that the screening results obtained from disk diffusion method and MIC determination must be confirmed by other methods such as detection of resistance genes by PCR analysis in order to avoid false-negative results. Hence, an unnecessary use of mupirocin and spread of resistant strains in hospital settings can be avoided by appropriate treatment decisions.

In this study, antibiotic susceptibility pattern of MRSA and MSSA strains were examined, that indicated antibiotic resistance among MRSA was much higher than MSSA. The highest resistance of MRSA isolates was related to erythromycin and all MSSA and MRSA strains were susceptible to linezolid, fusidic acid and vancomycin.

## Conclusion

Since the HCWs play an important role as a reservoir for resistant isolates in the hospital setting, regularly screening should be performed for identification of nasal carriers. Consequently, because of antibiotic resistance among staphylococcal strains, thus antibiogram is a recommended method prior to treatment in order to select the best remedy.

## Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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