

# Genotyping of *Staphylococcus aureus* strains among healthcare workers and patients in the tertiary referral Children's Medical Hospital in Tehran, Iran

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Accepted: 7 November 2012

## Introduction

*Staphylococcus aureus* is one of the main pathogens to cause infections in the hospital setting, and is associated with considerable morbidity and mortality.<sup>1</sup> An important source of nosocomial staphylococcal infection is nasal carriage among hospital personnel.<sup>2</sup> Carriers of *S. aureus* have an increased risk of infection by the strains they carry.<sup>3</sup> There is a strong correlation between staphylococcal infection and its colonisation of the human nasal epithelium.<sup>4</sup>

The association between *S. aureus* nasal carriage and staphylococcal disease was first reported by Danbolt in 1931.<sup>5</sup> Colonised healthcare workers (HCWs) are capable of transmitting *S. aureus* to patients<sup>6-8</sup> via transiently colonised hands or transient/permanent colonisation of the nares or oropharynx,<sup>8,9</sup> and this risk is three to six times higher than non-carriers and low-level carriers.<sup>10</sup> Molecular typing such as that using the repetitive element polymerase chain reaction (Rep-PCR), which is a rapid and reliable method, is essential to track the dissemination of specific strains and may facilitate the analysis of transmission and aid infection control measures.<sup>11</sup>

The aim of this study is to evaluate *S. aureus* nasal colonisation in HCWs and its association with *S. aureus* infection in children using molecular methods, and also investigate the antibiotic susceptibility pattern of these isolates.

## Materials and methods

Random staff members ( $n=190$ ) from different wards were asked to undergo screening for nasal carriage of *S. aureus*.

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## ABSTRACT

Nasal carriage among hospital personnel is an important source of nosocomial staphylococcal infection. Therefore, this study aims to evaluate *Staphylococcus aureus* nasal colonisation among healthcare workers (HCWs) and its association with infection in children through analysis of antibiotic susceptibility profiles and genetic similarity. Nasal swabs were taken from the anterior nares of HCWs and also a total of 130 strains that had been isolated from various clinical samples were examined. Antibiotic susceptibility profiles of the strains were determined using the disc-diffusion technique and genotyping was performed by amplification of the enterobacterial repetitive intergenic consensus sequences (ERIC-PCR). Approximately 48% of clinical strains obtained were methicillin-resistant *S. aureus* (MRSA), whereas only 24.7% of strains from HCWs were MRSA. Among isolates from HCWs, cephalothin, cefazolin, chloramphenicol, rifampicin and vancomycin were most effective, with susceptibility rates of 100%. In this study, the ERIC-PCR profiles did not reveal any genetic similarity among the *S. aureus* strains from HCWs and the clinical samples. In contrast, MRSA strains showed clonal dissemination, with clones D and A2 predominant among patients and HCWs, respectively. No association was observed between the MRSA nasal carriers and infections in patients. These findings suggest that MRSA nasal carriage among HCWs may not be the source of related infections in the group studied.

**KEY WORDS:** Genotyping techniques.  
Healthcare workers.  
Nasal carriage.  
Patients.  
*Staphylococcus aureus*.

In addition, a total of 133 strains isolated from various clinical samples from hospitalised patients in the tertiary referral Children's Medical Hospital in Tehran, Iran, from March to August 2010, were included in the study. The inclusion criterion for *S. aureus* clinical isolates was the expectation that the patient was hospitalised for at least four days in one of the wards.

## Data collection

Informed oral consent was obtained from all HCW staff prior to specimen collection. Ethical considerations, including privacy of personal data, were considered during all steps of the research. Data collected included gender, age, ward, years of service, level of education (e.g., university

graduate, high school graduate, or secondary school) and occupation (e.g., nurse, doctor, auxiliary nurse, orderly).

#### Microbiological methods

Specimens were collected from the anterior nares of HCWs. A sterile moistened swab was inserted into each nostril to a depth of approximately 1 cm and rotated five times. For each specimen, both nostrils were sampled using the same swab. Trypticase soy broth was used as the transport medium. Samples were sent to the laboratory and were inoculated on mannitol salt agar plates and incubated at 35 °C for 48 h. The isolates were identified as *S. aureus* based on morphology, Gram stain, catalase test, coagulase test and mannitol salt agar fermentation. Methicillin-susceptible *S. aureus* (MSSA) strains were differentiated from MRSA using Mueller-Hinton agar containing 2 mg/mL oxacillin with 4% NaCl, and isolates growing on the plates were considered to be MRSA, while isolates that did not grow on the antibiotic-containing medium were considered to be MSSA.

All presumptive MRSA isolates were checked and confirmed by *mecA* PCR. The reaction mix contained 200 mmol/L deoxynucleoside triphosphates, 5 mL 10x reaction buffer (100 mmol/L Tris-HCl [pH 8.3], 500 mmol/L KCl), 2.0 mmol/L MgCl<sub>2</sub>, 20 pmol *mecA*F (ACTGCTATCCACCCTCAAAC) and *mecA*R (CTGGTGAAG TTGTAATCTGG) primers, 2.5 units *Thermus aquaticus* (*Taq*) DNA polymerase and 10–1000 ng template DNA. The volume was adjusted to 50 mL with sterile water.<sup>12</sup> A standardised Kirby-Bauer disc-diffusion method was performed on Mueller-Hinton agar.<sup>13</sup>

The panel of antibiotics used in sensitivity tests included oxacillin, vancomycin, clindamycin, rifampicin, amikacin, amoxiclav, penicillin, chloramphenicol, trimethoprim-sulphamethoxazole, cefazolin and cephalothin.

The strains recovered from patients and HCWs were typed by enterobacterial repetitive intergenic consensus PCR (ERIC-PCR), as described previously.<sup>14</sup> Comparison of ERIC-PCR banding patterns was performed using Gelcompar II, version 6.5 (Applied Maths, Sint-Matens-Latem, Belgium). Isolates producing fingerprints showing 100% relatedness (Dice coefficient/unweighted pair-group method with arithmetic mean [UPGMA]) were allocated to the same ERIC-PCR type.

## Results

During the study period, 190 HCWs were screened for nasal staphylococcal carriage and 130 were found to be positive. The staphylococcal isolates were obtained from 51 (39.2%) nurses, 13 (10%) doctors, 10 (7.7%) auxiliary nurses, 30 (23%) orderlies and 26 (20%) office personnel. Mean age was 34 years (range: 19–63 years) and the male-to-female ratio was 0.43. Median length of hospital service was 8.22 years (range: one month to 28 years).

Among the 130 samples, 83 (63.8%) were coagulase-negative staphylococci and 47 (36.2%) were coagulase-positive *S. aureus*. Of the 47 nasal carriers of *S. aureus*, 40 (85.1%) carried MSSA and seven (14.9%) carried MRSA. The frequency of MRSA and MSSA carriage varied according to the ward and the individual's characteristics (e.g., gender, age, occupation) (Table 1). The highest prevalence of nasal carriage of MRSA was found on the surgical ward (28.5%).

**Table 1.** Demographic details of the HCWs taking part in the study.

| Variable             | Nasal carriers (n) |          |
|----------------------|--------------------|----------|
|                      | MSSA (%)           | MRSA (%) |
| Age (mean years)     | 34.87              | 36.28    |
| <30                  | 14 (35)            | 2 (28.6) |
| 30–60                | 26 (65)            | 5 (71.4) |
| Working (mean years) | 94.15              | 104.17   |
| 0–5                  | 22 (55)            | 4 (57.1) |
| 6–10                 | 6 (15)             | –        |
| 11–15                | 4 (10)             | –        |
| >15                  | 8 (20)             | 3 (42.9) |
| Department           |                    |          |
| Emergency            | 2 (5)              | –        |
| Operating room       | 7 (17.5)           | 1 (14.3) |
| Immunology           | 2 (5)              | –        |
| Urology              | 4 (10)             | 1 (14.3) |
| Neurology            | 1 (2.5)            | 1 (14.3) |
| Nephrology           | 2 (5)              | –        |
| Dialysis             | 1 (2.5)            | –        |
| Surgical             | 3 (7.5)            | 2 (28.5) |
| Infection            | 1 (2.5)            | –        |
| Oncology             | 1 (2.5)            | –        |
| NICU                 | 5 (12.5)           | 1 (14.3) |
| PICU                 | 2 (5)              | –        |
| Physiotherapy        | 1 (2.5)            | 1 (14.3) |
| Administration       | 8 (20)             | –        |
| Education            |                    |          |
| University graduate  | 14 (35)            | 3 (42.9) |
| High school graduate | 5 (12.5)           | –        |
| Secondary school     | 21 (52.5)          | 4 (57.1) |
| Occupation           |                    |          |
| Doctor               | 4 (10)             | –        |
| Nurse                | 10 (25)            | 3 (42.9) |
| Auxiliary nurse      | –                  | 1 (14.2) |
| Office personnel     | 8 (20)             | –        |
| Orderly              | 18 (45)            | 3 (42.9) |

The highest prevalence of nasal carriage of MSSA (40%) was found in office workers without any carriage of MRSA. Almost one-third of *S. aureus* isolates recovered in nasal cultures from nurses were resistant to oxacillin; however, the resistance ratio to this antibiotic among nasal *S. aureus* isolates obtained from orderlies was 1:6 (Table 1).

The average age of the studied patients was 2.4 years (range: one day to 14 years) and the majority of patients (60%) were male. Thirty-five (26.4%) were on the infection unit, with the remainder on the surgical ward (*n*=26, 19.5%), NICU (*n*=18, 13.5%), emergency ward (*n*=10, 7.5%), ICU (*n*=10, 7.5%), rheumatology ward (*n*=9, 6.8%), gastroenterology ward (*n*=6, 4.5%), oncology ward (*n*=6, 4.5%), nephrology ward (*n*=5, 3.8%), urology ward (*n*=4, 3%) and CICU (*n*=4, 3%). Clinical isolates were obtained from blood (*n*=40), eyes (*n*=20), urine (*n*=12), trachea (*n*=7), wounds (*n*=20), ear (*n*=6), abscess (*n*=5), skin (*n*=5),

**Table 2.** Antibiotic susceptibility of *S. aureus* isolates from HCWs and patients.

| Antibiotics                    | MRSA (n [%]) |          |           |           | MSSA (n [%]) |           |           |           |
|--------------------------------|--------------|----------|-----------|-----------|--------------|-----------|-----------|-----------|
|                                | Nasal        |          | Clinical  |           | Nasal        |           | Clinical  |           |
|                                | R            | S        | R         | S         | R            | S         | R         | S         |
| Cephalothin                    | 0            | 7 (100)  | 50 (78.1) | 14 (21.9) | 0            | 40 (100)  | 1 (1.4)   | 68 (98.6) |
| Cefazolin                      | 0            | 7 (100)  | 51 (79.7) | 13 (20.3) | 0            | 40 (100)  | 5 (7.2)   | 64 (92.8) |
| Trimethoprim-sulphamethoxazole | 1 (14.3)     | 6 (85.7) | 53 (82.9) | 11 (17.1) | 9 (22.5)     | 31 (77.5) | 15 (21.7) | 54 (78.3) |
| Chloramphenicol                | 0            | 7 (100)  | 14 (21.9) | 50 (78.1) | 0            | 40 (100)  | 7 (10.1)  | 62 (89.9) |
| Oxacillin                      | 7 (100)      | 0        | 64 (100)  | 0         | 0            | 40 (100)  | 0         | 69 (100)  |
| Penicillin                     | 6 (85.7)     | 1 (14.3) | 64 (100)  | 0         | 39 (97.5)    | 1 (2.5)   | 69 (100)  | 0         |
| Amikacin                       | 5 (71.4)     | 2 (28.6) | 58 (90.6) | 6 (9.4)   | 39 (97.5)    | 1 (2.5)   | 50 (72.4) | 19 (27.6) |
| Co-amoxiclav                   | 2 (28.6)     | 5 (71.4) | 63 (98.4) | 1 (1.6)   | 28 (70)      | 12 (30)   | 51 (74)   | 18 (26)   |
| Rifampicin                     | 0            | 7 (100)  | 3 (4.7)   | 61 (95.3) | 0            | 40 (100)  | 4 (5.8)   | 65 (94.2) |
| Vancomycin                     | 0            | 7 (100)  | 0         | 64 (100)  | 0            | 40 (100)  | 0         | 69 (100)  |
| Clindamycin                    | 1 (14.3)     | 6 (85.7) | 17 (26.5) | 47 (73.5) | 5 (12.5)     | 35 (87.5) | 5 (7.2)   | 64 (92.8) |

catheters ( $n=8$ ), pericardium ( $n=4$ ), genitals ( $n=2$ ) and other sites ( $n=4$ ). Among the 133 clinical isolates, 64 (48%) were MRSA and 69 (52%) were MSSA.

All isolates considered to be MRSA (HCWs and clinical) on Mueller-Hinton agar containing 2 mg/mL oxacillin with 4% NaCl were confirmed by *mecA* PCR and all harboured the *mecA* gene.

The sensitivity of *S. aureus* isolates (MSSA and MRSA) from HCWs and clinical sources to the tested antibiotics is shown in Table 2. The sensitivity pattern of all 47 isolated strains of *S. aureus* from HCWs showed that none were resistant to vancomycin, cefazolin, rifampicin, chloramphenicol and cephalothin. The highest resistance rate among the MSSA strains from HCWs for penicillin and amikacin was 97.5%, while the highest resistance among MRSA strains was 85.7% and 71.4%, respectively.

All isolates were sensitive to vancomycin, whereas no isolate showed sensitivity to penicillin. Notably, these data showed that resistance to cephalothin and cefazolin was only seen in clinical MRSA isolates (78.1% and 79.7%, respectively). Further comparison of staphylococcal isolates showed that MRSA isolates from HCWs were more susceptible than were clinical MRSA isolates to trimethoprim-sulphamethoxazole (82.9% versus 14.3%), penicillin (100% versus 85.7%), amikacin (90.6% versus 71.4%), amoxiclav (98.4% versus 28.6%) and clindamycin (26.5% versus 14.3%).

Only 28.6% of MRSA isolates from HCWs were resistant to amoxiclav; however, resistance among HCW MSSA, clinical MRSA and MSSA isolates was 70%, 98.4% and 74%, respectively.

Using ERIC-PCR on *S. aureus* isolates from HCWs, three clusters (designated types A1, A2 and B) were recovered. Thirty-three isolates (70.2%) belonged to the A1 cluster, eight (17%) to the B cluster and six (12.8%) to the A2 cluster. Most of the nasal MRSA carriers were in the A2 cluster ( $n=6$ , 86%) while one isolate (14%) was in the B cluster. Four clusters were generated for *S. aureus* clinical isolates by ERIC-PCR genotyping, designated types C1, C2, D and E. Most ( $n=92$ , 69.1%) belonged to the D cluster, half of which were MRSA isolates. Clusters C1 and C2 comprised 33 (24.9%) and six

(4.5%) isolates, respectively, whereas only two isolates were in cluster E. The A1 and A2 clusters and C1 and C2 clusters showed similarities of over 80% and were considered to be clonally related isolates. Clones D and A2 were predominant among patients and HCWs carrying MRSA strains, respectively (Fig. 1).

## Discussion

To the authors' knowledge, the present study is the first from Iran to evaluate the genotyping of *S. aureus* among HCW nasal carriers and clinical isolates from patients. The prevalence of *S. aureus* carriage among HCWs in developing countries varies considerably. This study showed a prevalence of 24.7% (47/190) for nasal carriage of *S. aureus* among HCWs, of which only one-seventh were MRSA. Other studies in Iran and Saudi Arabia have reported a higher prevalence of *S. aureus* carriage among HCWs.<sup>15,16</sup> Mean nasal MRSA carriage in HCWs was 4.1% in 104 studies,<sup>17</sup> which is comparable to the 3.7% found in the present study.

The present study reports 48% MRSA among *S. aureus* clinical isolates, whereas earlier studies conducted in the same hospital have shown a higher prevalence of 89% between 2001 and 2005,<sup>18</sup> and 60% between 1996 and 2000.<sup>19</sup> Some studies have reported comparable levels of prevalence: 96.2% in the ICU of a university hospital in Iran, 28.3% in the north of Iran,<sup>20</sup> and 36% in Tehran.<sup>21</sup> Studies show that the epidemiology of MRSA in different areas of Iran is not uniform, probably due to differential clonal expansion, quality and size of samples, the use of different techniques, and drug pressures in the community.<sup>22</sup>

In this study, MRSA isolates from HCWs showed the same genetic profile and were not clonally related to MRSA strains found in patients. This can be explained by prior MRSA exposure and previous MRSA infection or colonisation in HCWs. In the present study, MRSA colony numbers selected from the primary plate and the potential to miss other genotypes on the primary plate is possible. Alternatively, different genotypes found between HCW and clinical

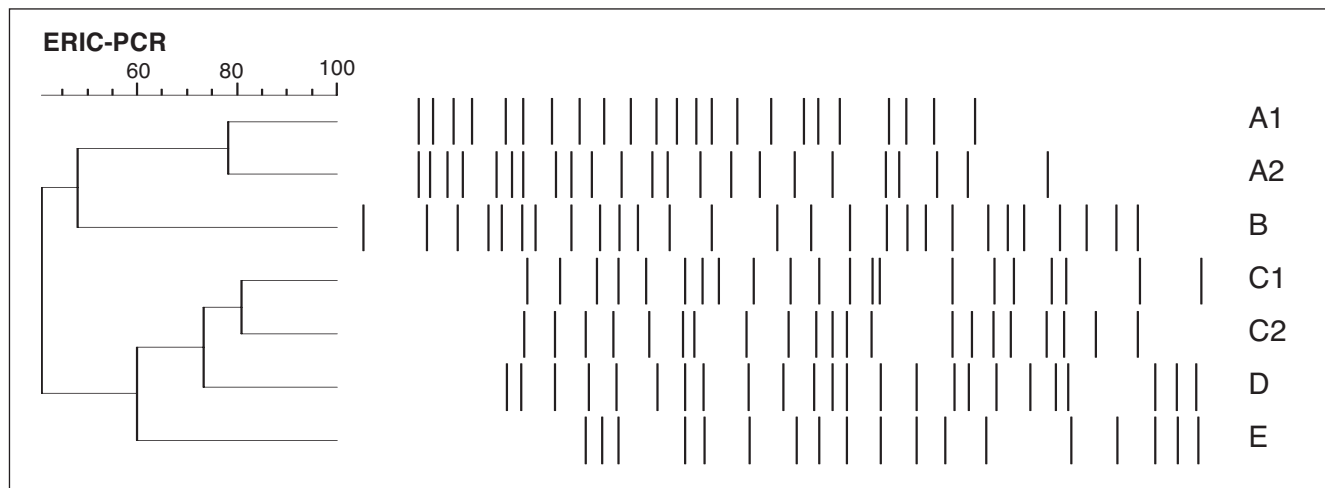


Fig. 1. Dendrogram of genotype analysis derived from all *S. aureus* isolates. The scale represents the genetic distance between isolates.

isolates could be explained by differences in colonisation of non-nasal sites in infected patients.<sup>23</sup>

Proven transmission of MRSA to patients from HCWs without clinical or subclinical symptoms has been reported previously.<sup>17</sup> The present study, along with a quarter of similar investigations (27/106), could not prove transmission between HCWs and patients.<sup>17</sup> Although most studies that examined the association between MRSA isolates from patients and HCWs found clonally related isolates,<sup>16</sup> some studies have reported unrelated isolates.<sup>24–28</sup>

In the present study, the finding of identical MRSA strains in HCWs as well as among clinical isolates indicates that there is a succession of *S. aureus* populations over a period of time. An important finding that the highest prevalence of MSSA nasal carriage (20%) was found in office personnel may be due to the lack of direct contact between these personnel and patients; a finding that highlights the effect of close contact on the transmission of bacteria from patients to personnel.

Antimicrobial resistance of staphylococci and the high prevalence of MRSA has become an important public health problem associated with serious consequences.<sup>29</sup> In the present study, the high resistance rate to amikacin and penicillin was seen not only in clinical isolates but also in *S. aureus* nasal isolates from HCWs. Notably, the rate of amoxiclav resistance among MSSA strains in this group was over twice the rate among MRSA isolates (70% versus 28.6%). This high prevalence in the region might be due to unrestricted use of these antibiotics in Iran.

In view of the high resistance rates to cephalothin and cefazolin, empirical treatment of *S. aureus* infections at the authors' hospital with these antibiotics may not be effective. In addition, the high susceptibility of *S. aureus* to vancomycin and rifampicin indicates that these antibiotics are effective for the treatment of *S. aureus* infections at the hospital. Against the *S. aureus* isolates recovered from HCWs in the current study, cephalothin, cefazolin, chloramphenicol, rifampicin and vancomycin proved very effective, with susceptibility rates of 100%.

In conclusion, no association was found between MRSA nasal carriage by HCWs and infection caused by this microorganism in patients. Identifying and addressing the important factors contributing to acquisition and transmission of *S. aureus* infection and antibiotic stewardship

programmes would be useful in order to achieve a significant reduction in MRSA colonisation and infection rates. □

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