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ORIGINAL ARTICLE

Elimination of *Staphylococcus aureus* nasal carriage in intensive care patients lowers infection rates

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Abstract

This study surveys the clinical relevance of the nasal *Staphylococcus aureus* colonization status on intensive care unit (ICU)–acquired *S. aureus* infections and compares molecular characteristics of isolates from the nose and infectious sites. The 390 patients included comprised 278 non-carriers and 112 carriers. Among the carriers, 56 were decolonized with mupirocin. Decolonization was verified through a second (negative) culture. Spa typing and virulence gene profiling were performed for all isolates. Twenty six *S. aureus* infections were detected in the carriage group and 20 in the non-carriage group. Eighteen of these 26 (69.2%) infections were among carriers, and 8 of these 26 (30.8%) infections occurred among decolonized carriers (p = 0.02). Overall, 31/112 (27.7%) of the colonized patients and 25/46 (60.1%) of infection were due to methicillin-resistant *S. aureus* (MRSA). The highest frequency virulence genes were *sea* and *hlg* (both 100%) in nasal isolates and *sea*, *hlg*, *fnb*, and *clf* (100%) for infectious isolates. t030 was the most abundant spa type overall. *S. aureus* carriers were more likely to develop *S. aureus* infection compared with decolonized and non-carrying patients. The sources of ICU *S. aureus* infection appear to be exogenous mostly, and a predominant clone (spa type 030) plays an important role. We confirm that nasal mupirocin treatment prevents ICU infections even when there is an increased prevalence of nosocomial MRSA.

Keywords *Staphylococcus aureus* · Nasal carriage · Nosocomial infections · Intensive care unit

Introduction

Staphylococcus aureus is an opportunistic human pathogen and part of the commensal flora. It causes many life-threatening infections in patients in intensive care units (ICUs). This includes bacteremia, ventilator-associated pneumonia, infections related to the presence of indwelling medical devices and wound, and surgical site infections. These infections are a leading cause of prolonged hospital stay, additional antibiotic use, higher morbidity and mortality, and increased healthcare-associated costs (e.g., [1]). Several virulence factors play a role in the pathogenicity of *S. aureus* including toxic shock syndrome toxin 1 (TSST-1), Panton-Valentine leukocidin (*PVL*), enterotoxins, hemolysin, exfoliative toxins, and various adhesive proteins [2]. Methicillin-resistant *S. aureus* (MRSA) strains acquired the *mecA* gene–containing staphylococcal cassette chromosome (SCC*mec*) [3]. Increased emergence of nosocomial multidrug resistance among MRSA strains has become a global concern in hospital environments [4]. About 30% of humans are nasal carriers of *S. aureus* and have a greater risk to develop endo-infections [5]. Thus, screening of high-risk patients (MRSA or methicillin-susceptible *S. aureus* (MSSA)-colonized) and eradication of *S. aureus* nasal carriage are essential for reducing the overall frequency of *S. aureus* infection in hospital settings and particularly in ICUs [5, 6]. In this regard, molecular typing methods are useful in tracing and monitoring

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of nosocomial outbreaks [7]. The purpose of this study was to determine the role of nasal *S. aureus* colonization in ICU-acquired *S. aureus* infections.

Materials and methods

Study design

The Vali-Asr Hospital is the largest medical training center in the city of Arak, capital of the central province in Iran. The current study was performed during a 9-month period (December 2013 to September 2014), and this trial was registered at the Iranian Registry of Clinical Trials with IRCT number 92-153-6. During this episode, the *S. aureus* nasal colonization status was checked by culture for all patients at admission in ICUs. Patients were classified into two groups: carriers and non-carriers. Half of the carriers were decolonized using mupirocin, confirmed by a negative nasal follow-up culture [8]. Patients were admitted to the ICU and screened for *S. aureus* infection during their stay. Exclusion criteria included allergy to mupirocin, taking antibiotics, a stay in the ICU < 48 h, a known *S. aureus* infection at ICU admission, or the development of an *S. aureus* infection during the first 48 h of ICU stay. Nasal and ICU-acquired *S. aureus* infectious isolates were investigated by spa typing, for methicillin resistance and for the presence of virulence genes.

S. aureus isolation and identification

Nasal swabs and infectious site samples were obtained by trained personnel. Sampling and transport were performed using the Transwab system and Amies transport medium (Medical Wire and Equipment Company, Corsham, UK). All samples were transferred to the Laboratory of Microbiology within 30 min. The specimens were incubated at 37 °C for 6–12 h, and swabs were cultured on sheep blood agar and mannitol salt agar. Plates were aerobically incubated at 37 °C for 24–48 h, after which smears were Gram-stained and biochemical tests as well as *ssa442* PCR were performed for identification of *S. aureus*–suspect colonies. All *S. aureus* isolates were stored in Luria-Bertani (LB) broth with 20% glycerol at – 70 °C.

MecA and virulence genes' PCR

Purification of DNA was accomplished using the Tissue Genomic DNA Extraction Mini Kit (FavorPrep, FavorGen, Taiwan) following the manufacturer's instructions. All PCRs were performed in a total volume of 25 μl containing 12.5 μl Super PCR Mastermix 2X (Taq DNA polymerase, dNTP, $MgCl_2$), 1 μl of each primer (10 μM), 1 μl template DNA (100 ng), and 9.5 μl nuclease-free water. PCR runs were carried out on a peQlab Thermocycler (peQlab, UK). The conditions were as follows: initial denaturation at 94 °C for 5 min, 30 cycles at 94 °C for 1 min with annealing temperature at 72 °C for 1 min in between, followed by a final extension at 72 °C for 5 min. Amplified DNA was visualized using electrophoresis in 1% agarose gel in 1× Tris-EDTA buffer.

Molecular spa typing

Spa typing was performed by PCR aimed at the polymorphic X region of the protein A gene and sequencing (Gene Fanavaran Company, Iran). Sequences were edited using the Chromas software (version 2.6.2, Australia). Spa types were assigned following the guidelines of the Ridom Spa database (http://www.spaserver.ridom.de). All *S. aureus* isolates from prior colonized patients ($n = 56$), decolonized patients ($n = 56$) , and infectious sites ($n = 46$) were spa-typed.

Statistical analysis

The frequency and proportions of *mecA*, virulence genes, and spa types between groups of isolates were calculated by SPSS version 24 (Microsoft Office, Chicago, IL, USA, ver. 24) by applying the Pearson chi-square test with significance at $p \leq 0.05$.

Results

Carriage status and infection isolates

In total, 490 patients were enrolled and 100 patients were excluded for reasons mentioned above. Among the remaining 390 participants, 112 (28.7%) were nasal *S. aureus* carriers and 278 (71.3%) were not colonized. Colonized patients were segregated into prior colonized and decolonized groups (each 56 cases). During the study period, 46 (11.8%) cases were infected with *S. aureus*. Twenty-six (56.5%) were carriers, 18 (69.2%(were prior colonized, and 8 (30.7%) were among the decolonized. Twenty (43.5%) were in the non-colonized group. The number of *S. aureus* infections in prior carriers was significantly higher than in decolonized patients ($p < 0.05$). Table 1 provides additional clinical detail.

Methicillin resistance and virulence genes' profiles

Out of the 112 *S. aureus* strains, 31 cases (27.7%) were MRSA and 81 (72.3%) were MSSA. Among 46 infectious isolates, 25 (54.3%) were MRSA and 21 (45.7%) were MSSA. A significantly higher MRSA frequency was found among patients with infections compared with nasal isolates only ($p < 0.05$). In *S. aureus* isolated from nasal cavities, the highest frequency virulence factor genes were *sea* and *hlg* (both 100%) followed by *fnb* (98.2%), *clf* (97.3%), *can* (64.3%), *arcA* (63.4%), *pvl* (8%), and *sec* (1.8%) (Table 2). In *S. aureus* isolated from infections,

Table 1 Frequency of *S. aureus* isolated from sites of infection

S. aureus isolated from:		Infectious sites					
		Lung	Wound	Blood	Urine	CSF	Total
Non-carrier		10	6	3	1	0	20 (43.5%)
Carrier	Prior colonization	13	3	1	0	1	18 (39.1%)
	Decolonized	5	2	0	0	1	8 (17.4%)
Total		28 (60.8%)	11 (23.9%)	4 (8.7%)	1 (2.2%)	2 (4.3%)	46 (100%)

the most frequent virulence factor genes were *sea*, *hlg*, *fnb*, and *clf* (all at 100%) followed by *can* (93.5%), *arcA* (71.7%), and *pvl* (17.4%), whereas *sec* was not found (Table 2). There was a significantly higher *arcA* frequency in stains from infections ($p < 0.05$). The frequencies of *sea*, *sec*, *hlg*, *fnb*, *clf*, *can*, and *pvl* genes did not differ ($p > 0.05$).

Spa typing

Spa typing defined 19 different types (Table 3). The most frequent spa type was t030: 43 (38.4%) for carriers and 28 (60.9%) for infectious isolates. The spa type t14386 was first reported in Iran. Spa types t019, t346, t376, t969, t1149, t3649, and t4242 were detected only in isolates from infectious sites. Spa types t238, t304, t136, t491, t1358, t14386, and t4242 were detected only in isolates from nasal cavities. Spa types t030, t084, t012, t021, t325, and t937 were detected in both groups (Fig. 1). Thirteen identical spa types were found for infectious and colonizing isolates from individual patients suggesting autoinfection.

Discussion

Carriage and infection

Our patients displayed a similar nasal carriage rate for *S. aureus* (28.7%) as previously reported for the population of central Iran (22.1% [9] and 20.1% [10]). The MRSA nasal colonization rate (27.7%) was higher than reported for institutes in the USA [11], China [12], and Turkey [13], though lower than the 46% recorded in Brazil [14]. A high MRSA prevalence of 54.3% was found in this study which was comparable with that found by previous local studies (42.8% and 42%) [15, 16]. The frequency of MRSA in infection was two times (54.3% versus 27.67%) higher than in nasal specimens ($p = 0.01$) which indicated the presence of endemic MRSA in our ICUs. This likely causes an increased risk of MRSA acquisition. Our *S. aureus* infection incidence in ICUs (11.8%) was much higher than the 2%, 2.3%, and 6% recorded in previous studies [17, 18]. *S. aureus*–colonized patients had a 1.3 times increased risk of ICU-acquired *S. aureus* infection compared with non-carriers (56.5% versus 43.5%).

Virulence gene profiles

The *pvl* positivity rate among clinical isolates (17.4%) was higher than among nasal isolates (8%). Ayepola et al. [19] showed that the *pvl* prevalence among infectious isolates (80.2%) was higher than among isolates from carriers (53.4%) which matched our study results. All 9 *pvl*-positive *S. aureus* isolates obtained from nasal cavities were MSSA, and a significant difference was found between *pvl*-positive strains and the absence of the *mecA* gene ($p = 0.01$). The prevalence of the *pvl* gene in our MSSA isolates was higher than that in MRSA isolates and in another study from our

Table 2 Virulence gene frequencies of *S. aureus* isolated from infectious sites and the nasal cavity of colonized patients

S. aureus isolated from:		Virulence genes								*mecA*
		Sea	*hlg*	*fnb*	*clf*	*cna*	*arcA*	*Pvl*	*sec*	
Infectious sites	Non-colonized ($n = 20$)	20	20	20	20	19	15	7	0	8
	Prior colonized ($n = 18$)	18	18	18	18	17	13	1	0	7
	Decolonized ($n = 8$)	8	8	8	8	6	5	0	0	10
	Total ($n = 46$)	46 (100%)	46 (100%)	46 (100%)	46 (100%)	43 (93.5%)	33 (71.7%)	8 (17.4%)	0	25 (54.3%)
Nasal cavity ($n = 112$)		112 (100%)	112 (100%)	110 (98.2%)	109 (97.3%)	72 (64.3%)	71 (63.4%)	9 (8%)	2 (1.8%)	31 (27.6%)

Table 3 Spa types of infectious and colonizing *S. aureus* isolates

Number	Spa type	Infection isolates				Colonization isolates
		Non-colonized	Prior colonized	Decolonized	Total	
1	t030	12	10	6	28 (60.9%)	43 (38.4%)
2	t084	5	0	0	5 (10.8%)	5 (4.5%)
3	t012	1	2	0	3 (6.5%)	15 (13.4%)
4	t021	0	1	0	1 (2.17%)	37 (33%)
5	t019	0	1	0	1 (2.17%)	0
6	t325	0	0	1	1 (2.17%)	1 (0.9%)
7	t346	0	1	0	1 (2.17%)	0
8	t376	1	0	0	1 (2.17%)	0
9	t937	0	0	1	1 (2.17%)	2 (1.8%)
10	t969	0	1	0	1 (2.17%)	0
11	t1149	1	0	0	1 (2.17%)	0
12	t3649	0	1	0	1 (2.17%)	0
13	t4242	0	1	0	1 (2.17%)	0
14	t238	0	0	0	0	2 (1.8%)
15	t304	0	0	0	0	2 (1.8%)
16	t136	0	0	0	0	1 (0.9%)
17	t491	0	0	0	0	2 (1.8%)
18	t1358	0	0	0	0	1 (0.9%)
19	t14386	0	0	0	0	1 (0.9%)
20	Total	20	18	8	46 (100%)	112 (100%)

region [20]. All clinical and nasal isolates in this latter study carried the *sea* gene while the *sec* gene was absent in clinical isolates and found only in 1.8% of the nasal isolates. Nashev et al. [21] reported *sea* as the most abundant enterotoxin gene in *S. aureus* isolated from nasal specimens. In contrast, the *sec* gene was the most abundant enterotoxin encoding gene, followed by *sea*, *sed*, and *seb*, with a lower frequency in a study from Tehran [22]. Normannoa et al. [23] reported the highest levels of SED, followed by SEC, SEA, and SEB. In this study, the frequency of *acme* in clinical isolates (96.4%) was higher than in nasal isolates (63.4%). We found that *clf* and *fnb* were present among all clinical isolates and that *can* was observed among 93.5%. The same genes were less frequent in nasal isolates (97.3% for *clf*, 98.2% for *fnb*, and 64.3% for *can*). Ghasemian et al. [24] showed that the *clf* gene was present among all isolates and recorded 63%, 6%, and 63% for *fnbA*, *fnbB*, and *cna*, respectively. Similar to our results, Duran et al. [25] showed that 78.4% of their isolates carried the *cna* gene.

Spa typing

Spa typing revealed a broad range of types among both groups of isolates, 13 different spa types for strains from infections and 12 types for isolates from the nasal cavity. In a previous study in Iran, 11 different spa types were identified among *S. aureus* isolated from ICUs. Overall, 43% of these isolates belonged to spa types t030 and t037 [26]. In another study [27], only five different spa types were found among *S. aureus* isolates from ICUs of general hospitals in Tehran, Iran. The majority of the isolates belonged to spa types t970 (69.9%) and again t030 (33.3%). Also, t084 (74.8%), t2304 (5%), and t8441 (4.6%) were abundant in clinical isolates, and spa types t084 (38/7%), t091 (10/7%), t1931 (4%), and t8435 (4%) were most frequent among carrier isolates [19].

In our study, the spa type t030 was most common. This result is in concordance with the findings of Chen et al. [28] who showed that t030 (52%) was the most frequent clone among their Chinese isolates. In another study, the spa type t030 was the second most common [29]. A study from Malaysia showed that spa types t037, t10562, and t0421 were most common among carriers and spa types t037, t4184, and t10562 were the most frequent among clinical isolates [5]. In another study in Iran, spa types t304 and t7688 were reported as the most abundant types among clinical isolates [30]. ST239 MRSA has been reported as the dominant clone in Iranian hospitals [31], many of which were of the spa type t030, demonstrating the significant local spread of this type. It can be concluded that many infections acquired in the ICU originate from within the hospital and are hence exogenous.

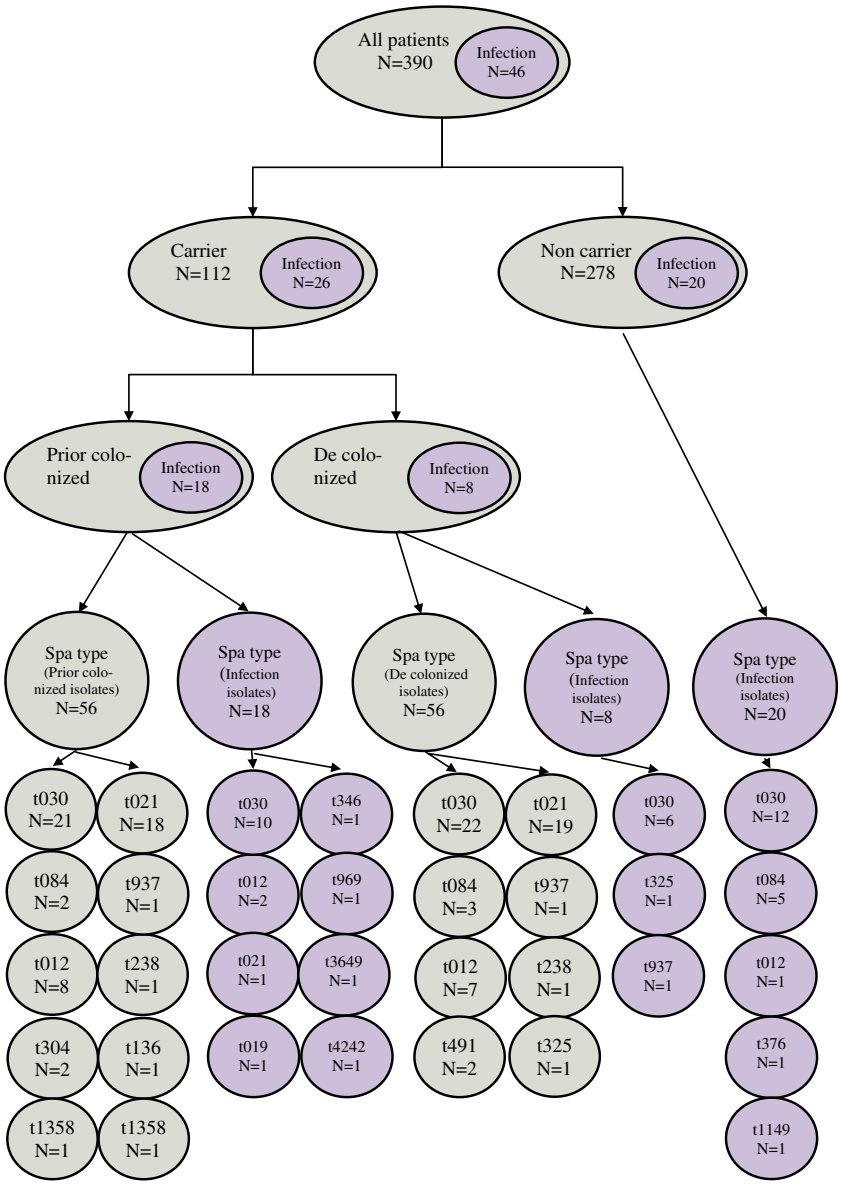

Fig. 1 Summary of the study

Concluding statement

This study again demonstrates that *S. aureus* nasal colonization is significantly associated with infection. Although many studies showed that *S. aureus* infection is of an endogenous nature, our results indicate that the source of ICU *S. aureus* infection can as well be exogenous and a dominant and locally circulating MRSA clone plays an important role in our ICU infections. Given the apparent fact that *S. aureus* causes serious problems in the hospital setting, the use of appropriate measures to prevent the transmission of these strains between patients, personnel, and hospital environment is necessary. We show that nasal *S. aureus* decolonization during ICU stay protects patients against infection [6], even in the presence of easily circulating nosocomial MRSA clones.

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Authors' contribution EGR, AVB, and HS conceptualized, designed, and supervised the study. LA and SF were involved in the sample collection and performed laboratory experiments. ZS managed the decolonization of patients and all other activities in the ICUs. All the authors contributed in writing and editing of the draft and have seen and agreed to the submitted version of the paper.

Compliance with ethical standards

Conflict of interest AVB is an employee of BioMérieux, a company designing, developing, and selling infectious disease tests. The authors report no other conflicts of interest.

Disclaimer The company had no influence on the design and execution of the study or in the writing of the manuscript.

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