ORIGINAL ARTICLE

Prevalence and risk factors for Staphylococcus aureus and methicillin-resistant Staphylococcus aureus nasal carriage inpatients in a tertiary care hospital's chest clinic in Turkey

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Abstract

Aim: We aimed to determine the prevalence and associated risk factors for nasal methicillin-sensitive and methicillin-resistant $Staphylococcus\ aureus\ (MSSA/MRSA)$ carriage among patients admitted to a chest clinic of a tertiary care hospital in this study. **Materials and Methods:** Nasal samples were taken from anterior nares were cultured in CHROMagar S. aureus plates, MRSA was determined by disc diffusion method (cefoxitin 30 μ g) according to the Clinical and Laboratory Standards Institute guidelines and CHROMagar MRSA plates. A questionnaire was applied to determine the demographic characteristics of the participants and risk factors for carriage. Fisher's exact test, univariate and multivariate logistic regression analysis were used. A P < 0.05 indicated a statistically significant difference.

Results: This is a cross-sectional study covering all the patients (*n* = 431) admitted to Kayseri Training and Research Hospital's Chest Clinic from January 1st to 31st 2014. Of all these patients 55 (12.8%) were nasal *S. aureus* carriers. MRSA positivity was in five among these patients. In multivariate analysis, being under 65 years of age (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.0–3.3), and having prosthesis (OR, 4.8; 95% CI, 1.6–13.9) were found as risk factors for MSSA colonization. **Conclusion:** The prevalence of nasal carriage of MSSA was low in our study population. The only risk factors playing role in carriage were found as being under the age of 65 and having prosthesis.

Key words: Carriage, chest clinic, inpatients, Staphylococcus aureus

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Introduction

Staphylococcus aureus may cause serious skin and soft tissue infections, the bacteria can also infect any tissue of the

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body, causing other serious or life-threating diseases, such as deep abscesses, endocarditis, osteomyelitis, pneumonia, and sepsis.^[1] Emergence and spread of antimicrobial resistance combined with increasing numbers of immune-compromised patients make infections increasingly difficult to treat.^[2] It is always a challenge to treat infections due to methicillin-sensitive *S. aureus* (MSSA), particularly

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isolates resistant to methicillin (methicillin-resistant *S. aureus* [MRSA]). Nowadays, MRSA is endemic in most hospitals in the world. Recent guidelines published by the Society for Health Care Epidemiology for America recommend surveillance cultures at the time of hospital admission for patients for high risk for MRSA carriage. Studies conducted to determine the risk factors for colonization at the time of admission are limited in the world and in Turkey. Selection of the sel

There are many studies on nasal MSSA and MRSA carriage and risk factors for nasal carriage worldwide^[3-13] and nose, especially the anterior nares are the main ecological site reported for *S. aureus* carriage in human.^[1,2]

Our primary objective in this study was to determine the nasal MSSA and MRSA carriage rates among a specific group like patients attending a tertiary care chest clinic because of an upper or lower respiratory disease. The secondary objective was to evaluate the possible risk factors at the time of hospital admission among them (including age, sex, having prosthesis, husbandry, presence of chronic disease, antibiotic usage in last 1 month, current use of antibiotics, hospitalization in the past 1 year, number of person in the same house, operation in the last 1 year, living in the same house with a member of hospital staff).

Materials and Methods

This study is a part of a Scientific Research Project called "Determination of S. aureus nasal carriage, investigation of risk factors, and virulence traits among outpatients and inpatients in Kayseri Training and Research Hospital's chest clinic" (no: 4674) founded by Erciyes University. In this part, there we aimed to share the results of the data about inpatients nasal carriage and risk factors.

It is a cross-sectional study conducted in a 125-bedded chest clinic of a tertiary care hospital. The number of patients hospitalized in this clinic in a month is approximately 400. We aimed to reach all the patients at the time they admitted to the services. This study was conducted in January from 1st to 31st 2014. The patients who did not want to participate, patients with dementia and consciousness disorders and the patients in intensive care were not included in the study (10 patients, the participation rate was 97.7%). The aim of this study was explained to the inpatients and all the volunteers signed a written informed consent form. The questionnaire elicited information on the following: Demographic characteristics (age, gender, profession, monthly income, and smoking), risk factors in carriage (husbandry, presence of chronic disease, antibiotic use in last 1 month, current use of antibiotics, hospitalization in the past 1 year, the number of people in the same house, operations experienced in the last 1 year, living in the same house with a member of hospital staff).

Nasal swabs were obtained from the anterior nares of the volunteers. The patients enrolled in this study were newly admitted ones to the hospital. Samples were collected from both nares by rotating a sterile Stuart agar gel medium transport swab and sent to Erciyes University Halil Bayraktar Health Services Vocational College's Microbiology Laboratory (Kayseri, Turkey). The swabs were immediately streaked on CHROMagar S. aureus (Biolife, Italiana). After incubation for 24 h at 37°C suspected violent colonies were isolated and subcultured on to 5% sheep blood agar plates. After incubation for 24 h at 37°C, the suspected colonies were confirmed to be S. aureus by standard biochemical techniques and conventional methods (colony morphology, Gram-stain, catalase activity, and tube coagulase test). The test for methicillin-resistance was performed by the Kirby-Bauer disc diffusion method, using cefoxitin (potency 30 µg) disc on Muller Hinton agar with 24 h incubation at 35.8°C. Results were interpreted according to the criteria of Clinical and Laboratory Standards Institute 2007 guidelines.[14] The reference strain S. aureus ATCC 29213 was used as an internal quality control. We also used CHROMagar MRSA for detecting of MRSA.

This study was planned and performed in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the Erciyes University Medical Faculty. Work permit from the Kayseri Training and Research Hospital's Scientific Committee was also taken.

For statistical analyses, all the data was expressed in numbers and frequencies. Fisher's exact test, univariate logistic regression analyses was used for comparison of categorical variables. The risk factors found statistically significant by univariate logistic regression analysis were evaluated by multivariate logistic regression analysis. In the univariate analyses of risk factors; age, number of household, and income were categorized. Age was categorized as elderly and others according to the definition of the World Health Organization. Number of household was categorized as <4 and ≥ 4 according to the other studies in the literature. Monthly income was categorized as <1000 New Turkish lira (YTL) and ≥ 1000 YTL according to the poverty threshold. A P < 0.05 indicated a statistically significant difference.

Results

A total of 431 adult patients were enrolled in this study. 254 patients (58.9%) were female. Out of 431 patients, 235 (54.4%) were under 65 years, and the remaining was 65 and above. 311 (72.2%) patients had a chronic disease [Table 1].

The prevalence of MSSA and MRSA nasal carriage were 11.6% and 1.2%, respectively. The overall carriage rate of *S. aureus* was 12.8% (55 patients). In 55 *S. aureus* nasal carriers,

Table 1: Characteristics of the patients admitted to Kayseri Training and Research Hospital's chest clinic and the results of univariate analysis of risk factors for nasal *S. aureus* carriage

| Characteristics | Number of inpatients | With MSSA colonization (55 patient) | Without MSSA colonization (376 patient) | OR (95% CI) | P |
|--------------------------------------|----------------------|--|---|---------------------|-------|
| | n=431 (x %) | n (xx %) | n (xx %) | | |
| Age groups | | | (44.77) | | |
| <65 | 235 (54.5) | 39 (16.6) | 196 (83.4) | 1 | |
| 65 years and above | 196 (45.5) | 16 (8.2) | 180 (91.8) | 0.447 (0.241-0.827) | 0.010 |
| Gender | | | | | |
| Male | 177 (41.1) | 21 (11.9) | 156 (88.1) | 1 | |
| Female | 254 (58.9) | 34 (13.4) | 220 (86.6) | 1.148 (0.642-2.053) | 0.642 |
| Having a chronic disease | | | | | |
| Yes | 313 (72.6) | 32 (10.2) | 281 (89.8) | 1 | |
| No | 118 (27.4) | 23 (19.5) | 95 (80.5) | 2.126 (1.185-3.813) | 0.011 |
| Engaged in animal husbandry | , , | , , | , , | , | |
| Yes | 25 (5.8) | 2 (8.0) | 23 (92.0) | 1 | |
| No | 406 (94.2) | 53 (13.1) | 353 (86.9) | 1.727 (0.396-7.536) | 0.756 |
| Antibiotic usage in the past 1 month | . , | , , | , , | . , | |
| No | 317 (73.5) | 39 (12.3) | 278 (87.7) | 1 | |
| Yes | 114 (26.5) | 16 (14.0) | 98 (86.0) | 1.164 (0.622-2.176) | 0.626 |
| Recent antibiotic usage | , , | , , | , , | , | |
| No | 291 (67.5) | 37 (12.7) | 254 (87.3) | 1 | |
| Yes | 140 (32.5) | 18 (12.9) | 122 (87.1) | 1.013 (0.554-1.851) | 0.967 |
| Hospitalization in the past 1 year | , , | , , | , , | , | |
| No | 252 (58.5)) | 34 (13.5) | 218 (86.5) | 1 | |
| Yes | 179 (41.5) | 21 (11.7) | 158 (88.3) | 0.852 (0.477-1.524) | 0.590 |
| Surgery in past 1 year | | | | | |
| No | 393 (91.2) | 47 (12.0) | 346 (88) | 1 | |
| Yes | 38 (8.8) | 8 (21.1) | 30 (79.8) | 1.963 (0.850-4.535) | 0.114 |
| Having prosthesis | | | | | |
| No | 412 (95.6) | 49 (11.9) | 336 (88.1) | 1 | |
| Yes | 19 (4.4) | 6 (31.6) | 13 (68.4) | 3.419 (1.242-9.409) | 0.017 |
| Number of people living with | | | | | |
| <4 | 216 (50.3) | 32 (14.8) | 184 (85.2) | 1 | |
| ≥4 | 213 (49.7) | 23 (10.8) | 190 (89.2) | 0.696 (0.393-1.234) | 0.215 |
| Living with healthcare worker | | | | | |
| No | 418 (97.0) | 54 (12.9) | 364 (87.1) | 1 | |
| Yes | 13 (3.0) | 1 (7.7) | 12 (92.3) | 0.562 (0.072-4.407) | 0.583 |
| Smoking | | | | | |
| No | 381 (88.4) | 51 (13.4) | 330 (86.6) | 1 | |
| Yes | 50 (11.6) | 4 (8.0) | 46 (92.0) | 0.563 (0.194-1.630) | 0.289 |
| Someone smoke at home | | | | | |
| No | 253 (58.7) | 27 (10.7) | 226 (89.3) | 1 | |
| Yes | 178 (41.3) | 28 (15.7) | 150 (84.3) | 1.562 (0.886-2.756) | 0.123 |
| Monthly income | | | | | |
| <1000 YTL | 325 (75.4) | 42 (12.9) | 283 (87.1) | 1 | |
| ≥1000 YTL | 106 (24.6) | 13 (12.3) | 93 (87.7) | 0.942 (0.485-1.831) | 0.860 |

x %=Column percentage; n (xx %)=Number of patients (row percentage). MSSA=Methicillin-sensitive S. aureus; S aureus=Staphylococcus aureus; S OR=Odds ratio; S Cl=Confidence interval

5 (9.1%) were MRSA. Table 1 shows the characteristics of patients admitted to the chest clinic and the results of univariate regression analysis of the risk factors for nasal *S. aureus* carriage.

The nasal carriage situation of patients with a chronic disease was shown in Table 2. No difference was found between

the nasal *S. aureus* carriage ratio in patients with asthma and without asthma. This result was same for other chronic diseases. The nasal carriage was 8.9% in patients with one chronic disease, 10.9% with two diseases 13.6% with three and above diseases. There was no statistically significant difference between the number of chronic disease a patient have and nasal *S. aureus* carriage (Chi-square = 0.926, P = 0.629).

Table 2: Nasal *S. aureus* carriage among patients with chronic diseases attending to Kayseri Training and Research Hospital's chest clinic

| Name of the chronic n (%) | | S. aureus | | OR (95% CI) | P |
|--|------------|-----------|----------|---------------------|-------|
| disease | | + (n=55) | -(n=376) | | |
| Asthma | 174 (40.4) | 18 | 158 | 0.671 (0.369-1.222) | 0.192 |
| COPD | 55 (12.8) | 6 | 48 | 0.837 (0.340-2.058) | 0.698 |
| Diabetes mellitus | 83 (19.3) | 9 | 74 | 0.798 (0.374-1.704) | 0.561 |
| Hypertension | 117 (27.1) | 10 | 107 | 0.559 (0.272-1.149) | 0.113 |
| Other (cardiac insufficiency, cancer, kidney disease etc.) | 68 (15.8) | 11 | 56 | 1.429 (0.696-2.932) | 0.331 |

Percentage was taken over 431 inpatients. COPD=Chronic obstructive pulmonary disease; S. aureus=Staphylococcus aureus

Table 3: Multivariate logistic regression analysis of the risk factors associated with MSSA colonization in patients newly admitted to Kayseri Training and Research Hospital's chest clinic

| Risk factors* | OR | 95 CI % | P |
|------------------------|-------|--------------|-------|
| Under 65 years of age | 1.991 | 1.017-3.898 | 0.044 |
| Having chronic disease | 0.526 | 0.276-1.002 | 0.051 |
| Having prosthesis | 5.101 | 1.758-14.795 | 0.003 |
| Constant | | | |

^{*}The risk factors which were found significant in the univariate analysis for nasal S. aureus carriage were included in multivariate analysis.

MSSA=Methicillin-sensitive S. aureus; S. aureus=Staphylococcus aureus;
OR=Odds ratio; CI=Confidence interval

Table 4: The characteristics of the five inpatient with MRSA colonization newly admitted to Kayseri Training and Research Hospital's chest clinic

| Characteristics | MRSA positivity $(n=5)$ | |
|--|-------------------------|--|
| The mean age | 57.0±10.3 | |
| Being male | 5 | |
| Having a chronic disease | 5 | |
| Antibiotic usage in the past 1 month | 4 | |
| Recent antibiotic usage | 4 | |
| Hospitalization in the past 1 year | 5 | |
| Having a surgery in the past 1 year | 2 | |
| Having asthma | 4 | |
| Having COPD | 2 | |
| Having prosthesis | 1 | |
| The number of household more than 4 | 2 | |
| Living with a person working in hospital | 1 | |
| Someone smoking at home | 3 | |
| Monthly income < 1000 YTL | 3 | |

COPD=Chronic obstructive pulmonary disease; MRSA=Methicillin-resistant *S. aureus*; *S. aureus*=Staphylococcus aureus; YTL=New Turkish lira

The result of multivariate logistic regression analysis for the risk factors, which were found statistically significant in the univariate logistic regression analysis, was shown in Table 3. Being under 65 years of age and having prosthesis were found as risk factors. Patients under 65 years of age had 1.991 times more nasal S. *aureus* carriage than patients above 65. In addition, patients with prosthesis have 5.101 times more carriage than the patients without prosthesis.

Of the 55 nasal carriers, 5 were MRSA. The characteristics of MRSA carriers were shown in Table 4.

Discussion

We wanted to determine the prevalence and risk factors of nasal *S. aureus* carriage among adult patients who newly admitted to a chest clinic. This is the first study about nasal carriage in our region on patients admitted to a tertiary care hospital's clinic. Now we know for a long time, that infections with *S. aureus* are endogenous origin. ^[12,13] By being aware of the risk factors, it is easy to determine the patients and prevent spreading.

The prevalence of nasal S. aureus and MRSA carriage in our group of patients was found as 12.3%, and 9.1%, respectively. There are different results in previous studies conducted in Turkey. [6-8] Citak et al. studied nasal carriage and methicillin resistance of S. aureus in patients in a tertiary referral center setting. [6] Nasal swabs were obtained from hospital staffs (121 participants), out-patients (123 participants) and in patients (194 participants). MSSA and MRSA were found 25.7% and 38%, respectively, among in patients. For in patients, unlike our study those with active nasal infection and remain hospitalized less than 4 days were not included in the study. Aykut Arca et al.[7] evaluated 3599 preoperative nasal cultures for a year and found 16.6% MSSA, and 0.08% MRSA. Poyraz et al.[8] investigated nasal carriage in patients with chronic diseases (chronic renal failure, chronic obstructive pulmonary disease, chronic ischemic heart disease, and diabetes mellitus) and found 12% MSSA carriage among patients with COPD. MRSA epidemiology differs largely in different geographical areas around the world. [3,5,9,13] Lu et al. [3] from Taiwan found 3.8% MRSA carriage among adult patients visiting the emergency department. Hidron et al.[5] studied the prevalence of and risk factors for MRSA colonization at the time of hospital admission among patients cared for at a 1000-bedded public inner-city hospital. Anterior nares cultures were obtained within 48 h after admission during a 1-month period like our study. They found 7.3% MRSA, and 16.4% MSSA carriage. Lestari et al.[9] studied determinants of carriage of resistant *S. aureus* in both hospitalized patients and individuals from the community in two urban centers in Indonesia. They found 9.1% *S. aureus* carriage rate. Moniri *et al.*^[13] from Iran studied the nasal colonization of MRSA in 100 hospitalized patients and found high *S. aureus* and MRSA carriage (38% and 52.6%, respectively). Jernigan *et al.*^[15] investigated prevalence of MRSA colonization among patients presenting for hospital admission in a tertiary-care academic medical center and isolated MSSA from 179 (18.4%) of the patients and isolated MRSA from 26 (2.7%) of the patients.

The risk factors associated with *S. aureus* carriage were evaluated in many studies. In the literature, age, sex, prior hospitalization, antibiotic usage, surgical operation, smoking, diagnosis of skin or soft tissue lesions, having a chronic disease, living with a healthcare worker, and having prosthesis were found as significant risk factors. [3,4,5,12,13,15-20] In this study, all these risk factors were analyzed and multivariable analyses identified the risk factors as being under 65 years of age, and having prosthesis.

There are different reports among studies on age as a risk factor. Al-Janabi^[10] found higher carriage rate among 10–20 age group. Even Sfeir *et al.*^[17] found 65 years of age and above as a significant risk factor for carriage, Citak *et al.*^[6] found the prevalence of carriage was the same among the age groups. Munckhof *et al.*^[18] found higher carriage rate among 18–39 years of age than 60 years and up like our study.

Having prosthesis was found as a significant risk factor in our patients group. Sfeir *et al.*^[17] found intravascular device and prosthesis as a significant risk factor among 1526 Lebanese outpatients. This risk factor plays a role in increasing the carriage of *S. aureus*, and it may be related to health care exposure.

The strength of our study is taking samples from a specific patient group which was not studied in our region before. The limitation of this study is sample size. We could take a sample from the patients admitted to the clinic during a season or for a year.

Conclusion

The prevalence of MRSA colonization rate at the time of patient admission was not low (9.1%). We have to conduct new studies on large patient groups to identify the risk factors.

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Conflicts of interest

There are no conflicts of interest.

References

- Johannessen M, Sollid JE, Hanssen AM. Host- and microbe determinants that may influence the success of S. aureus colonization. Front Cell Infect Microbiol 2012;2:56.
- Tong SY, Chen LF, Fowler VG Jr. Colonization, pathogenicity, host susceptibility, and therapeutics for Staphylococcus aureus: What is the clinical relevance? Semin Immunopathol 2012;34:185-200.
- Lu SY, Chang FY, Cheng CC, Lee KD, Huang YC. Methicillin-resistant Staphylococcus aureus nasal colonization among adult patients visiting emergency department in a medical center in Taiwan. PLoS One 2011;6:e18620.
- Karabay O, Otkun MT, Yavuz MT, Otkun M. Nasal carriage of methicillin-resistant and methicillin-susceptible Staphylococcus aureus in nursing home residents in Bolu, Turkey. West Indian Med J 2006;55:183-7.
- Hidron AI, Kourbatova EV, Halvosa JS, Terrell BJ, McDougal LK, Tenover FC, et al. Risk factors for colonization with methicillin-resistant Staphylococcus aureus (MRSA) in patients admitted to an urban hospital: Emergence of community-associated MRSA nasal carriage. Clin Infect Dis 2005;41:159-66.
- Citak S, Bayazit FN, Aksoy F. Nasal carriage and methicillin resistance of Staphylococcus aureus in patients and hospital staff in a tertiary referral center setting. Afr J Microbiol Res 2011;5:1615-8.
- Aykut Arca E, Karabiber N, Sen S. Investigation of Staphylococcus aureus in pre-operative nasal cultures. Turkish Bullein of Hygiene and Experimental Biology 2007;64:23-6.
- 8. Poyraz O, Oztop Y, Ozyazici S. Investigation of nasal carriage for Staphylococcus aureus and resistance to several antibacterial agents in patients having chronic diseases. Cumhuriyet Mediacl Journal 2000;22:201-6.
- Lestari ES, Duerink DO, Hadi U, Severin JA, Nagelkerke NJ, Kuntaman K, et al. Determinants of carriage of resistant Staphylococcus aureus among S. aureus carriers in the Indonesian population inside and outside hospitals. Trop Med Int Health 2010;15:1235-43.
- Al-Janabi OH. The carriage rate of nasal Staphylococcus aureus in persistent allergic rhinitis patients. Med J Babylon 2014;11:139-43.
- Mainous AG 3rd, Hueston WJ, Everett CJ, Diaz VA. Nasal carriage of Staphylococcus aureus and methicillin-resistant S aureus in the United States, 2001-2002. Ann Fam Med 2006;4:132-7.
- Chen CS, Chen CY, Huang YC. Nasal carriage rate and molecular epidemiology of methicillin-resistant Staphylococcus aureus among medical students at a Taiwanese university. Int J Infect Dis 2012;16:e799-803.
- Moniri R, Musav GA, Fadavi N. The prevalence of nasal carriage methicillin-resistant Staphylococcus aureus in hospitalized patients. Pak J Med Sci 2009:25:656-9.
- Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing, Informational Supplement. 17th ed. USA: Clinical Laboratory Standards Institute; 2007.
- Jernigan JA, Pullen AL, Flowers L, Bell M, Jarvis WR. Prevalence of and risk factors for colonization with methicillin-resistant Staphylococcus aureus at the time of hospital admission. Infect Control Hosp Epidemiol 2003;24:409-14.
- Lu PL, Chin LC, Peng CF, Chiang YH, Chen TP, Ma L, et al. Risk factors and molecular analysis of community methicillin-resistant Staphylococcus aureus carriage. J Clin Microbiol 2005;43:132-9.
- Sfeir M, Obeid Y, Eid C, Saliby M, Farra A, Farhat H, et al. Prevalence of Staphylococcus aureus methicillin-sensitive and methicillin-resistant nasal and pharyngeal colonization in outpatients in Lebanon. Am J Infect Control 2014:42:160-3.
- Munckhof WJ, Nimmo GR, Schooneveldt JM, Schlebusch S, Stephens AJ, Williams G, et al. Nasal carriage of Staphylococcus aureus, including community-associated methicillin-resistant strains, in Queensland adults. Clin Microbiol Infect 2009;15:149-55.
- Halablab MA, Hijazi SM, Fawzi MA, Araj GF. Staphylococcus aureus nasal carriage rate and associated risk factors in individuals in the community. Epidemiol Infect 2010;138:702-6.
- Liang Z, Zhang Q, Thomas CM, Chana KK, Gibeon D, Barnes PJ, et al. Impaired macrophage phagocytosis of bacteria in severe asthma. Respir Res 2014;15:72.