

Nasal Carriage and Resistance Pattern of Multidrug Resistant *Staphylococcus aureus* Among Healthy Children in Kashan, Iran

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Background: Nasal carriage of *Staphylococcus aureus* is a substantial source of human infections. Detection and treatment of nasal carriage in children with methicillin-resistant and multidrug resistant *S. aureus* (MRSA and MDRSA, respectively) may be an important modality in prevention of infections.

Objectives: This study determined the prevalence, antibiotic resistance patterns and risk factors for nasal carriage of MDRSA among healthy children.

Patients and Methods: This cross-sectional study was carried out on 350 one-month to 14-year-old healthy children in Kashan city, Iran. From all health-care centers, four were chosen by simple random sampling. Nasal samples were cultured in blood agar medium for *S. aureus* and antibiotic susceptibility profile was determined by disc diffusion and E-test. Risk factors for nasal carriage of MDRSA were also determined.

Results: A total of 92 (26.3%) *S. aureus* isolates were obtained, of which 33 (35.9%) were MRSA and 27 (29.3%) were MDRSA. Of MRSA strains, 19 (70.4%) were MDRSA. *S. aureus* isolates showed 52.2% resistance to cephalothin, 33.7% to co-trimoxazole, 26.1% to clindamycin, 26.1% to ciprofloxacin, 4.3% to vancomycin, and 35.9% to oxacillin. The risk factors for nasal carriage of MDRSA were antibiotic usage during the last three months ($P = 0.006$), family size of more than four members ($P = 0.044$), and parental smoking ($P = 0.045$).

Conclusions: MDRSA was not uncommon among healthy children in Kashan and prevention of its spread in the population is judicious.

Keywords: *Staphylococcus aureus*; Nasal; Carriers; Multidrug Resistance; Healthy; Child

1. Background

Staphylococcus aureus is a major cause of healthcare and community-associated infections worldwide (1-3). *S. aureus* colonizes different regions of healthy human beings such as anterior nares, vagina, skin and gastrointestinal tract (4). Its prevalence was reported 17.3% in nasal cavity of healthy Turkish children (5) and 26.6-52.3% in other investigations (6-9). *S. aureus* can cause skin and soft tissue infections, severe necrotizing pneumonia, urinary tract infections, endocarditis and osteomyelitis (10, 11).

Asymptomatic nasal colonization with *S. aureus* is an important risk factor for many infections (12). *S. aureus* has become resistant to many commonly used antibiotics. Multidrug Resistant *S. aureus* (MDRSA) isolates have been emerged in various parts of the world. Resistance to β -lactams and other antibiotic groups is associated with longer hospitalization and more cost of treatment (13). Elliott et al. (14) showed that more than one half of Staphylococcal infections were caused by community-as-

sociated Methicillin-resistant *S. aureus* (MRSA); thus, empiric therapy with cephalosporins or penicillins could be inappropriate. Combination therapy with penicillinase-resistant penicillins or cephalosporins and clindamycin or quinolones is recommended by some physicians (15). Eradication of nasal MRSA colonization has been reported to reduce the incidence of infections (16).

Due to the noticeable increase in antimicrobial resistance, determination of antibiotic susceptibility profile is judicious for decolonization and treatment of *S. aureus* infections. In spite of many investigations about nasal carriage and resistance patterns of *S. aureus* and MRSA as well as their associated risk factors among healthy children, we did not find any study about the associated risk factors for colonization with MDRSA. In this study, antibiotic susceptibility profile and risk factors for nasal carriage of MDRSA were evaluated among healthy children.

2. Objectives

The aim of this survey was evaluation of prevalence, antibiotic resistance patterns and associated risk factors for nasal carriage of MDRSA among healthy children.

3. Patients and Methods

3.1. Study Participants

During this cross-sectional investigation, 350 one-month to 14-year-old healthy children were evaluated from July 2012 to March 2013. At first 360 children were enrolled in the study, but 10 cases were excluded due to lack of parental cooperation. From all (10 centers) healthcare centers in Kashan, Iran, four were selected by simple random sampling. The weighted sample size in each center was proportionate to its population coverage. Nasal specimens were collected by simple random sampling in each center. Sampling was conducted by the laboratory personnel from Shahid Beheshti Hospital. The data were extracted according to the internship thesis, which was supported by Kashan University of Medical Sciences, by a physician. Cases were presented to health centers for growth monitoring, vaccination, or periodic examinations. Physical examination was performed by a physician. Children with acute or chronic respiratory infections, cases of skin infections, chronic medical conditions, those who needed emergency care or hospitalization, and children with noncooperative parents were excluded from the study.

Parental informed consent was obtained following explanation about aims of the study. An interview was performed with the accompanied parent and a questionnaire was filled by a physician. The questionnaires included the demographic characteristics of children as well as the associated risk factors for nasal colonization with MDRSA, such as age, gender, family size, sleeping with parents, parental smoking, history of admission and antibiotic usage in the past three months. Ethical considerations such as obtaining written parental consent, keeping children's medical privacy and no impose of expenses to the cases were respected. The project was approved by the Ethics Committee of Kashan University of Medical Sciences (approval code: 823/2012).

The sample size was estimated by considering 28.4% prevalence of nasal *S. aureus* colonization (7), CI = 95%, d = 0.06 and design effect of 1.5. It was calculated 327 and due to probable diminution during the study 360 cases were enrolled, which finally reduced into 350.

3.2. Nasal Sampling and Bacterial Isolation

Sampling was performed by double rotating a prewetted sterile cotton swab with sterile saline in vestibule of both anterior nares. The collected swabs were inserted in Amies tube transport media with charcoal (HiMedia, Mumbai, India) at 2-4°C and transported to the microbiology laboratory of Kashan Shahid Beheshti Hospital within

four hours. The swabs were cultured on mannitol salt agar (MSA) (Merk, Germany) at 35°C for 48 hours. The yellowish growing colonies on MSA were subcultured on blood agar (Merk, Germany) for a day. The colonies were recognized as *S. aureus* by morphology of colony, Gram staining and catalase, coagulase and DNase production tube tests.

3.3. Antimicrobial Susceptibility Pattern

Antibiotic resistance screening test was conducted by Kirby-Bauer disc diffusion test based on the guidelines of Clinical and Laboratory Standard Institute (CLSI) on positive cultures (17). The cultured colonies on blood agar were transmitted by a sterile loop to Mueller-Hinton agar (Merk, Germany) media and antibiotic discs (Mast, UK) were put on them for 24 hours at 35°C. The discs comprised of cephalothin (30 µg), co-trimoxazole (trimethoprim/sulfamethoxazole) (1.25/23.75 µg), ciprofloxacin (5 µg) and clindamycin (2 µg), oxacillin (1 µg), and vancomycin (30 µg). After 24 hours, the inhibition zones of the strains surrounding the discs were measured and compared to the standard guidelines (17). Inhibition zones of ≤ 14 mm around cephalothin, ≤ 10 mm around oxacillin, ≤ 14 mm around vancomycin, ≤ 10 mm around co-trimoxazole, ≤ 14 mm around clindamycin, and ≤ 15 mm around ciprofloxacin were considered resistant (17). American type culture collection (ATCC) 25923 *S. aureus* was used as the control strain in antimicrobial susceptibility determination (17).

Minimal inhibitory concentration (MIC) breakpoints of ≥ 32 µg/mL, ≥ 8/152 µg/mL, ≥ 4 µg/mL, ≥ 4 µg/mL, ≥ 4 µg/mL, and ≥ 16 µg/mL for cephalothin, co-trimoxazole, clindamycin, ciprofloxacin, oxacillin, and vancomycin, respectively were methicillin resistant (17). MICs were measured by strip E-tests (Liofilchem, Italy). Strip E-tests were placed on Mueller-Hinton agar plates, which were inoculated by solution of isolates with optical density of 0.5 McFarland standards by sterile loops. MIC was measured at the bottom of inhibition zone, intersected by E-test strip. Following screening by disc diffusion test, resistant isolates were confirmed by E-test. Furthermore, E-test was used to detect oxacillin and vancomycin resistance in all positive *S. aureus* cultures. MDRSA was defined as those resistant to at least three different antibiotics (18).

3.4. Statistical Analysis

Data were analyzed by SPSS statistical software version 16. Descriptive results were defined using frequencies and percentages. Data distributions were detected by Kolmogorov-Smirnov test and due to abnormal distribution of family members and age; they were compared between two independent groups by Mann-Whitney U test. Demographic characteristics and associated risk factors for MDRSA were analyzed using the chi-square and Fisher's exact tests, odds ratio and confidence interval. Multiple logistic regression models were used for some variables, if bivariate analysis had P value less than 0.1. P

values less than 0.05 were considered significant and all of them were two sided.

4. Results

Three hundred and fifty children were enrolled in the study with equal number of males and females. The median age of cases was seven years old with inter quartile ratio (IQR) of 8. Mean ages of males and females were 6.84 ± 4.42 and 7.29 ± 4.08 , respectively, which was not significantly different ($P = 0.3$). The age groups were ≤ 7 and > 7 years old with frequency of 190 (54.3%) and 160 (45.7%), respectively. The median family number of children was four with IQR of 1. Out of all cases, 92 (26.3 %) had positive nasal cultures for *S. aureus*, of which 62 (67.4%) were male and 30 (32.6%) were female. The mean age of positive and negative nasal cultures was 6.65 ± 4.46 and 7.21 ± 4.14 years old, respectively ($P = 0.22$). Of 92 positive cultures, 33 (35.9%) individuals were MRSA and 27 (29.3%) were MDRSA. Of MRSA cases, 19 (57.6%) were MDRSA and of methicillin-sensitive

S. aureus (MSSA) cases, 8 (13.6%) were MDRSA ($P < 0.001$, OR = 8.65, 95% CI: 3.1-23.9). Of positive *S. aureus* cultures, 22.8% were resistant to one, 21.7% to two, 16.3% to three, 5.4% to four, 4.3% to five, and 3.3% to six antibiotics, and 26.1% were sensitive to all the antibiotics. The highest resistance was against cephalothin (52.2%) and the lowest to vancomycin (4.3%) (Table 1). The most common pattern of multidrug resistance for *S. aureus* isolates was the combination of cephalothin, co-trimoxazole and oxacillin 13 (14%).

Using multiple logistic regression analysis, the associated risk factors for *S. aureus* colonization were antibiotic usage during the last three months ($P = 0.001$, OR = 3.07, CI:1.57-6.04), parental smoking ($P < 0.001$, OR = 8.8, CI: 3.6-21.2), and family size larger than four members ($P < 0.001$, OR = 4.1, CI: 1.9-8.6). Risk factors of MRSA nasal carriage were male gender ($P = 0.006$, OR = 11.9, CI: 2.05-70.2) and antibiotic usage in the last three months ($P = 0.032$, OR = 4.4, CI: 1.1-17.4). The associated risk factors for nasal carriage of MDRSA are showed in Table 2.

Table 1. Antibiotic Susceptibility Among Children With Nasal Carriage of *Staphylococcus aureus* ^{a,b}

Antibiotics	<i>S. aureus</i>		MRSA		MDRSA	
	S	R	S	R	S	R
Cephalothin	44 (47.8)	48 (52.2)	9 (27.3)	24 (72.7)	3 (11.1)	24 (88.9)
Co-trimoxazole	61 (66.3)	31 (33.7)	18 (54.5)	15 (45.5)	7 (25.9)	20 (74.1)
Ciprofloxacin	68 (73.9)	24 (26.1)	20 (60.6)	13 (39.4)	8 (29.6)	19 (70.4)
Clindamycin	68 (73.9)	24 (26.1)	18 (54.5)	15 (45.5)	10 (37)	17 (63)
Oxacillin	59 (64.1)	33 (35.9)	0 (0)	33 (100)	8 (29.6)	19 (70.4)
Vancomycin	88 (95.7)	4 (4.3)	29 (87.9)	4 (12.1)	24 (88.9)	3 (11.1)

^a Abbreviations: *S. aureus*, *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multi-drug resistant *S. aureus*; S, sensitive; R, resistant.

^b All the values are present as No. (%).

Table 2. Univariate and Multivariate Analysis of Potential Risk Factors for Nasal Carriage of Multidrug-Resistant *Staphylococcus aureus* in Children ^{a,b}

Variables	MDR ^a		P Value	Logistic Regression	
	No	Yes		OR (95% CI)	P Value
Gender			0.005		
Male	38 (58.5)	24 (88.9)			
Female ^b	27 (41.5)	3 (11.1)			
Age group, y			0.014		
> 7	35 (53.8)	7 (25.9)			0.24
≤ 7 ^b	30 (46.2)	20 (74.5)			
Family size			< 0.001		
> 4	28 (43.1)	26 (96.3)		11.7 (1.07-126.8)	0.044
≤ 4 ^b	37 (56.9)	1 (3.7)			
Admission in 3 months before			< 0.001		
Yes	21 (32.3)	20 (74.1)			0.42
No ^b	44 (67.7)	7 (25.9)			
Antibiotic usage in the past 3 months			< 0.001		
Yes	27 (41.5)	26 (96.3)		34.29 (2.7-430.2)	0.006
No ^b	38 (58.5)	1 (3.7)			
Parental smoking			< 0.001		
Yes	24 (36.9)	26 (96.3)		11.8 (1.06-131.7)	0.045
No ^b	41 (63.1)	1 (3.7)			
Sleeping with parents			0.005		
Yes	35 (53.8)	23 (85.2)			0.16
No ^b	30 (46.2)	4 (14.8)			

^a Abbreviations: CI, confidence interval; MDR, multi-drug resistant; OR, odds ratio.

^b All the values are present as No. (%).

5. Discussion

Three hundred fifty healthy children, one month to 14 years old, were enrolled in this study. The prevalence of nasal colonization with *S. aureus* was 26.3%, of which 35.9% was MRSA and 29.3% was MDRSA. During an investigation in Hamadan, Iran on 500 1 to 6-year-old children, attending to day care centers, 26.9% had positive nasal cultures for *S. aureus* (significantly more prevalent in males), of which 4.1% were MRSA and no resistance of MRSA to vancomycin was detected (19). Furthermore, none of the strains were resistant to clindamycin and just one MRSA isolate was resistant to co-trimoxazole. Our study showed similar prevalence of *S. aureus*, but larger MRSA carriage rate, 4.3% vancomycin resistance, substantially more resistance to clindamycin and co-trimoxazole and no association between nasal carriage of *S. aureus* and gender. In an investigation by Tabbarai et al. (20) on 1193 school-age children, nasal carriage of *S. aureus* was 16.3%, of which 34.8% were MRSA, the peak age of nasal colonization was 6-12 years old, and vancomycin resistance was reported in 1.7%. Our data showed more nasal carriage of *S. aureus*, but approximately equal MRSA colonization and greater vancomycin resistance rate; moreover, there was no significant difference of *S. aureus* nasal carriage between the age groups in our survey. Ghadiri et al. (21) reported about 20% nasal carriage rate among children less than 18 years old, of which 96.4% and 3.6% were MRSA and vancomycin resistant, respectively. Colonization and vancomycin resistance rate of their study were approximately consistent with our results, but MRSA colonization rate was substantially higher than ours.

Ramana et al. (22) presented 16% prevalence of *S. aureus*, of which 19% were MRSA among 5 to 15-year-old children. Co-trimoxazole-resistant *S. aureus* was reported 14.3%. All of these data were lower compared to our investigation. In another survey on 489 children (5-15 years old) by Chatterjee et al. (6), nasal carriage of *S. aureus* was reported in 52.5% of children, of which 3.9% were MRSA. They lived in mud hatch homes as a risk factor for nasal colonization. *S. aureus* carriage rate was greater, but MRSA was lesser than our study. According to some studies, the carriage rate of nasal *S. aureus* was lower in resource-limited countries. The carriage rate of nasal *S. aureus* was indicated age-dependent in some studies previously. The peak colonization rate of nasal pathogen may be seen during 2-3 years of age. At this age range, a lot of microbes such as *Pneumococcus*, *Haemophilus influenza*, *Moraxella catarrhalis* and *S. aureus* compete for anterior nares colonization. The mechanism, by which colonization with an isolate prevents colonization by another one, has a major role in elimination or establishing a strain over others (23). In our survey, no significant association between the age groups and *S. aureus* nasal carriage, MRSA or MDRSA was detected. Pathak et al. (24) reported significant association of *S. aureus* nasal carriage with family size of 10 or more members compared to families \leq four members,

which was compatible with our investigation. It could be due to overcrowding and poor sanitation. Some studies showed the major role of household's close contacts with parents in distribution of nasal *S. aureus* colonization among children (25), which was concordant with our report. Hospitalization was not significantly associated with nasal carriage of *S. aureus* (24), which was comparable with our results. Our survey demonstrated recent antibiotic usage as an associated risk factor for nasal carriage of *S. aureus*, MRSA and MDRSA, which was not consistent with Pathak et al. (24) results, who reported no association between recent antibacterial usage and nasal colonization with *S. aureus*. In our investigation, 26.3% of children who were included in the study received an antibiotic during the last three months which reflected its association with nasal *S. aureus* colonization, MRSA and MDRSA. In the present study, the highest sensitivity of MRSA was to vancomycin (87.9%) and the lowest to cephalothin (27.3%).

Huang et al. (26) results showed no resistance of MRSA to vancomycin, 99.1% resistance to penicillin, and 91% resistance to clindamycin (45.5% in our study). Congruent results were reported in some investigations (24), but Ko et al. (8) results showed clindamycin sensitivity of 61.1%, which was more than that of our and aforementioned researches. During a research on 500 healthy, \leq 16 years old children in Chicago, 24.4% were nasal *S. aureus* carriers, of which 2.5% were MRSA and all of community-associated nasal MRSA strains were sensitive to co-trimoxazole and clindamycin (27). These findings were not consistent with our study. Comparison of the present study to others showed the emergence of *S. aureus* isolates as well as community-associated MRSA to antimicrobials, especially clindamycin and co-trimoxazole, and an increase in MDRSA; thus, judicious prescription of antibiotics in children is mandatory. Some simple sanitary modalities such as hand washing are efficacious in prevention of resistant microbial spread in populations. For instance, by implementation of a preventive program in some Swedish day care centers with alcohol-based hand washing for children, the absenteeism rooted from day cares was significantly diminished (12%) (28). Despite the fact that the majority of children with community-associated nasal carriage of MRSA are self-limited during a year (29), some of them will acquire recurrent skin and soft tissue infections; so, decolonization of them can be prudent (30). This study indicated that risk factors for nasal colonization with MRSA were antibiotic usage during the last three months and male sex. Furthermore, our investigation revealed that antibiotic usage in the last three months, family size of more than four members and parental smoking, were the associated risk factors for nasal carriage of MDRSA. Unfortunately, we could not find any study about the risk factors for nasal colonization with MDRSA among healthy children to compare our results. Therefore, further studies in this field are recommended.

Our investigation had some limitations; we did not

conduct molecular studies to detect antibiotic resistance genes especially for MRSA and MDRSA isolates due to financial restrictions. Our study was cross-sectional and did not differentiate transient and persistent nasal colonization; so, a cohort design to take the second nasal culture after a year is recommended in future surveys to determine persistent carriage, an important source of community infections. In this research, the isolated microbes may not have been representative of the population; so, more comprehensive investigations with larger sample sizes are recommended in future. Socioeconomic statuses of families were not evaluated in this study; thus, it can be considered in further investigations. Finally, we did not perform a combination of quantitative and qualitative nasal cultures for prediction of persistent *S. aureus* carriage (31) and more studies are offered in future. The strong point of our study was determination of the associated risk factors with nasal colonization with MDRSA among healthy children which has not been performed elsewhere and may be a novel idea.

In conclusion, this study indicated the high rate of nasal carriage of MDRSA as well as the presence of the commonly used antimicrobial resistance, which is disturbing. Therefore, judicious use of antibiotics accompanied by strategies for prevention of community spread of MDRSA is highly recommended.

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Authors' Contributions

Development of original idea: Babak Soltani, Mahzad Erami. Study concept and design: Babak Soltani, Abbas Taghavi Ardakani, Mahzad Erami. Analysis and interpretation of data: Alireza Moravveji. Data collection: Mahzad Erami, Mostafa Haji Rezaei. Preparation of manuscript: Babak Soltani, Mostafa Haji Rezaei, Siamak Soltani. Laboratory testing: Mahzad Erami, Rezvan Moniri. Revision of the manuscript: Babak Soltani.

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