Methicillin-Resistant *Staphylococcus aureus* Nasal Colonization in Children in Jerusalem: Community vs. Chronic Care Institutions

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Abstract

Background: Nasal colonization with methicillin-resistant *Staphylococcus aureus* in the community is being increasingly reported, but there is a general lack of data on MRSA colonization in children in chronic care institutions and on colonization rates in Israeli children.

Objectives: To define the rate of MRSA nasal colonization in a generally healthy pediatric population in Jerusalem, to compare it with that of children in chronic care institutions, to define risk factors for colonization, and to compare community and hospital-acquired MRSA strains.

Methods: Anterior nares culture for the presence of methicillin-sensitive and methicillin-resistant *S. aureus* was taken from 831 healthy children attending primary pediatric clinics or emergency departments and from 118 children hospitalized in three chronic care institutions in Jerusalem.

Results: Of the 831 healthy children, 195 (23.5%) were colonized with *S. aureus,* as compared to 43 of 118 (36.4%) chronically institutionalized children ($P < 0.005$). Five of the 195 *S. aureus* isolates from healthy children (2.6%) were MRSA, as compared to 9 of 43 (21%) from chronically institutionalized children ($P < 0.001$). Older age and a family member who is a healthcare worker were associated with *S. aureus* colonization in the population of healthy children, and older age was associated with MRSA colonization in the chronically institutionalized children. The antibiotic susceptibility pattern was similar for both groups, and pulsed field gel electrophoresis of the isolates showed a wide and random distribution in both groups.

Conclusions: MRSA colonization in the studied pediatric community in Jerusalem was very low, whereas that of patients hospitalized in chronic care institutions was significantly higher. In the small number of isolates detected, no significant differences were found in antibiotic susceptibility or PFGE pattern between hospital-acquired and community-acquired strains.

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Staphylococcal infections are very common in the pediatric age group, accounting for most superficial and deep-seated soft tissue infections. Traditionally, community-acquired strains are sensitive to methicillin, and usual antibiotic regimens for these infections include beta-lactams with appropriate anti-staphylococcal coverage.

In the 1990s, methicillin-resistant *Staphylococcus aureus* strains were increasingly recognized in the community, and varying rates of community-acquired MRSA infection and nasal colonization in both adults and children have been reported [1–15]. Data are available on MRSA colonization rates in both pediatric hospitals and child day-care centers [16,17], and an outbreak of MRSA infection was recently described in a chronic care institution for mentally retarded adults in Israel [18]. Nevertheless, there is a paucity of data regarding MRSA colonization in pediatric chronic care institutions.

It has been suggested that community-acquired MRSA strains differ from hospital-acquired strains with regard to genotypes and antibiotic susceptibility pattern. Community strains are said to be more sensitive than hospital strains to multiple anti-staphylococcal agents such as clindamycin, erythromycin, trimethoprim-sulfamethoxazole, aminoglycosides and fluoro-quinolones [1,5,6,9, 10,11–15,19–21].

Sattler et al. [14] recently reported an alarming rate of 35–51% of MRSA in community-acquired infection in Houston, Texas. Even higher rates, also from Texas, were published by Fergie and Purcell [13,15]. These high rates, although not yet reported from other states in the U.S. or elsewhere, mandate careful monitoring of the presence of MRSA in the community.

Colonization rates vary greatly from country to country as well as within different regions in the U.S. Hence, no extrapolation can be made from one community to another. Community MRSA nasal colonization in Israel was studied in adults in the early 1990s by Dan et al. [22], who found that the *S. aureus* nasal colonization rate in 350 individuals presenting at a general hospital emergency room was 10.2%, 3.2% of which were MRSA. There are virtually no data available on the rate of community MRSA nasal colonization in Israeli children in general, and in the population of Jerusalem in particular. Hence, the aims of this study were: first, to determine the MRSA colonization rate in healthy children attending emergency department and primary pediatric clinics in the Jerusalem area; second, to compare this rate to that of chronically institutionalized children; third, to evaluate risk factors for MRSA colonization in both groups; and finally, to compare the antibiotic susceptibility patterns and molecular genotyping of the strains from both groups.

Patients and Methods

The local ethics committee approved the study and the parents of the enrolled patients gave oral informed consent prior to enrollment. In the chronic care facilities the consent was given by the caregivers.

Patients

- *Healthy children*: The study group included children in normal health aged 0.5–17 years attending outpatient clinics in different regions in Jerusalem and the surrounding area. Subjects were enrolled from both urban and rural clinics in

MRSA = methicillin-resistant *Staphylococcus aureus*
PFGE = pulsed field gel electrophoresis

both Jewish and Arab neighborhoods, representing the diversity of Jerusalem's pediatric population. Also included were children in normal health who were seen in the Pediatric Emergency Room of Shaare Zedek Medical Center. Colonization rates of *S. aureus* in this study group were expected to represent rates of community acquisition.

- *Chronic care facilities*: This study group included children aged 0.5–17 years hospitalized at three chronic medical institutions in Jerusalem: two of these institutions are for severely mentally retarded children, where patients stay for years, and the third is a rehabilitation institution, primarily for patients with chronic orthopedic or neurologic handicaps and for patients with a chronic requirement for mechanical ventilation.

Samples

Nasal swabs were collected from both anterior nares using a nasopharyngeal swab (Transwab, Medical Wire & Equipments co., Corsham, UK), placed in a transport medium and transferred within 24 hours to the Microbiology Laboratory of Shaare Zedek Medical Center.

Laboratory methods

All isolates were identified as *Staphylococcus aureus* by Pastorex STAPH PLUS (Bio-Rad, USA) and those with a minimum inhibitory concentration lower than 4 μg/ml were classified as MRSA. MIC was determined by using the E-test (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions. *S. aureus* isolates were also screened for methicillin resistance on Mueller-Hinton agar containing 4% NaCl and 6 μg/ml oxacillin. MRSA strains were tested for the presence of PBP2a by MRSA-Screen (Denka-Seiken, Tokyo, Japan) latex agglutination test.

Pulsed field gel electrophoresis of MRSA strains

All the MRSA strains were analyzed by PFGE, as previously described [18]. The analysis was performed at the Microbiology Laboratory of Soroka Medical Center, Ben-Gurion University of the Negev, Beer Sheva, Israel.

Epidemiologic data

A questionnaire was completed for every subject enrolled in the study. For the healthy children the following parameters were recorded: age, gender, ethnic origin, residency, education, number of family members, crowding (i.e., the number of family members sharing the same apartment divided by the number of rooms in the apartment), use of antibiotics during the 6 months prior to the study, hospitalization in the 6 months prior to the study, and having a household contact who is a healthcare worker. For the children in chronic care institutions the parameters recorded were: age, gender, ethnic group, name of institution, time in the institution, use of antibiotics during the 6 months prior to the study, and hospitalization in a general hospital in the 6 months prior to the study.

MIC = minimum inhibitory concentration

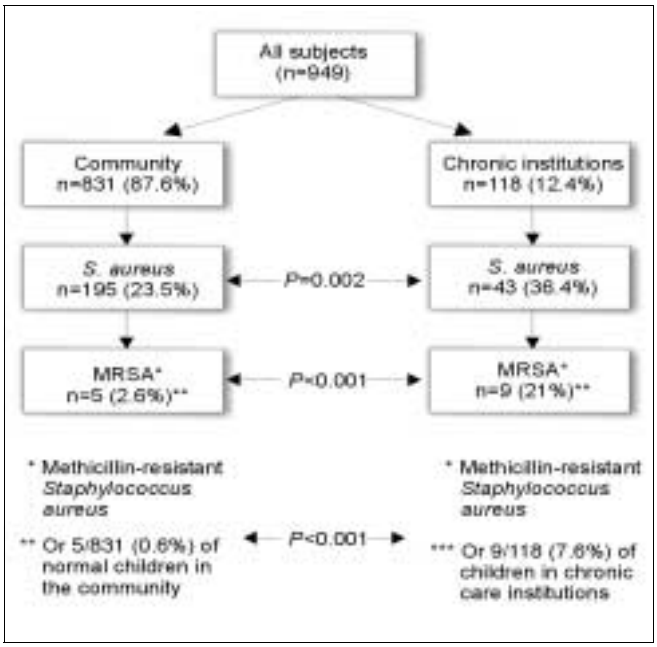

Figure 1. Study outline

Statistical analysis

Data were analyzed by the Epi Info 6.04 d software package (CDC, USA) applying the *t*-test and chi-square test. Binomial logistic regression analysis was done by SPSS software package version 10.0.

Results

Figure 1 summarizes the outline of the study. During the study period 949 subjects were enrolled: 831 healthy children visiting outpatient clinics or the pediatric emergency room, and 118 children in chronic care institutions. Of 831 healthy children, 195 (23.5%) were colonized by *S. aureus* as compared to 43 of 118 (36.4%) of the chronically institutionalized children ($P = 0.002$). Five of the 195 *S. aureus* isolates from healthy children (2.6%) were methicillin-resistant strains, as compared to 9 of 43 (21%) of the chronically institutionalized children ($P < 0.001$). From a different perspective, 5 of the 831 healthy children (0.6%) were colonized with MRSA, compared to 9 of the 118 chronically institutionalized children (7.6%) ($P < 0.001$).

Risk factors

Risk factors for colonization with *S. aureus* in healthy children are presented in Table 1. The data were analyzed by both univariate and multivariate analysis. In the generally healthy population as well as in the chronically institutionalized children, older age correlated with *S. aureus* colonization. In addition, having a household contact who is a healthcare worker was significantly associated with colonization in the generally healthy pediatric population. Risk factors for MRSA colonization in the healthy population were not calculated due to the very small number of isolates. In the chronically institutionalized children, older age was the only significant risk factor for colonization with *S. aureus* (10.3 ± 3.9 vs. 8.9 ± 4.6 years, $P = 0.037$).

Table 1. Risk factors for *S. aureus* nasal colonization in the community

		Staphylococcus aureus colonization		*P* value (univariate analysis)	*P* value (logistic regression)
	No. of cases*	No N (%)	Yes N (%)		
Total	831	644 (77)	195 (23)		
Age	831	4.04 ± 3.9	5.80 ± 4.3	<0.0001	<0.0001
Gender				NS	NS
Male	425	326 (51)	99 (51)		
Female	384	297 (46)	87 (45)		
Ethnic group				NS	NS
Jewish	732	569 (78)	163 (84)		
Non-Jewish	107	75 (12)	32 (16)		
Resident				0.032	NS
Rural	221	157 (36)	64 (33)		
Urban	516	406 (63)	110 (56)		
Education				<0.001	NS
Day care	132	113 (18)	19 (10)		
Home	242	195 (30)	47 (24)		
Kindergarten	183	147 (23)	36 (19)		
School	226	142 (22)	84 (43)		
Other	3	3 (.5)	0 (0)		
Antibiotics use**				NS	NS
No	505	379 (59)	126 (65)		
Yes	331	263 (41)	68 (35)		
Anti-staphylococcal antibiotics use**				NS	NS
No	718	348 (85)	170 (87)		
Yes	121	96 (15)	25 (13)		
Hospitalization**				NS	NS
No	779	598 (93)	181 (93)		
Yes	58	45 (7)	13 (7)		
Healthcare worker***				0.04	0.021
No	778	605 (94)	173 (89)		
Yes	59	38 (6)	21 (11)		
Family members	688	5.70 ± 2.13	6.00 ± 2.14	NS	NS
Crowding ****	675	1.60 ± 0.7	1.67 ± 0.8	NS	NS

* When individual cells do not add up to the total number of cases, it is due to missing data
** In the 6 months prior to study
*** First-degree family member who works in a healthcare facility
**** Number of people per room
NS = not significant

Table 2. Risk factors for colonization with methicillin-resistant *Staphylococcus aureus* in chronic care institutions

		Staphylococcus aureus type		Univariate analysis (*P* value)	*Logistic* regression (*P value*)
	No. of cases*	Sensitive** N (%)	Resistant*** N (%)		
Total	43	34 (79)	9 (21)		
Age	43	9.71 ± 3.9	12.67 ± 3.1	0.041	<0.01
Gender				0.024****	NS
Male	20	95	5		
Female	23	65	35		
Ethnic group				NS	NS
Jewish	29	72	28		
Non-Jewish	14	93	7		
Institution				NS	NS
Aleh	7	5 (15)	2 (22)		
Alyn	8	7 (21)	1 (11)		
St. Vincent	28	22 (64)	6 (67)		
Antibiotics use*****				NS	NS
No	30	11 (32)	1 (11)		
Yes	12	22 (65)	8 (89)		
Anti-staphylococcal antibiotic use*****				NS	NS
No	32	27 (79)	5 (55)		
Yes	11	7 (21)	4 (45)		
Hospitalization*****				NS	NS
No	30	24 (71)	6 (67)		
Yes	12	9 (26)	3 (33)		
Duration in institution (yrs)	39	4.27 ± 2.5	4.11 ± 2.5	NS	NS

* When individual cells do not add up to the total number of cases, it is due to missing data
** Methicillin-sensitive *S. aureus*
*** Methicillin-resistant *S. aureus*
**** Fisher's exact test
***** In the 6 months prior to study

Risk factors for colonization with MRSA, as compared to methicillin-sensitive *S. aureus* organisms in the chronically institutionalized children, are presented in Table 2. As shown, older age correlated with MRSA colonization.

Antibiotic sensitivity

Overall, the MRSA strains were sensitive to many other antibiotics, with a non-significant trend towards decreased susceptibility to clindamycin, erythromycin and ciprofloxacin in the isolates from institutionalized children.

Pulsed-field gel electrophoresis

All the MRSA strains were analyzed by PFGE, and the results are presented in Figure 2. As shown, there was a random distribution of strains but no clustering of a specific strain among isolates from the same institution.

Discussion

The emergence of MRSA in the community is of great importance and is the subject of multiple studies in a variety of clinical settings and from many parts of the world. This study was designed to answer several specific questions. First, the actual rate of *Staphylococcus aureus* colonization, whether sensitive or resistant to methicillin, in healthy children in the vicinity of Jerusalem was as yet unknown. We studied healthy children from various neighborhoods in Jerusalem, representing a variety of ethnic, socioeconomic and demographic sectors of the diverse Jerusalem population. We also included a group of otherwise healthy children visiting the emergency department, based on the studies of Frank et al. [6] and Hussain et al. [9] that demonstrated similar rates of MRSA colonization in both groups in Chicago. We detected a 23.6%

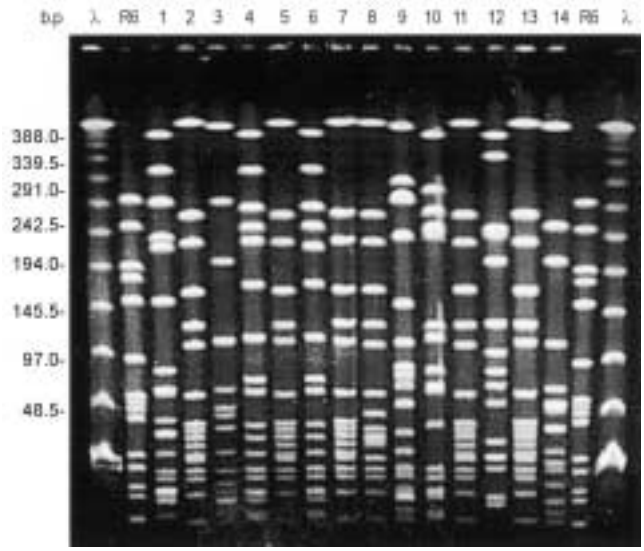

Figure 2. PFGE of 14 community and nosocomial acquired MRSA strains. Strains 1-9: hospital strains (1-6 Hospital #1, 7-8 Hospital #2, 9 Hospital #3). Strains 10-14: community strains. λ R6: Molecular markers.

Strains # 2,5,7,8,11,13	PFGE clone A	Strains # 9	PFGE clone D
Strains # 1,4,6	PFGE clone B	Strains # 10	PFGE clone E
Strains # 3,14	PFGE clone C	Strains #12	PFGE clone F

S. aureus colonization rate, 2.6% of which were MRSA. Expressed differently, 0.6% of the studied subjects were colonized with MRSA. These rates were similar within different subpopulations in the study (data not shown). These figures of low MRSA colonization are in the same range as those reported in other studies, such as those of Nakamura et al. [12] recently reported from Nashville, but are far lower than those reported by others [13–15]. This wide range of colonization rate emphasizes the critical role of geographic differences and the need for local surveillance studies. The information obtained in this study is highly relevant for clinicians in pediatric departments in Jerusalem. Evolving protocols in the U.S. for empiric treatment of community-acquired infections likely to be caused by *S. aureus* often include clindamycin, TMP/SMZ and vancomycin, due to the increasing rate of MRSA [14,15]. In contrast, our finding of a low MRSA colonization rate is reassuring in that beta-lactam agents with anti-staphylococcal activity can be safely used empirically in these cases.

Second, although the rates of MRSA colonization within hospitals or chronic care elderly institutions have been studied, there is a paucity of data regarding MRSA colonization in pediatric chronic care institutions. The available data relate to pediatric hospitals, child day-care centers [16,17] and a mentally retarded adult chronic care institution [18]. These numbers do not necessarily represent those of institutions for the care of handicapped children. We studied the MRSA colonization rate in children living in three different chronic care facilities. These children have many underlying diseases, are frequently treated with antibiotics, and are often hospitalized for acute problems. Not surprisingly, the MRSA nasal colonization rate was significantly higher than in healthy children. Overall, 43 of 118 patients studied (36.4%) were colonized with *S. aureus* and 9 of those (21%) were MRSA. Expressed differently, 9 of 118 studied patients (7.6%) were colonized with MRSA. This implies a rationale for more liberal use of clindamycin and vancomycin in the empiric treatment of suspected staphylococcal infection in these patients.

Third, we sought risk factors for colonization with MRSA in both healthy and institutionalized children. We assessed many known factors, comparing both the healthy and the chronically institutionalized children. In the generally healthy population, since the number of subjects with MRSA colonization was too small to analyze risk factors, we compared those who carry both types of *S. aureus* – methicillin sensitive and resistant – with those who do not. Two risk factors for colonization with *S. aureus* remained significant in multivariate analysis: older age and having a household contact who is a healthcare worker. Older age was also found to be a significant risk factor for MRSA colonization in chronic care facilities. The reason for this finding is not clear, and it is not commonly reported. We speculate that, in both populations studied, repeated exposures to the organism as the child grows could be a possible explanation.

Fourth, there is now growing evidence that community-acquired MRSA is intrinsically different to that of hospital origin. These differences manifest in both antibiotic susceptibility patterns and molecular genotyping. The community strains are typically more sensitive to various anti-staphylococcal agents than those of hospital origin. These antibiotics include clindamycin, erythromycin, aminoglycosides, fluoro-quinolones, and occasionally TMP/SMZ [1–11,12,15,1—21]. Genotypically, community strains have several clones that are different to those of hospital-acquired strains, as can be seen in molecular fingerprinting assays such as PFGE [19–21]. In this study we attempted to demonstrate such difference between the five community-acquired strains and the nine hospital-acquired strains, but failed to do so in either the antibiogram or the PFGE pattern. Furthermore, we assumed that among the subjects in the chronic institution we would find a dominant clone associated with a given institution, but this was not the case. This finding may imply that the high MRSA colonization rate in this institution is not due to horizontal spread but rather to other factors (such as multiple antibiotics use) that encourage MRSA colonization. The most likely explanation for our inability to demonstrate differences between chronic institution and community MRSA strains is the very small number of isolates tested. For example, in the study by Charlebois and co-workers [19], the number of isolates tested, which showed differences between community and hospital strains, was 536. Hence, it would be unrealistic to expect to find these differences in our 14 isolates. Nevertheless, the concept of differences between community and hospital is not yet fully established, and it is also possible that with our low community MRSA colonization rate, these differences do not exist.

In summary, this study demonstrates that the rate of MRSA nasal colonization in healthy children in Jerusalem is low, and that beta-lactam agents can continue to be used as empiric therapy for suspected staphylococcal infections. Not surprisingly, a significantly

TMP/SMZ = trimethoprim-sulfamethoxazole

higher rate of MRSA colonization in chronic pediatric institutions was also found. In this small number of organisms, the expected hospital-community differences could not be demonstrated.

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