Characteristics of SCC*mec* IV and V Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Israel

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ABSTRACT: **Background:** Isolation of methicillin-resistant *Staphylococcus aureus* (MRSA) in healthy individuals is not common in Israel. In our hospital, about 30% of MRSA isolates were SCC*mec* types IV and V.

Objectives: To identify the demographic and clinical characteristics of patients carrying MRSA SCC*mec* type IV or V, and to compare them with each other and with those of patients with SCC*mec* types I-III.

Methods: We conducted a case-control study that included 501 patients from whom MRSA was isolated: 254 with SCC*mec* type I, II, or III, and 243 isolates from SCC*mec* types IV or V.

Results: MRSA was isolated from surveillance cultures in 75% of patients and from a clinical site in 25%. The majority of our study population was elderly, from nursing homes, and with extensive exposure to health care. First, we compared characteristics of patients identified through screening. Statistically significant predictors of SCC*mec* V vs. IV were Arab ethnicity (OR 7.44, 95%CI 1.5–37.9) and hospitalization in the year prior to study inclusion (OR 5.7, 95%CI 1.9–16.9). No differences were found between patients with SCC*mec* types I-III and patients with SCC*mec* type IV or V. Analysis of the subset of patients who had clinical cultures yielded similar results.

Conclusions: SCC*mec* types IV and V were common in the hospital setting although rare in the community. It seems that in Israel, SCC*mec* IV and V are predominantly health care-associated MRSA.

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KEY WORDS: community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), hospital-acquired methicillin-resistant *Staphylococcus aureus* (HA-MRSA), SCC*mec* IV, SCC*mec* V

Methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as an important pathogen in the late 1970s when it spread in hospitals and other health care facilities, leading to severe nosocomial infections. Over the last two decades MRSA infections have been diagnosed with increasing frequency in patients from the community, affecting young and healthy individuals and causing primarily skin and soft tissue infections [1].

Methicillin resistance is coded by the *mec* gene which is carried on the staphylococcal chromosomal cassette *mec* (SCC*mec*). SCC*mec* I-III, which are large and code for multidrug resistance, have been mainly described in health care-associated infections. The SCC*mec* IV and V, which are small, do not code for multidrug resistance and were more often associated with community infections [2]. SCC*mec* types I-III have been described primarily in institutionalized patients with multiple comorbid conditions, while SCC*mec* IV and V tend to cause community-acquired infections and to affect patients with no obvious risk factors who were not hospitalized [3]. Studies from various parts of the world have shown that classical risk factors for MRSA are not found among patients with SCC*mec* IV and V [4]. Even when various clones of SCC*mec* IV cause nosocomial bacteremia, these risk factors do not apply to the affected patients [5]. Recently, we analyzed all MRSA strains isolated in an Israeli hospital from June 2006 to April 2008. Nearly 30% of the MRSA isolates were SCC*mec* types IV and V, despite the fact that the typical clinical presentation of community MRSA was rare. In Israel, the proportion of MRSA among all *Staphylococcus aureus* isolates in 2012 was 35%, similar to the proportion observed in southern Europe [6] and lower than in other Middle Eastern countries [7]. A recent report on mapping 315 MRSA strains from various parts of Israel also revealed a relatively high proportion of SCC*mec* types IV and V (27%), compared to studies from elsewhere [8]. This high proportion of SCC*mec* types IV and V, without the classical picture of community-acquired MRSA (CA-MRSA) as described in the United States and elsewhere, deserved further analysis.

In the present study we describe the demographic and clinical characteristics of patients carrying (or infected with) SCC*mec* types IV and V MRSA, determine if they were similar to each other, and compare them to patients with MRSA SCC*mec* types I-III.

PATIENTS AND METHODS

SETTING AND MICROBIOLOGICAL METHODS

Meir Medical Center is a 700-bed general hospital with about 60,000 admissions annually. Surveillance MRSA cultures upon admission are recommended for all high risk patients: those who were hospitalized during the previous year, patients who were transferred from another hospital, patients who reside in a long-term care facility (LTC), chronic hemodialysis patients, and those who are known prior MRSA carriers. All patients in the Respiratory and Surgical intensive care units (ICUs) are cultured upon admission and weekly until discharged from the unit. Close to 1700 swab samples were analyzed for MRSA carriage monthly, about one-third of all admissions.

During the study period, June 2006 to April 2008, 1008 MRSA-positive cultures were identified from either clinical or surveillance specimens and underwent complete phenotypic characterization. All MRSA isolates were validated by morphological and biochemical analyses following standard laboratory procedures [9] and growth on Mueller-Hinton oxacillin agar: 6 μg of oxacillin/ml according to the Clinical and Laboratory Standards Institute (CLSI) [10]. Additional identification was performed by VITEK II system (bioMérieux, France) or by 16S rDNA analysis. Screening for oxacillin resistance and other antibiotic resistance phenotypes was performed using the Kirby-Bauer methods or E-test according to CLSI guidelines [11]. All MRSA strains were later typed into the major SCC*mec* groups using an in-house quantitative real time-polymerase chain reaction (QRT-PCR) screening protocol for SCC*mec* typing and were screened for the presence of the Panton-Valentine leukocidin (*PVL*) gene [12].

STUDY DESIGN AND STATISTICAL ANALYSIS

We selected about 100 isolates from each type isolated from screening culture cases, and in view of the small number we included all isolates of SCC*mec* type III. For the second analysis we selected all isolates from clinical sites. A case-control study was conducted to compare the characteristics of patients from whom SCC*mec* IV or V MRSA was isolated with each other and with patients from whom SCC*mec* I-III was isolated.

Initially, we examined the differences between patients with SCC*mec* types I, II or II and after confirming that there were no statistically significant differences between them, we combined them into a single group I-III (data not shown). After this step we performed three analyses: patients with SCC*mec* IV compared to patients with SCC*mec* V, patients with SCC*mec* IV compared to patients with SCC*mec* I-III, and patients with SCC*mec* V compared to patients with SCC*mec* I-III. The analyses were done separately for patients detected in the surveillance and for infected patients with clinical isolates. If a patient had more than one isolate during the study period, only data from the first detection were analyzed. If a patient had MRSA isolated both from a surveillance culture and from a clinical specimen, the patient was categorized as being infected and having a clinical isolate.

Medical records were used to obtain patient information. A standardized data collection form was used to record the following data:

- *Demographics:* gender, year of birth, and place of residence (home or nursing home)
- *Clinical data:* place of MRSA acquisition, community (culture from the first 48 hours after admission) or hospital; comorbidities; previous hospitalizations and ambulatory clinic visits in the 12 months prior to hospitalization; antibiotic therapy in the 6 months prior to hospitalization; surgeries and outpatient procedures (such as peritoneal tap, endoscopy) in the 6 months prior to hospitalization; presence of a skin infection in the current hospitalization; and diagnosis on admission
- *Outcomes:* length of hospitalization and mortality 30 days post-culture. Mortality data were collected from the national population registry maintained by the Ministry of the Interior.

All data were analyzed using SPSS V19 (SPSS, Inc., Chicago, IL, USA). Patients were categorized based on MRSA SCC*mec* type into groups according to the a priori plan to compare SCC*mec* IV and V groups to each other and to the SCC*mec* I-III group. Univariate and multivariate comparisons between the groups were performed. Univariate analysis included Student's *t*-test for continuous variables and chi-square test for dichotomous variables. Multivariate analysis using logistic regression was performed. Variables with a P value < 0.1 in the univariate analysis entered the model and were maintained in the model when $P < 0.05$.

RESULTS

A total of 501 patients were included in the study: 254 with SCC*mec* types I, II or III, and 247 with isolates from SCC*mec* type IV or V (126 and 121, respectively). In 375 patients (75%), MRSA was isolated from surveillance cultures and in 126 (25%) the MRSA strain was isolated from a clinical site, most commonly the skin (76 cases, 60%).

PATIENTS WITH MRSA FROM SURVEILLANCE CULTURES (N=375)

The median age was 81 years (range 2–100); 210 (56%) were males. A total of 310 cases (83%) were hospitalized in an acute care hospital in the year prior to the MRSA isolation, 238 (63%) were admitted from LTC facilities, and 261 (70%) had received antibiotics in the 6 months prior to the index hospitalization. Only 12 had no previous connection to the health care system

Table 1. Characteristics of patients with MRSA isolates from screening (N=375)

Variable	Types I-III N=183 (%)	Type IV N=97 (%)	Type V N=95 (%)	I-III vs. IV *P* value	I-III vs. V *P* value	IV vs. V *P* value
Age (years)	78.7 ± 13	79.9 ± 157	77 ± 15	0.5	0.32	0.18
Female	83 (45%)	48 (49%)	34 (39%)	0.51	0.12	0.055
Arab ethnicity	14 (8%)	2 (2%)	13 (14%)	0.06	0.12	0.003
Nursing home	120 (66%)	68 (70%)	50 (53%)	0.44	0.04	0.013
Chronic illness	82 (45%)	41 (42%)	49 (52%)	0.68	0.28	0.20
Previous hospitalization	150 (82%)	72 (74%)	88 (93%)	0.13	0.02	0.001
Ambulatory care	97 (53%)	44 (45%)	52 (55%)	0.22	0.78	0.19
Bladder catheterization	67 (37%)	32 (33%)	38 (40%)	0.55	0.58	0.31
Invasive procedure	90 (49%)	38 (39%)	54 (57%)	0.11	0.22	0.01
Previous MRSA	30 (16%)	15 (15%)	15 (16%)	0.84	0.90	0.95
Community onset	170 (93%)	95 (98%)	86 (90%)	0.07	0.49	0.03
Length of stay	7.6 13	6.6 15	10.4	0.50	0.046	0.02
Death	40 (35%)	21 (34%)	24 (49%)	0.96	0.09	0.12
Previous antibiotics	134 (73%)	56 (58%)	71 (75%)	0.03	0.59	0.03
Beta-lactams	122 (67%)	51 (53%)	64 (67%)	0.046	0.91	0.04
Aminoglycosides	18 (10%)	6 (6%)	14 (15%)	0.30	0.22	0.052
Quinolones	34 (19%)	11 (11%)	29 (30%)	0.22	0.02	0.001
Metronidazole	17 (9%)	3 (3%)	9 (9%)	0.08	0.96	0.08
Macrolides	34 (17%)	10 (10%)	13 (14%)	0.07	0.30	0.47
Sensitivity to all but oxacillin	19 (10%)	66 (68%)	43 (45%)	‹ 0.001	‹ 0.001	0.001
Resistance to clindamycin/ erythromycin	155 (85%)	18 (19%)	40 (42%)	‹ 0.001	‹ 0.001	‹ 0.001
Resistance to rifampicin	3 (2%)	0	2 (2%)	0.55	1.0	0.24
Resistance to TMP/SMX	7 (4%)	7 (7%)	1 (1%)	0.21	0.27	0.06
Resistance to fusidic acid	0	1 (1%)	1 (1%)	0.35	0.35	1.0

MRSA = methicilin-resistant *Staphylococcus aureus*, TMP/SMS = trimethoprim/sulfamethoxazole

or known MRSA carriage. MRSA carriage was first discovered during the index hospitalization in 315 patients (84%), while the other 60 (16%) had a history of MRSA carriage extending up to 7 years prior to the index hospitalization. Patient characteristics and comparisons between the different groups are summarized in Table 1. Of all cases, 85 patients (23%) died within 30 days of culture.

• SCC*mec* TYPE IV VS. TYPE V (N=192)

We compared the 97 patients with SCC*mec* type IV to the 95 patients with SCC*mec* type V. The groups had a similar average age but differed in gender: SCC*mec* V group had more males (61% vs. 51%, $P = 0.055$) and more patients with Arab ethnicity (14% vs. 2%, $P = 0.003$), but fewer patients who were LTC residents (53% vs. 70%, $P = 0.013$).

Patients with SCC*mec* IV had fewer previous hospitalizations, less antibiotic treatment, and fewer invasive procedures, as well as fewer comorbid conditions and shorter length of stay compared to SCC*mec* V patients [Table 1].

After including these variables in a multivariate logistic regression model, the variables that remained in the model as independent statistically significant predictors of SCC*mec* V vs. IV were Arab ethnicity [odds ratio (OR) 7.44, 95% confidence interval (CI) 1.5–37.9] and hospitalization in the year prior to study inclusion (OR 5.7, 95%CI 1.9–16.9).

Based on these results, we felt these two groups differed from each other and that combining them for further analysis was inappropriate. Thus, we conducted separate comparisons between each of these SCC*mec* types and the combined group of SCC*mec* types I-III.

• SCC*mec* TYPE IV VS. TYPES I-III

We compared the 97 patients with SCC*mec* type IV to the 183 patients with SCC*mec* I-III. The two groups varied in several characteristics: the SCC*mec* IV group had fewer patients of Arabic ethnicity, were treated less often with antibiotics, and fewer had contracted MRSA in the hospital. None of these three variables remained significant after inclusion in a multivariate logistic regression model.

• SCC*mec* TYPE V VS. TYPES I-III

We compared the 95 patients with SCC*mec* type V to the 183 patients with SCC*mec* I-III. More patients with SCC*mec* V were admitted from home, were hospitalized in the previous year, and had received quinolones. None of these three variables remained significant after inclusion in a multivariate logistic regression model.

PATIENTS WITH MRSA FROM CLINICAL SITES [TABLE 2]

MRSA was isolated from a clinical site in 126 of the 501 study patients (25%): 71 were SCC*mec* types I-III, 29 type IV, and 26 type V. The median age was 76 years (range 23–98), and 61 (48%) were males. The majority of patients had been hospitalized in the previous year (83%) and had contact with ambulatory health care (56%). Seventy-six patients (60%) had a skin infection, but only 2 had a skin or soft tissue abscess. Other sources included respiratory specimens in 21%, blood culture in 9% and urine culture in 9%. Forty-three patients (34%) were previously known MRSA carriers. Of note, 122 of the126 patients with MRSA from a clinical site had classic risk factors for MRSA: a past hospital stay, LTC residence, or known history of MRSA carriage. The overall 30 day case-fatality rate among patients with MRSA infections was 30% [Table 2].

We compared patients identified through clinical sampling to be carrying SCC*mec* types IV and V. Community onset of infection was more common in patients carrying SCC*mec* type IV. Compared to patients in the SCC*mec* I-III MRSA group, patients carrying SCC*mec* type IV had fewer comorbidities, fewer invasive devices, and received beta-lactams prior to their hospitalization less often. After including these variables in a multivariate logistic regression model, the only one remain-

ing statistically significant was fewer comorbid conditions (OR 0.32, 95%CI 0.176–0.823).

Patients carrying SCC*mec* type V identified through clinical sampling were similar to the SCC*mec* I-III MRSA group [Table 2] in all parameters except invasive devices ($P = 0.01$).

ANTIBIOTIC SUSCEPTIBILITIES AND THE PVL TEST

We examined susceptibility patterns in the different SCC*mec* groups. MRSA susceptibility to all non beta-lactam antibiotics tested [Table 1] was found in 10% of SCC*mec* I-III isolates, 68% of SCC*mec* IV isolates, and 45% of SCCmec V isolates ($P < 0.001$ for all comparisons). Important statistically significant differences were found in the percentage of resistance to clindamycin and erythromycin among the groups. While 85% of SCC*mec* I-III were resistant to these two agents, 19% of type IV isolates and 42% of SCC*mec* type V isolates were resistant ($P < 0.001$ for all comparisons). SCC*mec* IV and V MRSA from clinical isolates were slightly more resistant than SCC*mec* IV and V from screening cultures. All study isolates were PVL negative, except for a single SCC*mec* type IV isolate.

DISCUSSION

This study compared the demographic and clinical characteristics of hospitalized patients carrying isolates of five SCC*mec* types. Initially, we compared patients carrying SCC*mec* type IV to those carrying SCC*mec* type V identified through screening and found that patients differed in ethnicity and in the percentage recently hospitalized. These differences have not been detected before and suggest a divergent epidemiology of these two SCC*mec* types, which are often grouped together and referred to as having a similar "community type" epidemiology. Our results demonstrate that SCC*mec* V is more common among Arab Israelis than among Jewish Israelis. In the study region, the two populations reside in separate towns and cities. Thus, either genetic differences or segregation by dwelling location could explain the higher prevalence of SCC*mec* V among Arab Israelis in our study population. No specific town was traced as a possible hub of SCC*mec* V. Although both SCC*mec* IV and V have been described as mainly of community origin, based on the proportion of health care exposures it seems that most patients acquired these strains at health care facilities: type V mostly in hospitals and type IV in LTC facilities.

Given the clinical and demographic differences observed between patients with SCC*mec* type IV and V, we felt that in our population it was inappropriate to combine the two groups, as was done in other studies [4]. When we compared patients carrying SCC*mec* type IV or V with patients carrying types I-III, we were surprised that only a few differences were found, mainly that patients with SCC*mec* types IV and V resembled the classical patients with hospital-acquired MRSA (HA-MRSA). Our institution conducts active MRSA screening focused on patients with health care exposure. This selection might have biased the results and, therefore, we might have missed some differences among the subtypes. A subgroup analysis of the patients who had clinical cultures yielded similar results. The majority was elderly, either in LTC or with previous hospitalizations. Few patients had no connection to the health care system as defined by the study protocol.

In the United States, CA-MRSA strains, particularly USA-300 strains with SCC*mec* IV, have been reported as the major MRSA strains in hospitalized patients [13,14]. Popovich et al. [14] reported that from 2003 to 2006, 49% of their hospital-onset MRSA bloodstream infections were due to CA-MRSA strains. Risk factors and patient characteristics were similar to those in patients with HA-MRSA strains, but the significant difference is that the American experience was part of a pro-

Table 2. Characteristics of patients with MRSA from clinical isolates (N=126)

Variable	Types I-III N=79 (%)	Type IV N=21 (%)	Type V N=26 (%)	I-III vs. IV *P* value	I-III vs. V *P* value	IV vs. V *P* value
Age (years)	72.9 ± 15	71.1 ± 21	72.1 ± 15	0.64	0.83	0.84
Female	37 (52%)	17 (57%)	11 (42%)	0.55	0.39	0.23
Arab ethnicity	9 (13%)	2 (7%)	6 (23%)	0.63	0.16	
Nursing home	35 (49%)	15 (52%)	11 (42%)	0.27	0.54	0.485
Chronic illness	54 (76%)	14 (48%)	19 (73%)	0.007	0.76	0.06
Previous hospitalization	63 (89%)	22 (76%)	19 (73%)	0.10	0.06	0.81
Ambulatory care	38 (53%)	15(52%)	18 (69%)	0.87	0.16	0.186
Skin infection	49 (57%)	24 (72.7%)	17 (56.7%)	0.11	0.23	0.57
Length of hospitalization	22.7 ± 28	12 ± 15	23 ± 41	0.06	0.95	0.19
Cx: days since admission	6.1 ± 9	4.6 ± 10	11.1 ± 16	0.47	0.06	0.07
Bladder catheterization	45 (63%)	12 (41%)	9 (35%)	0.04	0.01	0.61
Invasive procedure	39 (55%)	17 (59%)	16 (61%)	0.74	0.56	0.82
Previous MRSA	27 (38%)	9 (31%)	7 (27%)	0.50	0.31	0.74
Source skin	38 (53%)	21 (72%)	17 (65%)	0.08	0.30	0.57
Community onset	45 (63%)	24 (83%)	15 (58%)	0.06	0.60	0.04
Death	19 (47%)	14 (56%)	5 (28%)	0.50	0.16	0.07
Previous antibiotics Beta-lactams Aminoglycosides Quinolones Metronidazole Macrolides	54 (76%) 52 (73%) 5 (7%) 24 (34%) 11 (15%) 6 (8.5%)	19 (65%) 17 (58%) 3 (10%) 5 (17%) 3 (10%) 3 (9.1%)	21 (81%) 21 (81%) 4 (15%) 8 (31%) 5 (19%) 0	0.40 0.04 0.69 0.10 0.17 0.76	0.77 0.45 0.24 0.78 0.66 0.19	0.20 0.08 0.69 0.24 0.09 0.24
Sensitivity to all but oxacillin	7 (10%)	15 (52%)	6 (23%)	‹ 0.001	0.09	0.03
Resistance to clindamycin/ erythromycin	62 (87%)	11 (38%)	14 (54%)	‹ 0.001	‹ 0.001	0.24
Resistance to rifampicin	1 (1%)	0	0			
Resistance to TMP/SMX	3 (4%)	3 (10%)	1 (4%)	0.35	1.0	0.61
Resistance to fusidic acid	1 (1%)	1 (3%)	1 (4%)	0.50	0.47	1

cx = MRSA culture

cess. The first reports of MRSA SCC*mec* type IV came from patients in the community with a distinct demographic and clinical picture [1]. Later, the prevalence of those community cases increased dramatically in the community and in patients admitted to hospitals [15-17]. Only later were there reports of MRSA SCC*mec* type IV acquired in the hospital by patients with risk factors similar to those of classical HA-MRSA. Moreover, this replacement was gradual. The quick dispersal of CA-MRSA in the community, its (CA-MRSA) invasion into hospitals, and the replacement of classical HA-MRSA by CA-MRSA types were expected due to their faster growth patterns, as described by Okuma et al. [18]. D'Agatha et al. [19] modeled the invasion of CA-MRSA into the hospital environment and predicted the replacement of HA-MRSA by CA-MRSA based on its tendency to grow faster and on its heightened severity.

A possible explanation for our results could have been an unnoticed epidemic of MRSA in the community. This is implausible because two studies assessed the prevalence of MRSA in the community, focusing specifically on CA-MRSA types IV and V, and found MRSA carriage by healthy children and adults to be rare: 0.6% (5 of 831) in healthy children in the study by Schlesinger et al. [20] and 0.15% (5 of 3373) in healthy children and their parents in the study by Regev-Yochay and co-authors [21]. One exception was the finding of a higher carriage rate in the Bedouin pediatric population of southern Israel, where 2.4–4.4% of infants were found to be colonized in the first year of life, mostly by SCC*mec* IV MRSA. The Bedouin population is a semi-closed minority suffering from poverty, overcrowding and a high hospitalization rate. The Jewish pediatric population in the same area had a low MRSA carriage rate similar to the rest of the country (0–0.6%) [22].

It seems the MRSA SCC*mec* types IV and V arrived directly to acute and to LTC facilities and replaced the classical MRSA types in patients hospitalized in those facilities. As shown in our results, SCC*mec* type IV was more common in patients admitted from LTC facilities than in those admitted from home and was more common in patients from LTC facilities than was SCC*mec* types I-III. A report from Finland described an outbreak in a LTC facility, exemplifying its fast dispersal in a closed community [23].

It is likely that in Israel SCC*mec* types IV and V are HA-MRSA clones. A similar epidemiology can be found in parts of Europe. E-MRSA 15, which belongs to ST22, an SCC*mec* IV MRSA, has dominated colonization and infections in British hospitals since the 1990s, but was rarely found in the community (0.78% in older adults living in their home) [24] or in admissions of children with no risk factors [25].

LIMITATIONS

This study has several limitations. It was conducted in a single hospital and, therefore, the results might not represent the rest of the country. Of note, two other studies from Israel showed similar SCC*mec* type distributions among patients hospitalized in several hospitals located throughout Israel. The majority of isolates came from active screening of a high risk population, but, as mentioned, we repeated the analyses on patients with clinical isolates, and although the numbers were smaller the results were qualitatively similar.

CONCLUSIONS

SCC*mec* types IV and V are common in the hospital setting, although rare in the community. The differences found between patients carrying SCC*mec* IV and V was greater than between each of them and the classical HA-MRSA SCC*mec* types. It seems that in Israel, SCCmec IV and V are both part of health care-associated MRSA.

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