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Epidemiology of Methicillin-resistant and Methicillin-sensitive *Staphylococcus aureus* infections in Lebanon

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Abstract

Background. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a prevalent pathogen associated with significant morbidity and mortality. In Lebanon, MRSA rates have recently started to rise. We aimed to determine risk factors for acquiring MRSA and Methicillin-sensitive *Staphylococcus aureus* (MSSA) infections and identify independent risk factors for in-hospital mortality among patients with S. aureus infection. **Methods**. We used a case-case-control study design that included patients with infections and compared them to uninfected controls. Two multivariable regression models were constructed to determine variables associated with acquiring MRSA and MSSA infections. We explored independent predictors of mortality in the overall population compared with the MRSA subgroup. **Results**. 356 patients with S. *aureus* infections were identified and compared to 208 uninfected controls. A recent history of surgery and underlying diabetes were independent risk factors for acquiring both infections. Having a urinary catheter for more than 6 days and steroid therapy were unique risk factors for MRSA infection (aOR 28.1, 95% CI 3.5-223.6 and 3.7, 95% CI 1.6-8.7, respectively). Risk factors exclusively associated with MRSA infection included ICU admission, acute renal failure, and malignancy. **Conclusions**. Risk factors associated with MRSA infection are distinct from those associated with MSSA infection. This can be used to risk stratify patients and will aid in choosing empirical antibiotic therapy.

Key word: staphylococcus aureus, methicillin-resistance, antimicrobial-resistant.

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Introduction

Infections caused by *Staphylococcus aureus* are both common and costly. The average medical cost of S. aureus bacteremia was $12,078, and it was found that patients with MRSA had 1.32 times higher than the average costs of MSSA (1). Healthcare-associated methicillin-resistant S. *aureus* (HA-MRSA) represents significant mortality, morbidity, and economic burden on healthcare resources compared to methicillin-sensitive S. *aureus* (MSSA). In the United States (US), S. *aureus* was found to be the number one cause of nosocomial infection, of which a high percentage of isolates were methicillin-resistant (2).

MRSA is the causative pathogen of serious invasive infections both in the hospital and community settings (2). MRSA infection is commonly associated with multiple risk factors: prolonged hospitalization, smoking (3), recent hospitalization, intensive care admission, recent antibiotic use, invasive procedures, HIV infection, admission to nursing homes, open wounds, hemodialysis, discharge with long-term central venous access or long-term indwelling urinary catheter(4). Antibiotic use, particularly of cephalosporins (3) and fluoroquinolones (4), is known to increase the risk of MRSA infection and colonization (3). Furthermore, advancing age (>65 years) was indirectly considered a risk factor for the acquisition of MRSA(4). Another risk factor was living in a highly prevalent MRSA area or being admitted to a highly prevalent MRSA hospital (4). Nevertheless, it was found that previous MRSA colonization was the strongest risk factor for current MRSA infection (7).

The prevalence of MRSA in the Arab world is variable. In a recent review, the estimates reported in various studies ranged from 12% to as high as 60% (8). In Lebanon, a study based on retrospective nationwide compiled data found an MRSA prevalence of 27.6% (9). Due to the significant burden of this public health threat, we aim to determine the epidemiology, risk factors, and outcomes of infections due to MRSA compared to those caused by methicillin-sensitive

isolates (MSSA) among hospitalized patients at a tertiary care center in Lebanon.

Materials and methods

Study population and site

The American University of Beirut Medical Center (AUBMC) is a 420-bed hospital that provides tertiary medical care to patients from all over Lebanon and the region. All adult patients with a documented culture of *S. aureus* and who had been hospitalized for more than 48 hours were included in the study. Patients who were deemed to be colonized with *S. aureus* were excluded.

Study design

We used a retrospective case-case-control study design. A retrospective review of the medical records of patients admitted to AUBMC between 2015 and 2018 was performed. Potential subjects were identified through the microbiology laboratory database and the hospital admission records. The first group of cases consisted of patients with MRSA infections, while the second group of cases included those with MSSA infections. The control group consisted of patients admitted during the same period as the cases but who did not develop any infection during their hospital stay. Each patient was included in the study once, taking into consideration the first instance at which S. aureus was isolated during the period of the study.

Statistical analysis

Data were entered into a database using SPSS for Windows (SPSS Inc, Chicago, IL). Bivariable analysis was performed to detect statistical associations using the Chi-square test for categorical variables and the independent samples t-test for continuous variables. Backward stepwise multivariate logistic regression was performed to test for independent associations controlling for potential confounders. The logistic model included all variables for which a p-value of 0.15 or less was obtained in the bivariate analysis. This case-case-control study aimed to identify risk factors associated specifically with MRSA infection. Two different regression models were conducted. In the first, risk factors for MRSA infection were determined by comparing the first group of cases (patients with MRSA infections) to uninfected controls. The second group of cases (patients with MSSA infections) was compared to uninfected controls in the second analysis. By comparing and contrasting these two models, variables uniquely associated with MRSA infections were determined.

Ethical considerations

The Institutional Review Board approved the study at the American University of Beirut. Since this was a retrospective analysis, informed consent was waived.

Results

Patient characteristics

A total of 564 patients were included in the study, of which 151 had an MRSA infection. These were matched to 205 patients with MSSA infection and 208 uninfected controls. Table 1 shows the baseline characteristics of patients with MRSA and MSSA infections compared to uninfected controls. The most common site of infection was skin and skin structures in both the MRSA and MSSA groups (58.3% and 53.2%, respectively). Bloodstream infections accounted for around 8% of MRSA and MSSA infections. Of the MRSA infections, 49 (32.5%) were hospital-acquired, 37 were healthcare-associated (24.5%), and 65 (43.0%) were community-acquired. Most community-acquired infections were skin and soft tissue infections (70.8%), and only one patient had a community acquired-MRSA bacteremia. Previous exposure to antibiotics within 30 days of infection was higher in patients with MRSA infection (38.7% vs. 23.4%, p-value = 0.002).

Risk factors for infection

Comorbidities associated with both MRSA and MSSA infections were diabetes mellitus and renal insufficiency. Other common risk factors were steroid therapy, surgery, hospitalization, and invasive medical devices in the last 30 days before hospital admission. The results of the two regression models are shown in Table 2. Independent risk factors for both MRSA and MSSA infections compared to uninfected controls were diabetes and surgery within 30 days of hospital admission. While the adjusted odds ratios (aOR) for diabetes were comparable in both models (2.6 for MRSA and 2.1 for MSSA), there was a differential association with recent surgery (aOR 11.5 for MRSA vs. 3.4 for MSSA), suggesting that recent surgery predisposes to MRSA infection more often than to MSSA infection. Variables uniquely associated with the isolation of MRSA were recent steroid therapy (aOR 3.7; 95% CI 1.6-8.7) and recent urinary catheter placement for more than six days (aOR 28.1; 95% CI 3.5-223.6). On the other hand, body mass index and previous hospitalization were associated with isolation of MSSA but not MRSA.

Patient outcomes

The all-cause in-hospital mortality rate was 13.8% in the overall patient population and 11.9% in the MRSA group. Table 3 shows the risk factors for mortality among all patients with *S. aureus* infection and those with MRSA infection. Independent risk factors for mortality that were unique to MRSA were the need for ICU admission (aOR 57.9), acute renal failure (aOR 19.5), and underlying malignancy (aOR 9.0).

Table 1

Baseline characteristics of patients with MRSA and MSSA infections

Variable	Uninfected controls (n = 208)	MRSA (n = 151)	p-value (MRSA vs. controls)	MSSA (n = 205)	p-value (MSSA vs. controls)
Age, *years*	53.6 ± 18.8	53.7 ± 20.1	0.93	55.7 ± 20.6	0.28
Male sex	119 (57.2)	81 (53.6)	0.52	111 (54.1)	0.53
BMI, kg/m^2	28.6 ± 6.3	28.4 ± 7.1	0.81	27.2 ± 5.4	0.027
Diabetes	42 (20.2)	55 (36.4)	< 0.001	69 (33.7)	0.002
Renal insufficiency	12 (5.8)	25 (16.6)	< 0.001	27 (13.2)	0.01
Chronic pulmonary disease	26 (12.5)	15 (9.9)	0.45	13 (6.3)	0.03
Malignancy	46 (22.1)	44 (29.1)	0.13	45 (21.9)	0.97
Steroid therapy*	10 (4.8)	27 (17.9)	< 0.001	27 (13.2)	0.003
Surgery*	5 (2.4)	38 (25.2)	< 0.001	30 (14.6)	< 0.001
Hospitalization*			< 0.001		< 0.001
0-2 days	192 (92.3)	91 (60.3)		133 (64.9)	
3-5 days	12 (5.8)	27 (17.9)		31 (15.1)	
> 6 days	4 (1.9)	28 (18.5)		39 (19.0)	
ICU admission*			< 0.001		< 0.001
0-2 days	206 (99.0)	131 (86.7)		182 (88.8)	
3-5 days	2 (1.0)	11 (7.3)		16 (7.8)	
> 6 days	0	6 (4.0)		4 (1.9)	
Urinary catheter*			< 0.001		< 0.001
0-2 days	206 (99.0)	113 (74.8)		165 (80.5)	
3-5 days	1 (0.5)	12 (7.9)		15 (7.3)	
> 6 days	1 (0.5)	23 (15.2)		19 (9.3)	
Central venous catheter*			0.008		0.005
0-2 days	202 (97.1)	130 (86.1)		179 (87.3)	
3-5 days	2 (1.0)	4 (2.6)		11 (5.4)	
> 6 days	4 (1.9)	12 (7.9)		11 (5.4)	
Mechanical ventilation*			< 0.001		0.001
0-2 days	207 (99.5)	132 (87.4)		185 (90.2)	
3-5 days	1 (0.5)	9 (6.0)		12 (5.8)	
> 6 days	0	8 (5.3)		4 (1.9)	
Nasogastric tube*			< 0.001		0.001
0-2 days	207 (99.5)	134 (88.7)		185 (90.2)	
3-5 days	1 (0.5)	7 (4.6)		8 (3.9)	
> 6 days	0	7 (4.6)		7 (3.4)	

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; BMI = body mass index; ICU = intensive care unit.
Numbers represent no. (%) unless otherwise specified.
*****Within 30 days of hospital admission.*

Table 2

Multivariable analysis of risk factors for MRSA and MSSA infections

	MRSA vs. controls		MSSA vs. controls	
Variable	p-value	aOR† (95% CI)	p-value	aOR† (95% CI)
Surgery*	< 0.001	11.5 (3.7-35.5)	0.04	3.4 (1.1-11.3)
Diabetes	0.001	2.6 (1.5-4.4)	0.012	2.1 (1.2-3.6)
Urinary catheter* for > 6 days	0.02	28.1 (3.5-223.6)	NS	¾
Steroid therapy*	0.003	3.7 (1.6-8.7)	NS	¾
Hospitalization* for > 6 days	NS	¾	0.001	7.2 (2.3-22.3)
Hospitalization* for 3-5 days	NS	¾	0.016	2.9 (1.2-6.7)
BMI	NS	¾	0.028	0.95 (0.9-0.99)

MRSA = methicillin-resistant S. aureus; MSSA = methicillin-sensitive S. aureus; aOR = adjusted odds ratio; CI = confidence interval; BMI = body mass index; NS = not statistically significant.
†Adjusted for all variables with p-value < 0.2 on univariable analysis.
*Within 30 days of hospital admission.

Table 3

Multivariable analysis of predictors of mortality among all patients with S. aureus infection and patients with MRSA infection

	All *S. aureus*		MRSA	
Variable	aOR†	95% CI	aOR†	95% CI
MV at beginthe ning of infection	9.9	3.2-30.7	9.4	1.4-102.5
Cardiovascular event*	5.8	1.4-24.4	8.3	1.1-63.6
Need for MV*	37.1	3.8-358.8	¾	¾
Septic shock*	15.6	4.0-61.0	¾	¾
Hospital-acquired infection*	3.4	1.2-9.4	¾	¾
Charlson score	1.4	1.1-4.2	¾	¾
Need for ICU admission*	¾	¾	57.9	6.0-539.3
Acute renal failure*	¾	¾	19.5	2.1-179.1
Malignancy	¾	¾	9	1.7-13.3

MRSA = methicillin-resistant *S. aureus*; aOR = adjusted odds ratio; CI = confidence interval; MV = mechanical ventilation; ICU = intensive care unit.

†Adjusted for all variables with p-value < 0.2 on univariable analysis.

Empty cells indicate variables that were removed from the final regression model.

*Event occurring as a complication of the infection.

Discussion

This study provides an overview of clinical risk factors for MRSA and MSSA infections, along with independent predictors of mortality among S. *aureus* infections and MRSA infections in particular. We showed that diabetes mellitus and previous surgery within 30 days of infection are independent risk factors associated with MRSA and MSSA infection, which is consistent with published data (10). Diabetes is a well-known risk factor for *S. aureus* infections, particularly MRSA (11). Interestingly, a recent study has shown that 30-day mortality is lower among diabetic patients with MRSA bloodstream infection compared to non-diabetic patients (12). In our population, diabetes was neither protective against nor predictive of in-hospital mortality.

We found that placement of a urinary catheter for more than six days and recent steroid therapy are independently associated with MRSA but not MSSA infection. MRSA is an increasingly recognized cause of catheter-associated urinary tract infections (13). Evidence suggests that the presence of the urinary catheter alters bladder ecology and favors colonization and later infection with MRSA. This is, however, a modifiable risk factor, and efforts should always be geared toward decreasing the duration of catheterization in hospitalized patients. The relationship between MRSA infection and steroid therapy is established in the literature, especially among patients who are nasally colonized with MRSA (14). Given the retrospective nature of our study, it is not possible to determine the proportion of nasal colonization among our patient population.

We found several predictors for in-hospital mortality in our patient population, some of which are baseline variables while others are complications emanating from the staphylococcal infection itself. Most of the risk factors we found to be associated with in-hospital mortality are consistent with the existing literature, such as the development of septic shock (15), ICU admission (16), and renal failure (17). While these are classical and predictable factors determining survival, we also found that an underlying malignancy is associated with a considerable risk for death exclusively in the setting of MRSA infection. In our cohort, around 61% of the patients with MRSA who died had an underlying malignancy. In a retrospective study conducted on 1,168 patients over nine years, malignancy was shown to be a predictor of 30-day mortality, with lymphomas being the most commonly implicated type of malignancy (13). Another study from Japan showed similar findings (18). Malignancy is a significant mortality factor where a patient with malignancy and MRSA BSI have high mortality of 35.87% (19).

A meta-analysis focusing on vancomycin treatment failure based on MIC showed no statistically significant difference in mortality in patients with MRSA bacteremia treated with vancomycin based on different MIC values indicating that MIC may not be an optimal guide of vancomycin treatment (20).

This study has several limitations, the most important of which is the retrospective data collection. In addition, our population is limited to hospitalized patients, which is expected to skew the data toward a more severe form of illness.

Conclusions

In conclusion, unique and often modifiable risk factors are associated exclusively with MRSA infection compared to MSSA infections. These can be used in the risk assessment of patients suspected of having a staphylococcal infection to guide empiric antibiotic therapy in a country like Lebanon, where the incidence of MRSA is rising but is still not overwhelmingly high. It is worth noting that the study data is prior to the COVID-19 pandemic, during which time the massive use of antibiotics probably modified bacterial resistance profiles. Therefore, further studies are needed post-pandemic to highlight the changes the pandemic has

brought.

Authors' contributions

The authors confirm their contribution to the paper as follows: study conception and design: **Zeina Kanafani**; data collection: **Farah Abou Zeid, Sara Mourani, Jamil Kazma, Amal El Gharamti, Mohamad Yasmin, Salma Jabak, Tania Baban, Nisreen Sidani**; analysis and interpretation of results: **Zeina Kanafani**; draft manuscript preparation: J**amil Kazma, and Amal El Gharamti**. All authors reviewed the results and approved the final version of the manuscript. All authors agreed to be responsible for all aspects of the work to ensure the accuracy and integrity of the published manuscript.

Ethics approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of the American University of Beirut approved this study.

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

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Availability of data

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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