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Comparison of Outcomes of Community and Hospital-Acquired Methicillin- Susceptible and Methicillin-Resistant *Staphylococcus Aureus* Infections

Research Article

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Abstract

Introduction: *Staphylococcus Aureus (S. aureus)* causes community (CA) and hospital-acquired (HA) infections that kills millions of patients every year. It is unclear if Methicillin-resistant *Staphylococcus Aureus* (MRSA) have higher mortality and complication than Methicillin -susceptible *Staphylococcus Aureus* (MSSA) infections in CA and HA infections.

Methods: This retrospective study included confirmed of cases S. aureus infections, which classified as MSSA or MRSA and CA or HA infections We assessed 30-day mortality, rate of Septic Shock and Acute Renal Injury (AKI) as outcomes measures.

Results: Of the total 183 cases included, we found no differences between MRSA and MSSA cases in mortality (P=0.734) and other outcomes. Likewise, CA and HA cases Similar mortality. However, HA cases developed a higher rate of AKI compared to CA cases. We observed this increased rate of AKI only in HA MSSA cases.

Conclusion: This study offers a new perspective on HA MSSA as a serious pathogen as MRSA, that requires intervention to prevent its spread. Future research needed to identify new measures for MSSA prevention and investigate whether current MRSA prevention strategies are effective in MSSA.

Keywords: Methicillin-resistant; MRSA; MSSA; Saudi Arabia; *Staphylococcus aureus*

Introduction

Staphylococcus Aureus (*S. aureus*) is the commonest bacteria that causes infection inside and outside the hospitals. It is accountable for millions of deaths every year worldwide [1]. Treatment of *S. aureus* became more difficult and expensive due to the increasing rate of methicillin-resistant strains, which are now responsible for many hospital and community-acquired infections [2,3].

Studies have suggested that methicillin resistance and the location of acquiring *S. aureus* infection are the main determinants of its outcome. Still, it is controversial whether Methicillin-resistant *Staphylococcus Aureus* (MRSA) causes a worse outcome compared to Methicillin-susceptible *Staphylococcus Aureus* (MSSA) infections [4-7]. Another area of debate, whether hospital-acquired *S. aureus* (HA-*S. aureus*) has a worse outcome than community-acquired *S. aureus* (CA- *S. aureus*) infections [8-10]. Taken together, it remains an open question whether the setting of acquiring *S. aureus* infection and methicillin susceptibility are the main determinants of its outcomes.

In this study, we explored the outcomes of *S. aureus* infection and we adjusted for patients' comorbidities. The research question of the present article is whether hospital-acquired MSSA infection causes more morbidity and mortality than community-acquired MSSA infections. We also compared the mortality of HA-MRSA to CA-MRSA infections and MRSA to MSSA infections.

Methods and Materials

Subjects

We conducted this retrospective observational study between January 2017 and February 2018, in National Guard Hospital in Al-Madinah in Saudi Arabia. We included 15 years and older patients, who had a documented diagnosis of *S. aureus* infection in the electronic medical records during the study period. The diagnosis of *S. aureus* infection was verified by the existence of a positive culture of *S. aureus* from the infected site and documented signs and symptoms of infection. Institutional review board approved the study.

Microbiologic methods

S. aureus cultures were processed by BAC T/ALERT, version eight (BioMerieux). Antimicrobial susceptibility testing was performed by Broth micro-dilution method using VITEK 2, version eight (BioMerieux). *S. aureus* susceptibility breakpoints defined according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints [11].

Definitions and criteria

We classified infections as community-acquired *S. aureus* infections if the infection acquired in the community and within the last 3 months there were no history of hospitalization, surgery, residence in a long-term care facility, dialysis, presence of invasive medical devices or previous isolation of *S. aureus* [12]. Otherwise, the infections were classified as hospital-acquired. Outcome measures assessed were thirty-day all-cause mortality, duration of Intensive Care Unit (ICU) stay, rate of septic shock and rate of Acute Renal Injury (AKI).

The severity of *S. aureus* infection measured using the Sequential Organ Failure Assessment (SOFA) score and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II score). We used Charlson's comorbidity index to measure concurrent comorbidities [13].

Data analysis

Mean, the median, and the Standard Deviation (SD) calculated for continuous variables. We calculated proportions for categorical variables. Chi square, Fisher exact test and Logistic regression were used to compare categorical variables. Student t-test was used to compare continues normally distributed data and Wilcoxon Rank-Sum used to compare non-parametric variables. Multivariable logistic regression analysis was used to estimate the effect of risk factors on primary outcomes, to control for confounding and to assess for interaction. All P-values were two-tailed, and values of ≤0.05 were considered statistically significant. Analysis was performed using STATA version 13 (STATA cooperation, Texas, USA).

Results

MRSA compared to MSSA infections

This study reviewed 183 patients with invasive *S. aureus* infections from January 2017 to February 2018. First, we compared the outcome of MRSA with MSSA infections using Chi square and Fisher exact test (Table 1). The median age was 45 years, and the cases were predominately males (58%). Skin and soft tissue were the main infection sites (71.58%). Of all cases, 18 (9.84%) developed septic shock and 9 (4.92%) died. Of all *S. aureus* isolates, MRSA was recovered in 84 (45.9%) cases. There were no significant differences between MRSA and MSSA infections regarding bacteremia (P=0.686), days of ICU stay (P=0.422), septic shock (P=0.999) and 30-day mortality (P=0.734).

Table 1: Baseline characteristics of patients with invasive *Staphylococcus Aureus* infections (January 2017- February 2018).

Characteristics	Total	MRSA	MSSA	P-value
	n/(N %)	n/(N %)	n/(N %)	
	183(100%)	84(45.90)	99(54.10)	
Age (Year)				
Mean (SD)	43(28)	44(28)	42(29)	0.448
Median (IQR)	45(17-68)	43(25-68)	47(9-66)	
Male	107(58.47)	48(57.14)	59(59.60)	0.765
Bacteremia	29(15.85)	12(14.29)	17(17.17)	0.686
Thirty-day mortality	9(4.92)	5(5.95)	4(4.04)	0.734
Site of the Infection				
Pneumonia	19(10.38)	10(11.90)	9(9.09)	0.629
Soft tissue infection	131(71.58)	57(67.86)	74(56.49)	0.327
Bone and joint infections	14(7.65)	8(9.52)	6(6.06)	0.415
Endocarditis	2(1.09)	2(2.38)	0(0.00)	0.209
Community- acquired	127(69.40)	55(65.48)	72(72.73)	0.335
Days of ICU stay (mean)	4.94(37)	7(53)	3(13)	0.422
Severity of Sepsis				
Sepsis	75(40.98)	35(41.67)	40(40.40)	0.881
Severe sepsis	15(8.20)	5(5.95)	10(10.10)	0.42
Septic shock	18(9.84)	8(9.52)	10(10.10)	1
Sofa score (mean)	3.85(1.64)	3.66(1.6)	4(1.66)	0.174
Sofa score (median)	3(3-4)	3(3-4)	3(3-4)	-
Acute renal failure	25(13.66)	9(10.71)	16(16.16)	0.388

Apache II Score				
Mean	8.2(7.7)	7.0(6.8)	9.3(8.3)	0.051
Median	6(3-12)	5(2-11)	7(4-14)	-
Charlson Comorbidity Index				
Mean	1.71(2.7)	1.5(2.7)	1.86(2.8)	0.437
Median	0(0-3)	0(0-2)	0(0-3)	-

MSSA: Methicillin-Susceptible Staphylococcus Aureus; MRSA: Methicillin-Resistant Staphylococcus Aureus; SOFA: Sequential (sepsis-related) Organ Failure Assessment; APACHE II score: Acute Physiologic Assessment and Chronic Health Evaluation; ICU: Intensive Care Unit; P value significant if <0.05

Hospital-acquired compared community S. aureus infections

Second, we compared the outcome of *S. aureus* hospital-acquired infection (HA *S. aureus*) with *S. aureus* community (CA *S. aureus*) infections. Of the total cases 56 (30%) were classified as HA *S. aureus* (Table 2). Of the those 29 (51.79%) cases were HA-MRSA. of the total CA *S. aureus* 55(43.31) were MRSA. In crude analysis, HA *S. aureus* infections had a higher rate of septic shock [odd ratio (OR) 4.19, 95% confidence interval (CI) ([1.529-11.48]; p<0.005)] ,AKI (OR 5.24 ,95% CI [2.15-12.79]; p<0.001) and higher 30-day mortality (OR 4.96 ,CI 95% [1.19-20.61]; p< 0.028) compared to CA *S. aureus* cases .In multivariable logistic regression analysis, we included the above significant variables and adjusted for chronic comorbidities and severity of illness .The only variable remained significant was AKI (adjusted OR 5.47 CI 95% [1.51-19.90]; p < 0.010) .This model also fitted with and without controlling for DM, and the above result remains unchanged.

In subgroup analysis we compared HA-MSSA and CA-MSSA to investigate further the above finding of a higher rate of acute renal failure in HA *S. aureus* compared to CA *S. aureus* infections. Of the total MSSA infections, 27 (27.27%) cases were hospital acquired (Table 3). In the unadjusted analysis, factors that significantly associated with HA-MSSA compared to CA-MSSA were the ICU days (OR 1.21,95% CI [1.02-1.43]; P<0.033) septic shock (OR 8.05 ,95%CI [1.91-34.012]; P<0.005) AKI (OR 9.21 ,95%CI [2.80-30.27]; P<0.001). In adjusted logistic regression we included the above significant variables, and we adjusted for chronic comorbidities and severity of illness using Charlson comorbidity and APACHE II scores. HA-MSSA infections had higher rates of AKI (adjusted OR 13.80 [2.81-67.83]; p<0.001) compared to CA-MSSA.

In subgroup analysis of MRSA infections (Table 4). We found no significant differences between HA-MRSA and CA-MRSA regarding rates of septic shock (P<0.438), mean days of ICU stay (P<0.327) and thirty-day mortality (P<0.999).

Table 2: Demographic Characteristics of Hospital-Acquired and Community-Acquired *Staphylococcus Aureus* infections cases.

Characteristics	All	HA - *S. aureus*	CA - *S. aureus*	P-value
		56(30.6%)	127(69.39%)	
Age (mean)	43.7(28)	46(29)	42(28)	0.3216
Age (median)	45.5(17-68)	50(24-73)	44.5(16-65)	-
Male	107(58.47)	33(58.9)	74(58.27)	0.999
Site of the Infection				
Bacteremia	29(15.85)	12(21.43)	17(13.39)	0.19
Pneumonia	19(10.38)	9(16.07)	10(7.87)	0.116
Soft tissue infection	131(71.58)	35(62.50)	96(75.59)	0.078
Bone and joint infections	14(7.65)	4(7.14)	10(7.65)	1
Endocarditis	2(1.09)	1(1.79)	1(0.79)	0.52
Thirty-day mortality	9(4.92)	6(10.71)	3(2.36)	0.028
Days of ICU (mean)	4(37)	6.46(19)	4.2(43)	0.721
Sepsis	75(40.98)	24(42.86)	51(40.98)	0.747
Severe sepsis	15(8.20)	4(7.14)	11(8.66)	1
Septic shock	18(9.84)	11(19.64)	7(5.51)	0.005
Sofa Score				
Mean	3.84(1.6)	4.08(2.02)	3.73(1.44)	0.5053
Median	3(3-4)	3(3-5)	3(3-4)	-
Acute Renal failure	25(13.66)	16(28.57)	9(7.09)	0.001
MRSA Isolates	84(45.90)	29(51.79)	55(43.31)	0.335
MSSA Isolates	99(54.10)	27(48.21)	72(56.69)	0.335
APACHE II Score				
Mean	8.2(7.7)	9.69(8.0)	7.67(7.5)	0.1616
Median	6(3-12)	9(2.5-16)	6(3-11)	-

Charlson Comorbidity				
DM				
Mean	1.17(2.79)	2.17(2.66)	1.50(2.83)	0.139
Median	0(0-3)	1(0-4)	0(0-2)	-

CA: Community-Acquired; HA: Hospital-Acquired; MSSA: Methicillin-Susceptible *Staphylococcus Aureus*; MRSA: Methicillin- Resistant *Staphylococcus Aureus*; SOFA: Sequential (sepsis-related) Organ Failure Assessment; APACHE II score: Acute Physiologic Assessment and Chronic Health Evaluation; ICU: Intensive Care Unit; P value significant if <0.05

Table 3: Demographic characteristics of hospital and community-acquired methicillin-sensitive *Staphylococcus Aureus* infections.

Characteristics	Total MSSA n /N(%) 99(100%)	HA- MSSA n / N(%) 27(27.27)	CA-MSSA n / N(%) 72(72.73)	P value
Age (Years)				
Mean	42(29)	43(28.66)	42(38)	0.814
Median	47(9-66)	52(15-66)	46(7-68)	-
Male	59(59.60)	15(55.56)	44(61.11)	0.651
Site of the Infection				
Bacteremia	17(17.17)	8(29.63)	9(12.50)	0.07
Pneumonia	9(9.09)	4(14.81)	5(6.94)	0.251
Soft tissue infection	74(74.75)	17(62.96)	57(79.17)	0.121
Bone and joint infection	6(6.06)	3(11.11)	3(4.17)	0.341
Thirty- days mortality	4(4.04)	2(7.41)	2(2.78)	0.299
Length of ICU (mean) days	3(13)	10(25)	0.347(1.48)	0.033
Severity of Sepsis				
Sepsis	40(40.40)	13(48.15)	27(37.50)	0.365
Severe sepsis	10(10.10)	1(3.70)	9(12.50)	0.278
Septic shock	10(10.10)	7(25.93)	3(4.17)	0.005
Charlson Comorbidity Index				
Mean	1.85(2.8)	2.51(2.56)	1.611(2.88)	0.176
Median	0(0-3)	2(0-5)	0(0-2.5)	-
Sofa Score				
Mean	4(1.66)	4.4(1.98)	3.84(1.50)	0.2913
Median	3(3-4)	4(3-6)	3(3-4)	-
Acute Renal Failure	16(16.16)	11(40.74)	5(6.94)	0.001
APACHE II Score				
Mean	9.34(8.32)	11(8)	8.7(8.39)	0.233
Median	7(4-14)	11(3-16)	6(5-12)	-

CA: Community-Acquired; HA: Hospital-Acquired; *MSSA: Methicillin-Susceptible Staphylococcus Aureus; MRSA: Methicillin- Resistant Staphylococcus Aureus*; SOFA Sequential (sepsis-related) Organ Failure Assessment

Table 4: *Hospital and community acquired methicillin- resistant Staphylococcus Aureus infections* (January 2017- February 2018).

Characteristics	All MRSA n/(N %) 84(100%)	HA-MRSA n/(N %) 29(34.52)	CA- MRSA n/(N %) 55(65.48)	P value
Age (Years)				
Mean	44(28.12)	49(29.5)	42(27.29)	0.2834
Median	43(25.5-68.5)	43(32-77)	44(17-65)	-
Male	48(57.14)	18(62.07)	30(54.55)	0.644
Bacteremia	12(14.29)	4(13.79)	8(14.55)	1
Thirty-days mortality	5(5.95)	4(13.79)	1(1.82)	0.999

Site of the Infection				
Pneumonia	10(11.90)	5(17.24)	5(9.09)	0.303
Soft tissue infection	57(67.86)	18(62.07)	39(70.91)	0.466
Bone and joint infection	8(9.52)	1(3.45)	7(3.45)	0.253
Endocarditis	2(2.38)	1(3.45)	1(1.82)	1
Days ICU(mean) days	7(53)	3(10)	9(65)	0.327
Severity of Sepsis				
Sepsis	35(41.67)	11(37.93)	24(43.64)	0.649
Severe sepsis	5(5.95)	3(10.34)	2(3.64)	0.335
Septic shock	8(9.52)	4(13.79)	4(7.27)	0.438
Acute renal failure	9(10.71)	5(17.24)	4(7.27)	0.264
APACHE II Score				
Mean	7.04(6.8)	8.44(8)	6.29(6)	0.863
Median	5(2-11)	6(2-12)	5(2-8)	-
Sofa Score				
Mean	3.66(1.6)	3.79(2.04)	3.59(1.36)	0.9255
Median	3(3-4)	3(3-5)	3(3-4)	-
Charlson Comorbidity				
Mean	1.53(2.78)	1.86(2.76)	1.36(2.80)	0.157
Median	0(0-2)	0(0-3)	0(0-2)	-

MRSA: Methicillin-resistant Staphylococcus Aureus; DM: Diabetes Mellitus; PVD: Peripheral Vascular Disease; MSSA: Methicillin-Sensitive Staphylococcus Aureus; CA: Community acquired; HA: Hospital acquired; P value significant if <0.05

Discussion

This study investigated the outcomes of community (HA) and hospital-acquired (CA) *S. aureus* infections, and it explored the impact of methicillin susceptibility on these outcomes. We found no significant difference in 30-day mortality, septic shock and length of ICU stay between MRSA and MSSA infections. Similarly, HA-MRSA and CA-MRSA developed comparable rates of septic shock, acute kidney injury (AKI) and 30-day mortality. However, cases of HA- *S. aureus* infections had more rates of AKI compared to CA- *S. aureus* cases. We observed this increased rate of AKI in HA-MSSA compared to CA-MSSA infections.

In this study, the mortality rate of *S. aureus* infection was low (4.9%) compared to the rates observed in other studies (7-50%) [14-18]. This low rate of mortality could be explained by the low rate of *S. aureus* bacteremia in this study compared to the rates in the other studies. Many studies have shown that *S. aureus* bacteremic cases have increased morality compared to non-bacteremic cases [19]. Cosgrove et al in a meta-analysis demonstrated similar mortality between MRSA and MSSA infections [5]. Those few studies showed a higher MRSA mortality rate in this meta-analysis have many confounders and they were conducted two decades ago, before the current improvement MRSA treatment [20,21].

We found a higher rate of AKI in HA-MSSA than in CA-MSSA cases. This could be attributed to the higher rates of chronic diseases in HA-MSSA than in CA-MSSA cases. However, it is less likely this the only explanation as we have adjusted for chronic diseases in our analysis. Besides, we did not observe a higher rate in AKI in HA-MRSA when compared to CA-MRSA cases. Another possible explanation for the higher AKI rates in HA-MSSA cases, HA-MSSA strains may have a direct effect on the kidneys [22,23].

Our finding of comparable mortality between HA-MRSA and CA-MRSA have been shown in many studies [24,25]. This could be due to CA- MRSA and HA- MRSA have similar virulence factors. Despite HA MRSA and CA MRSA isolates have different genes, now they are epidemiologically indistinguishable. Studies have shown CA-MRSA isolates caused nosocomial infections and HA-MRSA caused community-acquired infections [26]. In contrast, Kempker et al. showed increased risk of death in persons with CA-MRSA bacteremia due to USA300 MRSA strains compared to non-USA300 strains [27]. This study lack generalizability as it included high numbers of HIV-infected and intravenous drug users cases.

This study provides a new perspective on outcome of *S. aureus* infections and it has several implications. Our findings of MSSA and MRSA infections cause comparable outcomes. Emphasize that MSSA infections require prevention strategies similar to MRSA. The current hospital infection control interventions for MRSA such as surveillance programs, isolation precautions, and decolonization protocols may also help to interrupt MSSA transmission. Future research is need to identify HA-MSSA virulence factors, and to examine the effectiveness MRSA intervention to prevent MSSA infection.

Our study has several limitations. First, we may have underestimated the number of HA-*S. aureus* cases if its risk factors were not documented in the medical records. Yet, it is unlikely this influenced our findings, as our results are similar to the results of the studies used molecular genotyping to classify HA-*S. aureus* infections [24,26]. Second, in this study we reported all-cause mortality rather than attributable mortality, as the latter is difficult to determine. Third, we could not collect complete data on antimicrobial treatment. Therefore, we could not assess its potential association with *S. aureus* outcomes. However, we attempted to limit the effect of potential confounders by adjusting for infection severity and chronic comorbidities in our analysis.

Conclusion

In the present article, we investigated the outcome of community and hospital-acquired *S. aureus* infection. The results suggested that MRSA and MSSA have the similar clinical outcomes. Likewise, CA-MRSA and HA-MRSA have a comparable 30-day morality. However,

HA-MSSA associated with more cases of AKI compared to CA-MSSA infections. Taken together, this offers a new perspective on HA-MSSA as a serious pathogen as MRSA, that requires similar attention and intervention to prevent its spread. Future research may extend this work to identify additional measures for MSSA prevention and investigate whether current MRSA prevention strategies are also effective in MSSA prevention.

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Conflict of Interest

Author has no conflict of interest.

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