Relevance of vancomycin susceptibility on patients outcome infected with *Staphylococcus aureus*

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**Abstract**

**Background:** *Staphylococcus aureus* is a serious pathogen with high rates of complications. We aim to study the susceptibility and outcome of *S. aureus* infection.

**Methods:** A retrospective multicentre study conducted in three hospitals, Amman-Jordan. Between June 2013 and March 2014 laboratory records were reviewed for culture-positive samples growing *S. aureus*, also, medical records for the patients were reviewed for the demographic data, predisposing conditions, vancomycin MIC level, and outcome. Inpatients and outpatients were included, a case was classified as either hospital-associated (HA), community-associated (CA), or healthcare-associated (HCA). Data were entered as excel sheets and were statistically analyzed using SPSS version 21.

**Results:** A total of 127 patient (46% MRSA) were culture-positive for *S. aureus* collected from different sources. Of these, eighty (63%) were inpatients. High resistance rates to non-β-lactam antimicrobials were recorded. Glycopeptides agents were the antibiotics of choice for the treatment of infections caused by MRSA strains. Complications rates were higher in patients with MRSA infections including mortality, whereas hospital stay was longer for patients infected with MSSA.

**Conclusion:** Infection rates with MRSA were high among patients. There is a value for knowing vancomycin MICs for treatment of *S. aureus* and its implication for patients outcomes, though most outcomes were significantly worse due to MRSA infection.

**Keywords**
Vancomycin MICs; MRSA; Infection; Jordanian Patients.
Introduction

Staphylococcus aureus is a serious pathogen and a leading cause of both community- and healthcare-associated infections. Several factors may predispose patients to the development of S. aureus infections such as intensive care units (ICUs) stay, long-term care facility residents, surgical patients, immunocompromised conditions, patients on hemodialysis, and various invasive procedures [1-2]. According to some healthcare systems, S. aureus was the second most common isolate, accounting for 20% of cases, and a prospective analysis in 49 hospitals in the United States between 1995-2002, reported that the proportion of MRSA increased from 22% in 1995 to 57% in 2001 [3]. Among patients consecutively admitted in 1993 to the adult intensive care unit (ICU) in Jordan University Hospital in Amman-Jordan, the most frequent species isolated was S. aureus [4]. A single center study conducted in Jordan hospital over a period of 3-year, found S. aureus the third most common blood isolate in the ICU after coagulase-negative staphylococci and E. coli, and accounting for 9.8 percent of cases [5]. Nonetheless, there has been in the mid-1990s an increase in the number of MRSA infections among patients who lacked proper health care exposure. This increase has been associated with the recognition of a different MRSA strains, such as community-associated MRSA (CA-MRSA), and these strains have rapidly spread in the world causing infections in the general population [6-12]. In an analysis of 132 cases of MRSA bloodstream infections in patients admitted to a hospital in Atlanta-USA in 2004, molecular typing studies demonstrated that 34% of isolates were CA-MRSA, which was genetically distinct from the traditional strains HA-MRSA [13]. HA-MRSA strains carry a relatively large staphylococcal chromosomal cassette mec (SCCmec) belonging to type I, II, or III. These cassettes contain mecA gene, which is nearly universal, they are often resistant to many classes of antimicrobials.

Also, CA-MRSA isolates carry SCCmec type IV or V, though smaller elements and presumably mobile, but they are resistant to fewer non-β-lactam classes and frequently carry PVL genes [14]. Patients infected with MRSA strains need more care and have a poorer prognosis. Several studies have demonstrated increased mortality among patients infected with MRSA compared to MSSA infection [15-17].

This study aims to identify S. aureus susceptibility to vancomycin and the outcomes of its infection on patients in Jordan.

Materials and Methods

Study Design and Settings

This is an observational multicenter study included three private hospitals (Arab Medical Center, Al-Khalidi Hospital and Medical Center, and the University of Jordan hospital, Amman, Jordan. The study was approved by the institutional review board (IRB) in every hospital. Outpatients, and inpatients who had positive cultures of S. aureus were recruited over the period (June 2013 through March 2014). Records of the inpatients were reviewed, and patients were followed during hospitalization and after discharge. A case report form was filled included the following items: patients’ demographic data; age, sex, weight, length of stay (LOS), admission location; ICU, medical, surgical, gynecology and pediatric. The chief complaint for admission, diagnoses, source of culture, infectious diagnosis, surgical procedures, previous antibiotic use, the antimicrobial susceptibility of S. aureus isolates, predisposing clinical conditions and comorbidities, malignancy, administration of steroids > 20 mg/day of prednisone use or its equivalent for more than 14 days prior to specimen culture, antineoplastic chemotherapy in the 3 months prior to culture collection, long-term facility residence, indwelling catheters, intravenous drug use, diabetes mellitus, kidney disease,
hemodialysis, skin or soft tissue lesions, respiratory illness, surgery wound and surgery requiring more than 48 h of hospitalization in the 30 days prior to admission, invasive procedures including cardiac catheterization, arterial angiogram, upper endoscopy, colonoscopy, bronchoscopy, tracheostomy, bone marrow aspiration, renal biopsy, hospitalization in the previous 12 months, and a history of previous MRSA infection and/or colonization. The patient’s data about the use of antibiotics in the last three months and/or last week, frequent use of antibiotics prior vancomycin or other anti-MRSA agent exposure were recorded.

**Inclusion criteria**

*S. aureus* culture-positive specimens from inpatients and outpatients were included. The isolated *S. aureus* were classified as HA, CA, and HCA. CA-*S. aureus* is considered if the first isolate was recovered within 48 h of hospitalization, and if obtained from an outpatient source or the isolate was recovered within 48 h of hospitalization but believed to have had been incubating on admission, HCA cultures were considered from patients that frequently need healthcare attention or invasive procedures, but not admitted e.g. hemodialysis patients (CDC Definition). Non-duplicate strains for *S. aureus* isolates were considered. The outcome evaluated were vancomycin MIC distribution in relation to improved and discharged, discharged without improvement, switch to another antibiotic, relapse-progression, ≤ 30-days readmission, infection-related readmission, and all cause of mortality among patients suffering of *S. aureus* infection.

**Identification of *S. aureus***

*S. aureus* was identified by the routine standard hospital microbiology laboratory procedure, methicillin resistance was detected by the oxacillin and cefoxitin Kerby-Bauer disk diffusion, E-test (Retro C80TM, AB Biodisk, Sweden), or by VITEK 2 (bio-Mérieux) for identification and antibiotic susceptibility testing of gram-positive cocci was used to measure vancomycin MICs. Vancomycin susceptibility was defined according to The CLSI breakpoints (M100, Performance Standards for Antimicrobial Susceptibility Testing [18]); susceptible ≤ 2 mg/L, intermediate 4-8 mg/L, and concentrations ≥16 mg/mL as resistant.

**Statistical Analysis**

Statistical analyses were performed using the SPSS 21 (Statistical Package for the Social Sciences, Version 21, Inc. IBM Corporation, Chicago, IL, USA), and tables were initially analyzed by Microsoft Excel (Microsoft Corporation). All data were calculated by non-parametric analysis due to low numbers or groups. Numbers were transformed to frequencies and analyzed as relative frequencies among MSSA and MRSA covariates and outcomes. Wilcoxon Sign Rank test was used to analyze MRSA and MSSA paired differences for the covariates and outcomes. Regression analysis for the relation between MIC and the days for the length of hospital stay. Kruskal Wallis tests to the asses the difference among means. P-value < 0.05 was considered statistically significant.

**Results**

A total of 127 patients with their records for positive *S. aureus* cultures were recruited from the three hospitals in a 10-month period (June 2013-March 2014). Males constituted 87 (69%) and females 40 (31%). Out-patients were 47 (37%); infected with 59.6% MSSA and 40.4% MRSA respectively, whereas in-patients were 80 (63%); infected with 51.3% MSSA and 49.7% MRSA, respectively (Figure 1). The age of the patients was distributed into groups, they were almost similar in numbers, but less for the age group <20, elder inpatients were more than the other age groups, and the outpatients elder age group were smaller in number. The total distribution of *S. aureus* susceptibility consis-
Demographic features were collected from 80 patients with *S. aureus* infection based on their oxacillin susceptibility. Comorbidities; (BMI>25, CVD, diabetes, chronic kidney diseases, chronic respiratory diseases, and malignancy were significantly different in the distribution between MSSA and MRSA (P < 0.05). However, there was no significant difference for smoking, CNS disorders and skin diseases (P > 0.05). There was a significant difference between the numbers of MSSA and MRSA for the use of antimicrobials either within the prior 3 months or 12 months of the study isolate (P < 0.05), and there were significant differences between both isolates based on the ward from which they were isolated (P < 0.05) (Table 2).

Both strains of *S. aureus* almost matched for their vancomycin susceptibility. The majority of MSSA isolates (20) and MRSA isolates (29) were in the range of 0.5-1.0 mg/L. There were 4 MSSA and one MRSA and 3 MSSA and 3 MRSA in the range MIC >1 -1.5 mg/L, and 1 MSSA, 2 MRSA in the range MIC > 1.5-2 mg/L and zero for both for the MIC >2 mg/L (Figure 2). Both strains were tested for susceptibilities based on the location of isolation as inpatients or outpatients. After the exclusion of the antimicrobials with zero susceptibility rates from MRSA like carbapenems and cephalosporines. In the MSSA there were statistically significant differences (P < 0.05) between inpatients and outpatients with better inpatient susceptibility for clindamycin and erythromycin, but better outpatient for quinolones, and TMP-SMX. For MRSA
Table 2. Other demographic features and characteristics based on S. aureus oxacillin susceptibility.

| Demographic data                                      | All Patients | Inpatients | P  |
|-------------------------------------------------------|--------------|------------|----|
| S. aureus infections (N = 80)                         |              |            |    |
| N %                                                   | 41 51        | 39 49      |    |
| Type of infection acquisition                         |              |            |    |
| CA                                                    | 6 2          | 0.014      |    |
| HCA                                                   | 20 26        | 0.000      |    |
| HA                                                    | 15 11        | 0.000      |    |
| BMI >25                                               | 14 34        | 21 83.9    | 0.000 |
| Tobacco smoking                                       | 16 39        | 16 41      | 1.00 |
| CVD                                                   | 17 41.4      | 15 38.5    | 0.000 |
| Diabetes mellitus                                     | 18 44        | 20 51.3    | 0.000 |
| Chronic kidney disease                                | 10 24.4      | 11 28.2    | 0.002 |
| Chronic respiratory illness                           | 7 17         | 4 10.3     | 0.008 |
| CNS disorders                                          | 3 7.3        | 2 5        | 0.083 |
| Malignancy                                            | 9 21.9       | 2 5        | 0.003 |
| Skin disease                                           | 5 12.1       | 5 12.8     | 1.00 |
| Previous hospital admissions                          |              |            |    |
| Within prior 3 months                                 | 15 36.6      | 12 30.8    | 0.000 |
| Within prior 12 months                                | 32 78        | 28 71.8    | 0.000 |
| Antibiotics within the last 3 months                  | 12 29        | 14 36      | 0.001 |
| Length of hospital stay in days (range)               | 14.4 1-81    | 11 1-84    | 0.000 |
| Hospital Service                                      |              |            |    |
| ICU                                                   | 9 21.9       | 12 30.7    | 0.003 |
| Medical ward                                          | 14 34.1      | 10 25.6    | 0.000 |
| Surgical ward                                         | 21 51.2      | 16 41      | 0.000 |
| Pediatric ward                                        | 4 10         | 2 5        | 0.046 |
| All-cause mortality                                   | 8 0.129      | 5 0.080    | 0.025 |

P value was tested by the Wilcoxon Sign Rank Test for the related MSSA - MRSA paired differences. CA: community-associated, HCA: healthcare-associated, HA: hospital-associated. CVD: cardiovascular disease, CNS: central nervous system, ICU: intensive care unit.

Figure 2: The Relative distribution rates for patients with MSSA = 27 and MRSA = 35, distributed according to the various Vancomycin MICs.

There was a significant differences (P < 0.05) between the inpatients and outpatients, better susceptibility rate in the outpatients for quinolones, gentamicin and rifampin, but better susceptibility rate among inpatients for erythromycin and TMP-SMX (Figure 3).

S. aureus susceptibility to vancomycin, teicoplanin, tigecycline and rifampin was 100%. Cephalosporines, carbapenems, penicillin and piperacillin/tazobactam were 0% active against MRSA. After exclusion of the antimicrobial agents with both 100% susceptibility, and those with one agent with 0% susceptible for either strain from statistical analysis. Susceptibility differences for the other antimicrobial agents (quinolones, clindamycin, erythromycin, TMP/SMX and gentamicin) were significantly different in favor of MSSA (P < 0.001) (Figure 4).

The outcome rates for S. aureus were plotted as a strain specific relative frequency for MSSA and MRSA, the MICs relative frequency differences between both strains for the range 0.5-1.0 mg/L. The other MIC ranges were not considered for analysis for being zero or few in numbers. For all outcomes the difference in the relative frequencies for patients with MSSA or MRSA was evident pointing at a worse MRSA outcome (P = 0.018), and for each outcome: improved and discharged (P = 0.008), relapse-
Figure 3: The Rates of MSSA and MRSA susceptibilities for several antimicrobial agents in inpatients and outpatients. For MSSA, there were statistically significant differences (P < 0.05) between inpatients and outpatients for Clindamycin and for erythromycin, quinolones, and TMP-SMX. For MRSA there were significant differences (P < 0.05) between the inpatients and outpatients for quinolones, gentamicin and rifampin, and for erythromycin and TMP-SMX. By 2-tailed Wilcoxon Sign Rank Test.

Figure 4: Antimicrobials Susceptibility Rates for S. aureus isolates from the outpatients.

Figure 5: The rates for patients with MSSA (20) and MRSA (29) for several measured outcomes. The Differences is measured by 2-tailed Wilcoxon Sign Rank Test: improved and discharged (P = 0.008), relapse-progression (P = 0.001), ≤ 30-days readmission (P = 0.005), infection related readmission (P = 0.008), and all-cause mortality (P = 0.025) but was not significant for: discharged without improvement (P = 0.083) and switch to another antibiotic (P = 0.083), (Figure 5).

Length of hospital stay was strongly associated with vancomycin susceptibility for MSSA, where it averaged 9.6 (n = 4, SD 5.86) when MIC was less than 0.5 mg/L, 14.06 days (n = 20, SD 20.79) for
MIC > 0.5-1 mg/L and 45 days (n = 2, SD 39.59) for MIC > 1-1.5 mg/L. Regression analysis showed perfect fit for the relation among MIC and length of hospital stay (R = 1, R² = 1), Kruskal-Wallis test showed no significant differences among the three length of hospital stay for the cited number of patients for each groups (P = 0.386).

Discussion

Our study showed that the MRSA rates among all isolates of *S. aureus* were 45.7%, these rates were lower than what was reported earlier by Frazee et al. (51%) and Kaplan et al. (76.4%) a decade earlier [7, 9] and 53.3% from Jordan [19]. The rates for the CA-MRSA (including HCA-MRSA) was 51.8%; consistent with a previous study where it ranged 50.5-79.5% [12]. Patients with MRSA were more likely to have a risk factor. In this study, 78% of MSSA cases and 71.8% of MRSA cases have a history of hospitalization in the last 12 months, those rates were not close to what was reported by Lescure, et al. which were 67% MSSA and 85% MRSA cases [20]. Comorbidities including BMI > 25, CVD, diabetes, chronic kidney diseases, chronic respiratory diseases, and malignancy were significantly higher in MRSA infected patients (P < 0.05). Smoking, CNS disorders and skin diseases were not different (P > 0.05). There was a significant increase in the length of hospital stay and cost for patients with MSSA infection (P < 0.05), like a recent study by E. Y. Klein [21], possibly due to the relatively earlier and higher MRSA mortality rate in our patients (P = 0.025). Other studies found higher mortality rate associated with MRSA infection and longer hospital length of stay [16, 17, 22].

Our data showed that *S. aureus* was mostly concentrated in the susceptibility range (0.5-1 mg/L), with almost no distribution difference in the relative frequencies between MSSA and MRSA, and only fewer strains were in < MIC 0.5 mg/L and > MIC 1 mg/L. Though the standard of care in the treatment of MSSA are the penicillinase-resistant semisynthetic penicillins or cephalosporines. Nevertheless, studies have shown that elevated vancomycin MIC for MSSA strains was associated with more treatment failures and mortality [23, 24]. Eight patients (2 cancer patients) with MSSA infection were treated with vancomycin, 6/8 (75%) had a poor outcome, and the other patients were younger (31 and 6 years old). Vancomycin is considered suboptimal therapy for the treatment of MSSA infection compared to the anti-staphylococcal β-lactams and is associated with the increased rates of treatment failure and high mortality rates. [25, 26] Despite the Infectious Diseases of America (IDSA) guidelines support using vancomycin for MRSA infections when are susceptible (MIC < 2 mg/L), some studies and systematic reviews demonstrated treatment failure when patients were treated with vancomycin with MIC ≥ 1.5 mg/L. This is due to the difficulty in attaining the PK/PD target of AUC/MIC ≥ 400 with the clinical doses [27-33]. Furthermore, poorer prognosis was associated with vancomycin MIC level of > 1 mg/dl [34]. Noteworthy, in our patients both MRSA and MSSA susceptibility to vancomycin showed almost similar MIC distribution, lucky enough the vast majority fell ≤ 1 mg/L, this would attain the PK/PD target when clinically achieving the serum trough levels of 15-20 mg/L. Also, our data demonstrated to some extent, that the higher *S. aureus* MIC for vancomycin, the longer the length of hospital stay for patients is noted, though regression and correlation among MICs and length of stay were perfect, but the difference between their means was not significant for the analyzed number of patients within each group (P = 0.386).

For several antimicrobials, MSSA and MRSA were compared respectively as inpatients and outpatients. For the MSSA, clindamycin and erythromycin showed significantly better efficacy among inpatient against MSSA (P < 0.05), and in the outpatient quinolones and TMP-SMX were
better (P < 0.05). For the MRSA, erythromycin and TMP-SMX showed significantly better anti-MRSA activity inpatient (P < 0.05), and in the outpatient, quinolones, gentamicin and rifampin were better (P < 0.05). The rest of the antimicrobials for both types of staphylococci showed no significant differences (Figure 3).

Susceptibility rates to the other antimicrobials were evaluated among outpatient MRSA isolates, these were 74% for quinolones and 69% TMP/SMX, respectively. An earlier study carried out in the Jordan University Hospital demonstrated that MRSA susceptibility to quinolones was 15%, clindamycin 68%, and gentamicin 68%, respectively [35]. In the current study, a relatively higher susceptibility rates were observed for quinolones 74%, clindamycin 56%, and gentamicin 94%, respectively. An older Saudi study from the 1980s [36] found imipenem to have had an excellent in vitro activity against MRSA isolates after vancomycin. Nevertheless, in this study the lack of sensitivity of MRSA isolates to β-lactam antibiotics exemplified by cephalosporines and carbapenems is consistent with other more recent studies [7, 37 38]. Our finding showed that the susceptibility to imipenem was 0% among 35 tested MRSA isolates. The rates of in vitro ineffective β-lactam for MRSA cases were 100% in this study, while up to decade earlier it was reported to be ineffective up to 78.7% by using empirical β-lactam prescriptions, and carried a poor prognosis [7, 39]. These results clearly demonstrated the escalating rates of resistance.

The outcomes of patients treatment were analyzed for the vancomycin (MIC range 0.5-1 mg/L), they could not be analyzed for the other vancomycin MIC distributions as they were low in count. Treatment of patients infected with MRSA evidently pointed at worse outcomes (P = 0.018). The outcome of each patient when analyzed separately, was significant (P < 0.05) for improved and discharged, relapse-progression, ≤ 30-days readmission, infection related readmission, and all-cause of mortality. However, the result was not significant (P > 0.05) for discharged without improvement or after the switch to another antibiotic.

Conclusion
The increasing MRSA rates leave limited treatment options. Evaluating S. aureus susceptibility to vancomycin with a minimum inhibitory concentration may help in predicting outcomes, nonetheless, our study significantly demonstrated worse outcome with MRSA infection.

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All Authors declare no conflict of interest related to this article.

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