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# Vancomycin Minimum Inhibitory Concentration for Methicillin-Resistant *Staphylococcus aureus* Infections; Is There Difference in Mortality Between Patients?

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**Background:** New data indicates that vancomycin may be less effective against methicillin-resistant *Staphylococcus aureus* (MRSA) infections with minimum inhibition concentration (MIC) within a sensitive range.
**Objectives:** The aim of this study was to determine the distribution of the vancomycin MIC between MRSA strains and observe the difference in mortality between patients, while the influence of changes in MIC on the efficacy of vancomycin was also examined.
**Patients and Methods:** A routine date-based study was conducted on 41 MRSA isolates in a hospital in Tehran, Iran. The isolates were assessed for MIC by using the E-test method, and results were categorized into three groups: A (MIC < 1.5 μg/mL), B (1.5 ≤ MIC < 2 μg/mL) and C (MIC ≥ 2 μg/mL) MRSA.
**Results:** Group A was the most common group, followed by groups C and B. Although there was no statistically significant difference between patients' mortality with the MIC group, the mortality rate of group A was higher than C and B.
**Conclusions:** Regarding Clinical and Laboratory Standards Institute (CLSI) definition for vancomycin susceptibility (MIC < 2 μg/mL), it seems that vancomycin may not be considered as the best antibiotic in order to treat heteroresistant vancomycin intermediate *S. aureus* (hVISA) and vancomycin sensitive *S. aureus* (VSSA) infections, and a new breakpoint for vancomycin and alternative antibiotics should be considered.

*Keywords:* Vancomycin; Minimum Inhibitory Concentration; Methicillin Resistant; *Staphylococcus aureus*; Mortality

## 1. Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been the common cause of various community acquired and nosocomial infections (1, 2), from skin and soft tissue involvements to life threatening conditions, such as bacteremia and pneumonia (3). Although vancomycin is the recommended drug for MRSA infections (4) and most MRSA isolates are sensitive to this antibiotic (2), heteroresistant vancomycin intermediate *S. aureus* (hVISA) and vancomycin intermediate resistant *S. aureus* (VISA) were introduced in the late 20$^{th}$ century (5). In 2006, the Clinical and Laboratory Standards Institute (CLSI) established the vancomycin minimum inhibitory concentration (MIC) susceptibility breakpoint as 2 μg/mL for *S. aureus* while the definitions of VISA and vancomycin resistant *S. aureus* (VRSA) changed to MIC of 4 to 8 μg/mL and ≥ 16 μg/mL, respectively (6). A few studies report the possibility of vancomycin treatment failure, even in cases with MICs between 1 and 2 μg/mL (1, 7-9). Although it is expected for hVISA isolates to be more common in higher MIC groups (10, 11), CLSI suggest some *S. aureus* isolates with MIC between 1 and 2 μg/mL may be hVISA (12).

## 2. Objectives

There has been a considerable problem with MRSA infections, thus this research was conducted to determine the distribution of vancomycin MIC among MRSA strains and observe the difference in mortality between patients. Furthermore, the influence of changes in MIC on the efficacy of vancomycin was examined to determine the most appropriate breakpoint at a hospital in Tehran, Iran.

## 3. Patients and Methods

A routine date-based study was conducted on 41 MRSA isolates gathered from June through to November 2012 in a private hospital in Tehran, Iran. Patients' samples were inoculated on blood agar plates (Oxoid Ltd, Basingstore, Hampire, UK), followed by incubation at 37°C for 24

hours, and recognition of significant isolates at species level by common bacteriological techniques. Methicillin and vancomycin susceptibility were determined by microdilution using CLSI methods. Portion (10 μL) of 0.5 McFarland from suspensions were pipetted onto brain hear infusion agar plates. Next, E-test strips (AB Biodisk, Solna, Sweden) for vancomycin and teicoplanin were applied on the same plate; followed by incubation at 35°C for 24 hours. Control organisms *Enterococcus faecalis* ATCC (American Type Culture Collection) 29212, *S. aureus* ATCC 29213 and 25923 (non-MRSA), ATCC 43300 (MRSA), 700698 (hVISA), 700699 (VISA), and *E. faecalis* ATCC 51299 were used to control the quality of media and evaluate color stability. Later, the results were analyzed (12).

We categorized each isolate into one of the three groups, according to E-test result as follows: Group A (MIC < 1.5 μg/mL), B (1.5 ≤ MIC < 2 μg/mL), and C (MIC ≥ 2 μg/mL) MRSA. We obtained the following data for all patients: age, gender, comorbidities, history of administration of vancomycin or previous MRSA infection, source of infection, the length of hospital stay, ward, vasopressors received, infection consultation, vancomycin MIC and outcome. The data were analyzed with the SPSS 16 software (descriptive analysis, Chi-square) (SPSS Inc. Chicago, IL). A P value of < 0.05 was considered statistically significant.

## 4. Results

Twenty-five patients were male (61%) and 16 were female (39%). The mean age of patients was 72.34 ± 15.2. The oldest patient was 92 and the youngest patient was 30 years old. Most of the patients (80.5%) belonged to the elderly group ( ≥ 65 years old). Twenty-six patients (63.5%) were admitted to the Intensive Care Unit (ICU). Three (7%), 11 (27%), and 1 (2.5%) of the cases were hospitalized in the Critical Care Unit (CCU), internal ward, and surgical ward, respectively. The length of stay at the hospital was three or more weeks for 24 patients (58%). Eleven (27%) and six (15%) patients were hospitalized for 1-2 weeks and 2- 3 weeks, respectively. Seventeen Out of 19 (89%) patients who received vasopressors died. None of the patients had a history of administration of vancomycin or previous MRSA infection. Infectious consult was provided for 37 patients (90%). As shown in Table 1, in terms of the source of isolates, sputum accounted for the greatest number [24 (58%)].

There was a statistically significant association between mortality and ICU admission (P < 0.005), duration of hospitalization (P < 0.005), or receiving vasopressors (P < 0.0001), whereas we found no statistically significant association between mortality and age, gender, patients' comorbidity, and source of the infections. Group A was the most common group [18 (44%)] followed by groups C [12 (29%)] and B [11 (27%)], respectively. There was no statistically significant difference between patients' mortality and the range of MIC (Table 2). There was no statistically significant association between the range of MIC and patients' age, gender, and comorbidities, source of infection, ICU admission, duration of hospitalization, and receiving a vasopressor.

**Table 1.** Frequency of the Source of MRSA Infection in a Private Hospital, Tehran, Iran, 2012

| Source of Infection | No. (%) |
|---|---|
| **Sputum** | 24 (58) |
| **Blood** | 8 (19.5) |
| **Urine** | 2 (5) |
| **Wound** | 2 (5) |
| **Synovial fluid** | 2 (5) |
| **Bronchoalveolar lavage (BAL)** | 1 (2.5) |
| **Peritoneal fluid** | 1 (2.5) |
| **Abdominal abscess** | 1 (2.5) |
| **Total** | 41 (100) |

**Table 2.** Association Between the Range of Vancomycin MIC and Outcome in Patients With MRSA Infection in a Private Hospital of Tehran

| | Outcome | |
|---|---|---|
| **The Range of Vancomycin MIC (μg/mL)** | **Alive, No. (%)** | **Dead, No. (%)** |
| **< 1.5** | 10 (42) | 8 (47) |
| **1.5-2** | 7 (29) | 4 (23.5) |
| **≥ 2** | 7 (29) | 5 (29.5) |
| **Total** | 24 (100) | 17 (100) |

## 5. Discussion

Regarding risk factors, Pastagia et al. (13), Takesue et al. (14), Soriano et al. (7) and van Hal et al. (15) showed that comorbidity, age, gender, admission to an ICU, source of infection, and requiring vasopressors contribute to mortality in MRSA infections, while Sakoulas et al. (8) found no significant association between these factors and death. In our research, the length of hospital stay, ICU admission, and receiving vasopressors were associated with outcome and mortality of patients. In this study, there was no significant association between the range of vancomycin MIC and patients' demographic information, which is similar to that reported by Soriano et al. (7), Charles et al. (10) and van Hal et al.'s (15).

In our study, although there was no statistically significant difference between patients' mortality and the MIC group, the mortality rate in MIC < 1.5 μg/mL (40%) was higher than MIC ≥ 2 μg/mL (29.5%). The mortality rate for 1.5 ≤ MIC < 2 μg/mL was noticeable (23.5%). Regarding CLSI definition for vancomycin susceptibility (MIC < 2 μg/mL) (12), it seems that vancomycin may not be considered as the best antibiotic in order to treat hVISA or VSSA infections.

In conclusion, E-test MIC for severe MRSA infections has

been recommended by recent studies (16, 17). Besides, reduced susceptibility to vancomycin and suboptimal clinical response in patients with MRSA were reported by certain researches (8, 18-20), and a systematic review and meta-analysis in 2012 has emphasized this matter (16). Therefore, a new breakpoint for vancomycin and alternative antibiotics should be considered.

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## Authors' Contributions

Conception and design of the study: Zohreh Aminzadeh, Davood Yadegarynia and Alireza Fatemi. Analysis and interpretation of data: Zohreh Aminzadeh, Davood Yadegarynia and Alireza Fatemi. Provision of study material of data: Zohreh Aminzadeh, Davood Yadegarynia, Alireza Fatemi, Elham Tahmasebian Dehkordi and Saeed Azad Armaki. Collection, assembly, and possession of raw data: Alireza Fatemi, Elham Tahmasebian Dehkordi and Saeed Azad Armaki. Statistical analysis: Zohreh Aminzadeh and Alireza Fatemi. Critical revision: Zohreh Aminzadeh, Davood Yadegarynia and Alireza Fatemi. Critical revision of the article for important intellectual content: Zohreh Aminzadeh, Davood Yadegarynia and Alireza Fatemi. Final approval of the study: Zohreh Aminzadeh, Davood Yadegarynia, Alireza Fatemi, Elham Tahmasebian Dehkordi and Saeed Azad Armaki. Obtaining funding for the study: Zohreh Aminzadeh, Davood Yadegarynia and Alireza Fatemi. Administrative, technical or logistical support: Zohreh Aminzadeh, Davood Yadegarynia, Alireza Fatemi, Elham Tahmasebian Dehkordi and Saeed Azad Armaki. Guarantor of integrity of the entire study: Zohreh Aminzadeh, Davood Yadegarynia, Alireza Fatemi, Elham Tahmasebian Dehkordi and Saeed Azad Armaki.

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