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# Methicillin-resistant *Staphylococcus aureus* (MRSA) Bacteremia : Correlation between Vancomycin Minimum Inhibitory Concentration Values by the Broth Microdilution Method and Treatment Outcome

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## ■Abstract

**Background:** There has been little research evaluating the correlation between vancomycin (VAN) minimum inhibitory concentration (MIC) and treatment outcome in MRSA bacteremia using the reference broth microdilution (BMD) for VAN susceptibility determination. Most previous studies used the E test for VAN MIC determination, but E test has been shown to provide VAN MIC results consistently higher than those provided by precisely performed reference BMD tests.

**Methods:** Using a reference BMD method, we determined the VAN MICs for MRSA isolated from 51 patients (pts) with MRSA bacteremia between December 2007 and December 2010 at St. Luke's International Hospital , a 530-bed ,acute care teaching hospital in Tokyo. We retrospectively reviewed medical records and compared the clinical background and 30-day mortality after the first positive blood cultures between MRSA infected pts with low VAN MIC (MIC=0.5 or 1.0μg/ml) versus high MIC (MIC=2.0μg/ml).

**Results:** Among 51 MRSA isolates, 23.5% (12 /51) had a MIC=0.5μg/ml, 60.8% (31 /51) had a MIC=1.0μg/ml, and 15.7% (8 /51) had a MIC=2.0μg/ml. Between the 43 pts with low MIC and the 8 pts with high MIC, there were no significant differences in age, baseline diseases, focus of infection, or prior use of VAN. Eight pts with end-stage malignancy or under palliative care were excluded from the evaluation of mortality. All of the remaining 43 pts (6 in high MIC and 37 in low MIC group) were initially treated with VAN. VAN was changed to linezolid in 16.6% (1 /6) high MIC pts and 10.8% (4 /37) low MIC pts due to adverse reactions to VAN in 4 pts and clinically resistant vascular graft infection in 1 low MIC pt. Combination therapy (5 pts：VAN+RFP+TMP/SMX, 4 pts：VAN+RFP) was given to 9 pts (23.2%) in low MIC group only.

The 30-day mortality associated with MRSA bacteremia was as follows: 23.3% (10 /43) in total, 27% (10 /37) in low MIC group, and 0% (0 /6) in high MIC group (p=0.31, Fisher's exact test)

**Conclusion:** For 30-day mortality associated with MRSA bacteremia, there was no significant difference between pts with high MIC and pts with low MIC as determined by the CLSI reference BMD method.

## ■Introduction

1. Most studies regarding prognosis of bacteremia patients infected with MRSA with a high VAN MIC (MIC=2.0 μg/ml) have used a E test.
2. However, E test has been shown to provide VAN MIC results consistently higher than those provided by precisely performed reference Broth microdilution (BMD) method .
3. There has been little research evaluating the correlation between VAN MIC and treatment outcome in MRSA bacteremia using BMD for VAN susceptibility determination.

## ■Purpose

1.To evaluate VAN MIC using a reference BMD method for MRSA isolated from MRSA bacteremia pts.
2.To compare the clinical background between MRSA infected pts with low VAN MIC (MIC=0.5 μg/ml or 1.0 μg/ml) versus high VAN MIC (MIC=2.0 μg/ml).
3.To compare the 30 day mortality after first positive blood cultures between low MIC versus high MIC MRSA infected pts.

## ■Methods

**1. Design :**
Retrospective review study of medical records

**2. Setting :**
St. Luke's International Hospital, Tokyo, Japan
(530-bed , tertiary-level community teaching hospital)

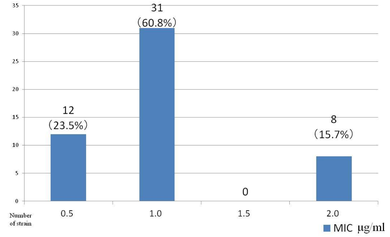
**3. Study period :**
December 2007 – December 2010 (3 years)

**4. Patient population and microbiologic method :**
All 51 pts with MRSA bacteremia in the study period were evaluated.
In all 51, MRSA was isolated from blood cultures and VAN MICs determined byCLSI reference BMD method.

## ■Results

### 1.VAN susceptibility testing results of 51 MRSA isolates by reference BMD method:

| Low MIC | | High MIC |
|---|---|---|
| MIC : 0.5 μg/ml | MIC: 1.0 μg/ml | MIC: 2.0 μg/ml |
| 23.5% (12/51) | 60.8% (31/51) | |
| 84.3%( 43/51) | | 15.7%(8/51) |




### 2. Comparison of clinical characteristics of the 43 patients with low MIC vs. the 8 pts with high MIC ：

| | MIC≦1.0μg/ml (n=43) | MIC=2.0μg/ml (n=8) | P-value |
|---|---|---|---|
| Age(mean±SD) | 72.4 ±12.8 | 70.6±29.4 | 0.770 |
| Sex: male (%) | 30 (67.4%) | 8 (100%) | 0.170 |
| **Baseline status** | | | |
| Diabetes (15) | 13 (30.2%) | 2 (25.0%) | 1.000 |
| Heart failure (8) | 7 (16.3%) | 1 (12.5%) | 1.000 |
| Cancer (17) | 12 (27.9%) | 5 (62.5%) | 1.000 |
| End stage cancer(8) | 6 (14.0.%) | 2 (25%) | 0.600 |
| Hemodialysis (4) | 4 (9.3%) | 0 (0%) | 1.000 |
| Recent surgery (4) | 4 (9.3%) | 0 (0%) | 1.000 |
| Immunosuppressant(3) | 1 (2.3%) | 2 (25%) | 0.061 |
| Liver cirrhosis (1) | 1 (2.3%) | 0 (0%) | 1.000 |
| Cerebrovascular diseases (11) | 7 (16.3%) | 4(50%) | 0.055 |
| COPD (3) | 1 (2.3%) | 2 (25%) | 0.061 |

| | MIC≦1.0μg/ml (n=43) | MIC=2.0μg/ml (n=8) | P-value |
|---|---|---|---|
| **MRSA Infection sites (n)** | | | |
| Central venous catheter (23) | 19 (44.2%) | 4 (50%) | 1.000 |
| Vascular graft or pacemaker (4) | 4 (9.3%) | 0 (0%) | 1.000 |
| Surgical wound (5) | 5 (11.6%) | 0 (0%) | 0.580 |
| Soft tissue (2) | 1 (2.3%) | 1 (12.5%) | 0.292 |
| Pneumonia (2) | 2 (4.7%) | 0 (0%) | 1.000 |
| Pleura (1) | 0 (0%) | 1 (12.5%) | 0.157 |
| Urinary tract (1) | 1 (2.3%) | 0 (0%) | 1.000 |
| Bone (3) | 3 (7.0%) | 0 (0%) | 1.000 |
| Intraabdominal (1) | 1 (2.3%) | 0 (0%) | 1.000 |
| unclear (9) | 7 (16.3%) | 2 (25.0%) | 0.619 |

| | MIC≦1.0μg/ml (n=43) | MIC=2.0μg/ml (n=8) | P-value |
|---|---|---|---|
| Number of Baseline diseases | 4.0 ±3.4 | 4.1 ±4.0 | 0.880 |
| Prior VCM use (23) | 20 (46.5%) | 3 (37.5%) | 0.720 |
| Antibiotic use in last 1 month (34) | 30 (71.4%) | 4 (50%) | 0.810 |

●There was no significant difference in age, gender , infection sites, baseline diseases, prior vancomycin use, or recent antibiotic use between pts with low MIC versus high MIC.

### 3. Treatment:

① Seven pts with end-stage malignancy or under palliative care and 1 pt who was transferred to another hospital were excluded from evaluation of treatment and prognosis.
A total of 43 pts（37 pts in low MIC and 6 pts in high MIC) were evaluated.

② All pts were initially treated with VAN.

③ VAN was changed to linezolid in 10.8% (4/37) of low MIC pts and in 16.6% (1/6) of high MIC pts due to adverse reactions to VAN in 4 pts and clinically resistant vascular graft infection in 1 low MIC pt.

④ Combination therapy was used in 23.2% (9/37) of low MIC pts only :
a) VAN+Rifampicin+TMP/SMX in 5 pts.
b) VAN+Rifampicin in 4 pts.

⑤ 65% (24/37) of low MIC pts and 83% (5/6) of high MIC pts were treated successfully with VAN only.

### Comparison of treatment between 37 pts with low MIC versus 6 pts with high MIC

| Treatment | MIC≦1.0μg/ml (n=37) | MIC=2.0μg/ml (n=6) | P-value |
|---|---|---|---|
| **Initial therapy** | | | |
| Vancomycin | 37 (1oo%) | 6 (100%) | 1.000 |
| **Subsequent therapy** | | | |
| Vancomycin only | 24 (64.8%) | 5 (83.3%) | 0.640 |
| Linezolid | 4 (10.8%) | 1 (16.6%) | 0.5472 |
| **Combination therapy** | | | |
| VCM+RFP+TMP/SMX | 5 (13.5%) | 0 (0%) | 1.000 |
| VCM+RFP | 4 (10.8%) | 0 (0%) | 1.000 |

### 4. Treatment Outcome：

① The 30-day mortality associated with MRSA bacteremia was 23.3% (10/43) in total .
② Comparison of 30-day mortality of pts with low MIC (MIC=0.5 or 1.0μg/ml) versus pts with high MIC (MIC=2.0 μg/ml) was as follows：

### Comparison of 30-day mortality of pts with low MIC versus pts with high MIC.

| 30 day mortality | MIC≦1.0μg/ml (n=37) | MIC=2.0μg/ml (n=6) | P-value |
|---|---|---|---|
| Died | 10 (27 %) | 0 (0 %) | 0.310 |
| Survived | 27 (73 %) | 6 (100 %) | |

●The 30-day mortality of high MIC pts was 0% and lower than that of low MIC pts (27%). There was no significant difference statistically between the two groups. (p=0.31, Fisher's exact test)

## ■ Summary and Conclusion

1) Using BMD method, 15.7% (8/51) of MRSA isolated from bacteremic pts showed high VAN MIC (MIC=2.0μg/ml).
2) Comparing the 43 pts with low MIC and the 8 pts with high MIC, there were no significant differences in age, baseline diseases, infection sites, prior use of VAN, or recent antibiotics use.
3)There was no significant difference in 30-day mortality associated with MRSA bacteremia between pts with low MIC (MIC=0.5 or 1.0 μg/ml) and pts with high MIC (MIC=2.0μg/ml) determined by the CLSI reference BMD method.
4) Most MRSA bacteremia pts infected with high VAN MIC (MIC=2.0g/ml) by reference BMD method were treated successfully with VAN.
5) In addition to VAN MIC, other clinical factors are likely associated with 30-day mortality in MRSA bacteremia pts.