



# Vancomycin Serum Trough Levels and Outcomes in Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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## ABSTRACT

### Background:

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is a major cause of morbidity and mortality. Vancomycin (VAN) is considered the first line antimicrobial agent for its treatment. Current IDSA guidelines recommend VAN trough levels between 15 and 20 mg/L for MRSA bacteremia. We sought to compare MRSA bacteremia outcomes in relation to VAN serum trough levels.

### Methods:

This is a retrospective study performed in an integrated 4 hospital health system in southeast Michigan. We evaluated consecutive patients with MRSA bacteremia who were only treated with VAN from 2011 to 2015. Patients were included if they were > 18 years of age and had evidence of positive blood culture for MRSA. Patients who received daptomycin, ceftaroline, or linezolid were excluded. We evaluated initial VAN serum trough level (collection within 30-72 hours from the first dose) and mean VAN level (mean of serial VAN serum trough levels). Patients were subdivided into 2 groups of low (<15 mg/L) and high (>15 mg/L) VAN serum trough levels. VAN MICs were determined by E-test for all isolates.

### Results:

Out of 587 patients, 187 met the inclusion criteria. The 2 groups had similar characteristics. There was significantly higher mortality within 60 days of index blood culture in the group with high initial VAN serum trough levels. Furthermore, mortality within 30 days of index blood culture was even more significantly higher in group with the high mean VAN serum trough level. Duration of bacteremia was also longer in the high mean VAN serum trough level group.

### Conclusion:

We demonstrated that high VAN serum trough concentrations >15 µg/ml were associated with worst outcomes. However, future prospective randomized trials are warranted.

## INTRODUCTION

- Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) is a major health concern worldwide, associated with significant morbidity and mortality both in the hospital and the community.
- Vancomycin (VAN) is the first line antimicrobial agent for multiple MRSA infections including complicated and uncomplicated. The higher serum trough levels; however, have not been shown to be more therapeutically effective in comparative clinical trials.
- In 2009, Infectious Disease Society of America and the Society of Infectious Disease Pharmacist outlined the practice guidelines for VAN dosing and monitoring. Trough serum vancomycin concentrations of 15–20 mg/L for optimal therapy of MRSA blood stream infections (BSI) were laid down.
- Some clinical trials show that higher serum trough levels are associated with worse outcomes.

## OBJECTIVE

- To evaluate clinical outcomes in patients with MRSA BSI in relation to low and high VAN serum trough levels

## METHODS

**STUDY DESIGN:** This was a retrospective study performed in an integrated 4 hospital health system in southeast Michigan, USA. We evaluated consecutive patients from November 2011 to August 2015 who were admitted to the hospital and had positive blood culture for MRSA. Bloodstream infections were identified via review of microbiology laboratory records. Data was reviewed using electronic medical records. Outcomes compared were duration of bacteremia, readmission within 30 days from the end of MRSA BSI treatment, mortality within 30 days (30d), mortality within 60 days (60d), and recurrence of MRSA BSI within 30 days of index blood culture.

## METHODS

### VARIABLE DEFINITION:

- Initial VAN trough level: first VAN trough concentration drawn between 30 to 72 hours after the first vancomycin dose.
- Mean VAN trough level: serial trough concentrations drawn after the first level until the end of treatment.

Each group was subdivided into low (<15 mg/L) and high(>15 mg/L) VAN trough concentrations.

### INCLUSION CRITERIA:

- Patients with at least 1 positive blood culture of MRSA
- >18 years old
- VAN as the only antibiotic for bacteremia

### EXCLUSION CRITERIA:

- Patients treated with daptomycin, ceftaroline, or linezolid
- Patients who did not have any trough levels.
- Patients who did not have trough level as defined by initial or mean.

### STATISTICAL ANALYSIS:

Comparisons were done using t-tests, chi-square tests or Fisher's Exact tests. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

- Out of 587 patients, 187 met the inclusion criteria. Patient characteristics were similar in both groups. There was significantly higher mortality within 60d of index blood culture in the group with low initial serum VAN trough level.
- Mortality within 30d of index blood culture was even more significantly higher in group with the high mean serum VAN trough level.
- Duration of bacteremia was noted to be longer in the high mean serum VAN trough level group.

Table 1. Comparing Low and High VAN Trough Levels in the Initial Group

INITIAL TROUGH LEVEL GROUP	All (N= 115)	Initial Low (N= 62)	Initial High (N= 53)	p-value
Complicated	69%	61%	77%	NS
Creatinine	1.5 ± 1.4	1.3 ± 1.2	1.6 ± 1.6	NS
Source of Bacteremia Skin/Wound	40%	44%	36%	NS
Endocarditis	7%	10%	4%	
CVC	13%	13%	13%	
None	17%	13%	21%	
Other	23%	21%	26%	
MIC	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	NS
Duration of Bacteremia	2.7 ± 2.0	2.7 ± 2.2	2.6 ± 1.7	NS
Readmission within 30d	15%	18%	11%	NS
Recurrence	8%	8%	8%	NS
Mortality within 30d	16%	10%	23%	NS
<b>Mortality within 60d</b>	<b>18%</b>	<b>11%</b>	<b>26%</b>	<b>0.040</b>

## RESULTS

Table 2. Comparing Low and High VAN Trough Levels in Mean Group

MEAN TROUGH LEVEL GROUP	All (N= 161)	Average Low (N= 33)	Average High (N= 128)	p-value
Complicated	68%	55%	71%	NS
Creatinine	2.0 ± 2.1	2.2 ± 2.5	1.9 ± 2.1	NS
Source of Bacteremia Skin/Wound	47%	48%	47%	NS
Endocarditis	6%	9%	5%	
CVC	13%	21%	11%	
None	13%	9%	14%	
Other	20%	12%	23%	
MIC	1.6 ± 0.2	33 1.6 ± 0.2	1.6 ± 0.2	NS
<b>Duration of Bacteremia</b>	<b>2.7 ± 2.3</b>	<b>2.1 ± 1.4</b>	<b>2.9 ± 2.5</b>	<b>0.025</b>
Readmission within 30d	17%	18%	17%	NS
Recurrence	9%	9%	9%	NS
<b>Mortality within 30d</b>	<b>11%</b>	<b>0%</b>	<b>14%</b>	<b>0.022</b>
Mortality within 60d	14%	6%	16%	NS

## LIMITATIONS

- This was a retrospective and single center study.
- Non-randomized analysis.
- Comorbidities were not evaluated.
- Serum creatinine levels were not followed during the treatment period.

## CONCLUSION

- Mortality within 30 and 60 days was higher in the group with high serum VAN trough levels.
- No significant difference was noted in characteristics of clinical outcomes such as recurrence of bacteremia within 30 days of index blood culture or readmission with MRSA BSI within 30 days of completion of treatment.
- We demonstrated that high serum VAN trough concentrations (>15 mg/L) were associated with worst outcomes.

## REFERENCES

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