Original Article

Association Between Vancomycin AUC and Clinical Failure in Patients with Streptococcal Bacteremia

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Abstract

Background: Monitoring of vancomycin using the area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio is now preferred for serious methicillin-resistant *Staphylococcus aureus* infections. Vancomycin AUC/MIC monitoring is being investigated but is not yet well elucidated with other bacterial pathogens. **Methods:** A retrospective cross-sectional study was conducted assessing patients with streptococcal bacteremia treated with vancomycin definitive therapy. AUC was calculated using a Bayesian approach, and classification and regression tree analysis was used to identify a vancomycin AUC threshold predictive of clinical failure. **Results:** Eleven patients had a vancomycin AUC <329 of which 8 (73%) experienced clinical failure, while 35 patients had a vancomycin AUC ≥ 329 of which 12 (34%) experienced clinical failure ($P=.04$). Hospital length of stay was longer in the AUC ≥ 329 group (15 vs 8 days, $P=.05$), whereas time to bacteremia clearance (29 [22-45] vs 25 [20-29] hours, $P=.15$) and toxicity incidence (13% vs 4%, $P=1$) were similar between groups. **Conclusions:** This study identified a VAN AUC threshold of <329 to be predictive of clinical failure in patients with streptococcal bacteremia which should be interpreted as hypothesis-generating. Studies evaluating VAN AUC-based monitoring for streptococcal bloodstream infections along with other infection types are needed before implementation into clinical practice can be recommended.

Keywords
anti-infectives, infectious diseases, monitoring drug therapy, pharmacokinetics

Introduction

Multidrug resistant *Streptococcus pneumoniae* is among the organisms listed in the Centers for Disease Control and Prevention's 2019 serious threats, with an estimated 6000 deaths and 150 000 hospitalizations annually.[1] Vancomycin (VAN) is an efficacious therapy against certain streptococcal strains and can be useful in the treatment of serious streptococcal infections in the setting of beta-lactam resistance and/or severe beta-lactam allergies.[2,3] Streptococcal infections have an overall low prevalence of positive follow-up blood cultures, but infections leading to positive follow-up blood cultures have been shown to require longer durations of antibiotic treatment.[4] Unfortunately, prolonged VAN courses confer an increased risk of nephrotoxicity.[5]

Pharmacokinetic/pharmacodynamic monitoring of VAN using the area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio is now the preferred monitoring approach to prevent nephrotoxicity and ensure clinical efficacy in serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[6] This raises the question as to whether utilizing VAN AUC/MIC monitoring in the treatment of other bacterial pathogens would reap the same benefits. With that said, VAN AUC/MIC monitoring is being investigated but is not yet well elucidated with other bacterial pathogens.[7,8] One study found VAN AUC/MIC <389 to predict 30-day mortality in patients with enterococcal bacteremia, while others have failed to replicate this association.[7,8]

To our knowledge, no studies to date have examined the relationship between VAN AUC and clinical failure in streptococcal bacteremia. The goal of our study is to elucidate if such a relationship exists, and if so, to identify the specific VAN AUC threshold predictive of clinical failure in patients with streptococcal bacteremia.

Materials and methods

A retrospective cross-sectional study was completed at The Ohio State University Wexner Medical Center (OSUWMC)

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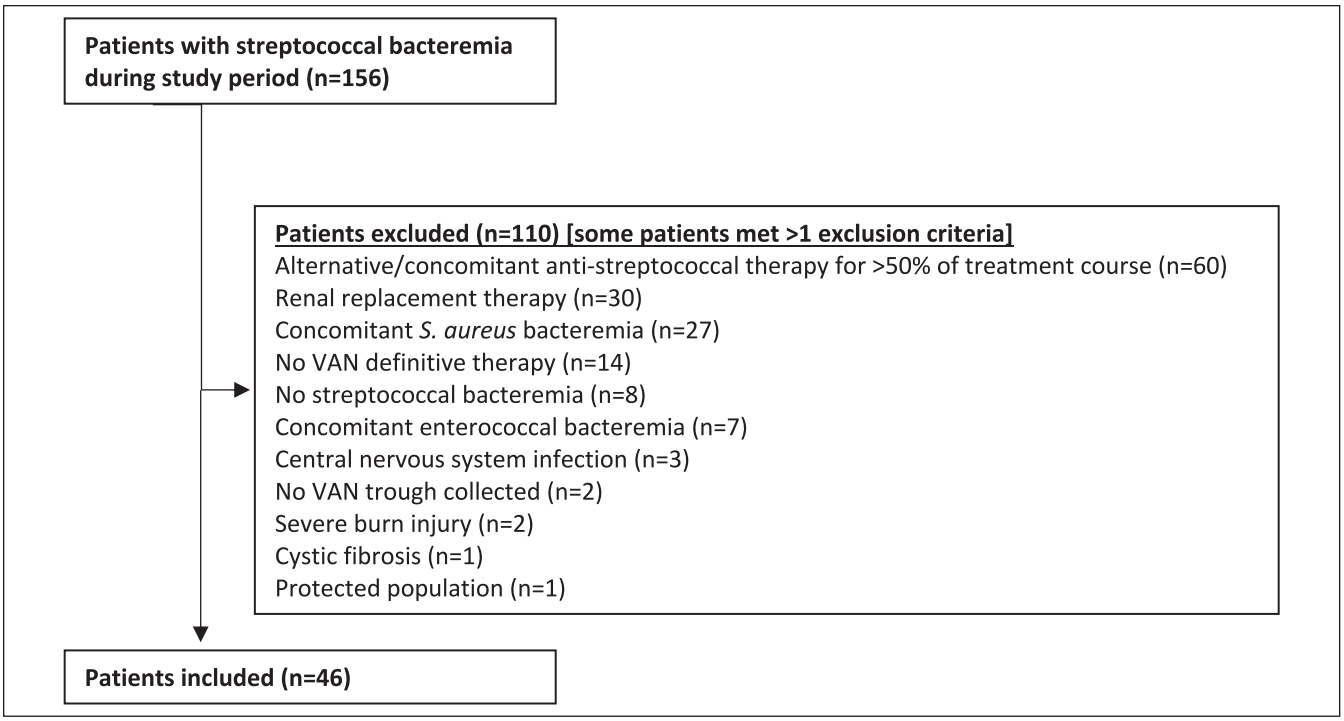

Figure 1. Streptococcal bacteremia patient screening for study inclusion.

inpatient facilities (Columbus, OH). Hospitalized adult patients with streptococcal bacteremia treated with VAN definitive therapy from January 1, 2011 to September 30, 2021 were screened for study inclusion. Patients were excluded if they were considered a protected population (i.e., those <18 and >89 years old, inmates, and pregnant patients), received alternative or concomitant anti-streptococcal therapy for more than 50% of their treatment course, or had concomitant *Staphylococcus aureus* or *Enterococcus* spp. bacteremia. Patient populations who did not qualify for Bayesian calculations were also excluded, including those who did not have a VAN trough collected, received renal replacement therapy, cystic fibrosis, severe burn injury, or central nervous system infection (Figure 1).

Demographic information collected included age, gender, intensive care unit (ICU) admission, ICU length of stay, injection drug use, baseline serum creatinine (SCr) (defined as SCr on the day of VAN initiation), Charlson Comorbidity Index, known human immunodeficiency virus (HIV), and immunosuppression (i.e., active chemotherapy, ≥20 mg of prednisone equivalents for ≥2 weeks, bone marrow or organ transplantation, immune deficiency, or CD4 count <200). Charlson Comorbidity Index scoring was calculated as previously defined.[9] Clinical characteristics collected included the presence of a positive blood culture with *Streptococcus* spp. and date of culture clearance (blood cultures are usually collected daily in bacteremic patients at OSUWMC); other microorganism(s) identified in blood during index admission and blood culture collection date; *Streptococcus* VAN MIC; bacteremia source; presence of infective endocarditis; nephrotoxic agents given concurrently and/or within 72 hours of VAN initiation; Pitt bacteremia score; VAN dose, frequency, and duration (days); and initial VAN trough concentration at steady state (i.e., before the fourth or later VAN dose), which at OSUWMC is reviewed by a pharmacist per a standardized dosing and monitoring protocol. Nephrotoxic agents included aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs), and iodinated contrast. Pitt bacteremia score components were included as previously outlined in the literature and collected 48 hours before or on the day of positive blood culture collection.[10,11]

The primary outcome was treatment failure, defined as a composite of recurrent bacteremia with *Streptococcus* spp., persistent streptococcal bacteremia, 60-day all-cause readmission, or 60-day all-cause mortality. Sixty-day all-cause readmission was assessed within 60 days of hospital discharge while 60-day mortality was measured from the date of initial positive blood culture collection. Persistent bacteremia was defined as a positive blood culture collected ≥24 hours from initial positive blood culture collection. Bacteremia recurrence was defined as a positive blood culture collected ≥72 hours from collection of a negative blood culture.

Secondary outcomes included time to bacteremia clearance, hospital length of stay, and nephrotoxicity. Nephrotoxicity was defined as a SCr ≥1.5x baseline or increase in SCr ≥0.3 mg/dL throughout the entirety of vancomycin therapy per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[12]

Streptococci were identified to the genus and/or species level from positive blood cultures using the VERIGENE® Gram-Positive Blood Culture (BC-GP) system (Luminex) and/or matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry (Bruker). VAN susceptibility testing was performed using the MicroScan WalkAway (Beckman Coulter) or VITEK 2 (bioMérieux) systems. VAN AUC was calculated retrospectively using Bayesian software (ClinCalc LLC) by inputting the first VAN trough.[13] VAN AUC/MIC was then calculated using the Bayesian software output and isolate specific MIC values.

Demographic and clinical information was analyzed using descriptive statistics. Continuous variables were assessed using the Student's *t*-test or Wilcoxon rank sum test to determine statistical significance. Categorical variables were analyzed using the chi-square or Fisher's exact test, based on sample size. All tests were performed at the $P \leq .05$ significance level.

Classification and regression tree analysis (CART) was conducted to identify the VAN AUC threshold for predicting clinical failure in patients treated with VAN for streptococcal bacteremia. A secondary CART analysis on VAN AUC/MIC was also completed. All statistical analyses were performed using SAS Statistical software, version 9.3 (SAS Institute, Cary, North Carolina).

Results

One-hundred fifty six patients with streptococcal bacteremia were identified during the study timeframe. Of these, 110 patients were excluded, most commonly for concomitant anti-streptococcal therapy for >50% of treatment course, followed by renal replacement therapy, and concomitant *S. aureus* bacteremia (Figure 1). Therefore, 46 patients were included in the analysis.

Overall 20 patients (41.7%) met the composite outcome of clinical failure. A CART analysis identified a VAN AUC threshold of 329 to be predictive of clinical failure. Eight of 11 (73%) patients with a VAN AUC <329 experienced clinical failure while 12 of 35 (34%) patients with a VAN AUC ≥329 experienced clinical failure ($P = .04$). Of the 20 patients experiencing clinical failure, 18 (90%) had 60-day readmission while 2 (10%) experienced 60-day mortality. Only 1 patient had infection-related 60-day readmission.

When comparing patients stratified by the VAN AUC threshold of 329, no significant differences in baseline or clinical characteristics were identified except bacteremia source (Table 1). Of the patients who were immunosuppressed, 11 (92%) patients were undergoing chemotherapy while 3 (25%) patients had a bone marrow or organ transplant in the past year. Nephrotoxic agents given during VAN therapy were primarily iodinated contrast (n = 28, 74%), followed by NSAIDS (n = 26, 68%) and aminoglycosides (n = 5, 13%).

Causative *Streptococcus* spp. identified did not differ between groups ($P = .870$). Viridans group streptococci were the most common species identified (n = 34, 74%), followed by *S. agalactiae* (n = 6, 13%), and *S. bovis* (n = 2, 4%). Seven (15%) patients had more than 1 *Streptococcus* spp. identified.

VAN characteristics are summarized in Table 2. Doses of VAN ranged from 500 to 2000 mg at frequencies of every 12, 24, or 48 hours. Initial steady state trough concentrations were significantly higher in the AUC ≥ 329 group (13.2 µg/mL vs 6.2 µg/mL, $P < .001$).The VAN MIC distribution was similar between the groups and ranged from 0.25 to 1 µg/mL for all *Streptococcus* spp. identified. The CART was repeated using VAN AUC/MIC and resulted in a comparable threshold value of 336 with similar outcomes observed when comparing the resulting groups; however, limitations in sample size resulted in a disparate proportion of patients in each group (data not shown).

Regarding secondary outcomes, hospital length of stay was longer in patients with a VAN AUC ≥ 329 (15 [9-22] days vs 8 [7-15] days, $P = .05$). Time to bacteremia clearance (29 [22-45] vs 25 [20-29] hours, $P = .15$) and the incidence of nephrotoxicity during VAN therapy (13 (37%) vs 4 (36%) patients, $P = 1$) were similar between the groups.

Discussion

This study determined that clinical failure was more common in patients with streptococcal bacteremia and VAN AUC <329. This identified AUC threshold predictive of clinical failure was similar to investigated thresholds in prior enterococcal bacteremia literature.[7,8] For example, Jumah et al[7] found a VAN AUC/MIC threshold of 389 predictive of 30-day all-cause mortality, but did not assess other outcomes that could be indicative of treatment failure such as readmission, bacteremia persistence, or recurrence.[7] The clinical failure rate in the present study was higher (40%) but was a composite endpoint including these other clinical variables beyond mortality alone and was driven mostly by all-cause readmissions. This composite outcome could be refined using infection-related readmission rather than all-cause readmission in future larger studies, but was impractical in this case given that it only occurred in 1 patient. When comparing mortality reported by Jumah et al to the present study, the rates were similar (17.5% vs 10%). The population included by Jumah et al had a similar PITT bacteremia score, ICU length of stay, nephrotoxicity rates, and vancomycin MIC values when compared to this study's patient population. Of note, at OSUWMC MIC values were determined via Microscan or VITEK, both of which can over- or underestimate MIC values by 1 dilution. Although broth microdilution may be preferred for determining precise MIC values, this methodology is impractical for many institutions and the MICs reported in this study are reflective of typical Streptococcal

Table 1. Baseline and Clinical Characteristics Stratified by VAN AUC.

Characteristic	Higher AUC group AUC ≥ 329 (n = 35)	Lower AUC group AUC < 329 (n = 11)	*P*-value
Age, years	52 [38-62]	62 [48-69]	.24
Male	15 (43)	6 (55)	.5
Skilled nursing facility/long term assisted care	2 (6)	0 (0)	1
Home	33 (94)	11 (100)	
Injection drug use	10 (29)	0 (0)	.09
Immunosuppressed	8 (23)	4 (36)	.44
Charlson Comorbidity Index	3 [2-5.5]	2.5 [2-3]	.18
Baseline SCr	0.77 [0.62-0.99]	0.74 [0.53-0.95]	.37
Peak SCr during VAN	0.99 [0.84-1.31]	0.95 [0.66-1.33]	.41
Concurrent nephrotoxin(s)	30 (86)	8 (73)	.37
Bacteremia source			.01
Line/tube/drain	9 (26)	3 (27)	
Mouth/oropharyngeal	8 (23)	0 (0)	
Bone/joint	7 (20)	1 (9)	
Infective endocarditis	7 (20)	0 (0)	
Skin/soft tissue	2 (6)	3 (27)	
Unknown	2 (6)	4 (36)	
Other	1 (3)	0 (0)	
Pitt bacteremia score	2 [0-2]	1 [0-2]	.20
ICU admission (days)	4 (11)	3 (27)	.33
ICU length of stay (days)	2.5 [1.5-15]	3 [3-4]	.46

Note. Data are presented as number (%) or median [IQR] as appropriate. SCr = serum creatinine; VAN = vancomycin; ICU = intensive care unit.

Table 2. Vancomycin Treatment Details Stratified by VAN AUC.

Characteristic	Higher AUC group AUC ≥ 329 (n = 35)	Lower AUC group AUC < 329 (n = 11)	*P*-value
Streptococcus VAN MIC			.23
0.25	2 (6)	0 (0)	
0.5	28 (80)	7 (64)	
1	5 (14)	4 (36)	
Inpatient VAN duration of therapy (days)	9 [5-15]	6 [5-8]	.08
Total VAN duration of therapy (days)	21 [14-42]	15 [15-43]	.74
Total initial steady state VAN trough (μg/mL)	13.2 [11.3-19]	6.2 [5.6-9]	<.0001
Initial steady state VAN trough by therapeutic range (μg/mL)	13.2 [11.3-19]	6.3 [5.6-9]	<.0004
<10	6 (17)	9 (82)	
10-20	22 (63)	2 (18)	
>20	7 (20)	0 (0)	

Note. Data are presented as number (%) or median [IQR] as appropriate. VAN = vancomycin; AUC = area under the curve.

MIC distribution.[2] Additionally, the VAN AUC thresholds reported in these studies are lower than the 400 to 600 target previously identified for optimal efficacy and safety in the management of MRSA bacteremia.[6,14-15] The lower VAN AUC breakpoint predictive of clinical failure with *Enterococcus* spp. and *Streptococcus* spp. may be explained in part due to reduced virulence mechanisms of these organisms in comparison to MRSA.

At the AUC breakpoint identified in this study, there was no difference in the incidence of nephrotoxicity which may be attributable in part to the lower VAN troughs targeted for Streptococcal bacteremia. The rate of nephrotoxicity in this study was comparable to the enterococcal bacteremia study by Nakakura et al[8] and colleagues that found a similar VAN AUC threshold. This is in contrast to MRSA bacteremia and VAN AUC literature identifying an increased risk of nephrotoxicity at higher AUC values.[15,16] For example, Poston-Blahnik and Moenster found a VAN AUC ≥550 to be an independent risk factor for experiencing acute kidney injury.[15]

Of note, hospital length of stay was longer in the higher AUC group in the present study. Other similar studies did not report this variable so it is unknown whether this finding is unique to this study or would have been comparable to others. Contributory factors may have included the numerically higher incidence of patients discharged to a skilled nursing facility and IV drug users, both of which can cause placement issues thereby extending the hospital length of stay.

Another noteworthy observation is that the majority of patients in the VAN AUC <329 group had a VAN trough <10 µg/mL. Past studies regarding MRSA bacteremia have failed to demonstrate a correlation between VAN trough and AUC.[16] Furthermore, VAN troughs have not been shown to correlate with clinical outcomes in patients with severe MRSA infections.[17] Therefore, the authors believe it is unlikely that low VAN troughs in the absence of low VAN AUC explain the clinical outcomes observed in the low AUC group of this streptococcal bacteremia study.

There are many limitations of this study. First, the sample size was limited by the observed population meeting inclusion criteria during the study timeframe. With that said, previous studies evaluating enterococcal bacteremia and VAN AUC had similar sample sizes to the present study.[7,8] Second, included patients were allowed to receive concomitant antistreptococcal therapy as long as it was not continued for more than half of their treatment course as this is reflective of real-world clinical practice; however, this could have impacted clinical outcomes in the affected patients. Nephrotoxic agent collection was limited to 3 and could have underestimated overall prevalence. Third, VAN AUC values were calculated using the first steady state trough and therefore did not necessarily reflect the VAN AUC at goal concentrations. It is unknown whether the use of later VAN AUC values would alter the results of the CART analysis. Fourth, data collection was limited to OSUWMC electronic medical records, so readmissions to or antimicrobials received at outside facilities were not captured. Next, given the retrospective nature of the study, patients with no documented infection source were recorded as having an unknown source which happened to occur more frequently in patients with clinical failure. Additionally, source control was not collected which could have impacted clinical outcomes. Lastly, the composite primary outcome was largely driven by 60-day all-cause readmission which in some cases may not have been infection-related, therefore, utilization of infection-related 60-day readmission could be used in future larger studies to refine the methodology.

Conclusion

This study identified a VAN AUC threshold of <329 to be predictive of clinical failure in patients with streptococcal bacteremia which should be interpreted as hypothesis-generating. The composite endpoint was driven largely by 60-day readmission, and as such, future larger studies including other endpoints could be valuable. Additionally, studies evaluating VAN AUC-based monitoring for streptococcal bloodstream infections along with other infection types are needed before implementation into clinical practice can be recommended.

Declaration of Conflicting Interests

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