**Impact of Area Under the Concentration-Time Curve-Based Vancomycin Dosing on Efficacy and Safety in Patients with Methicillin-resistant *Staphylococcus aureus* Bacteremia**

**Keywords:** vancomycin, *Staphylococcus aureus*, bacteremia, AUC

**Running Title**: Vancomycin Trough vs AUC in MRSA bacteremia

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**Abstract:**

Background: The optimal strategy for dosing and monitoring vancomycin continues to evolve. A vancomycin 24-hour steady-state area under the concentration-time curve/minimum inhibitory concentration (AUC/MIC) of ≥ 400 has been associated with positive clinical outcomes, while an AUC/MIC > 600-700 has been associated with increased risk of nephrotoxicity. The 2009 vancomycin dosing guidelines recommended target trough concentrations between 10-20 mcg/mL depending on infection; however, recent pharmacokinetic data suggest that most patients can achieve target AUC/MIC with trough concentrations < 15 mcg/mL. While existing literature has demonstrated reduced nephrotoxicity with AUC-guided dosing, there are limited data evaluating efficacy and other clinical outcomes. Therefore, this study compared the clinical efficacy of vancomycin using trough-guided (TGD) versus AUC-guided dosing (AGD) in patients with confirmed methicillin-resistant *Staphylococcus aureus* bacteremia.

Methods: This was a retrospective, observational, quasi-experimental, non-inferiority study of adult patients who received vancomycin for treatment of MRSA bacteremia. Patients with central nervous system infections, weighing > 200 kg, with acute kidney injury, or receiving hemodialysis/continuous renal replacement therapy were excluded. The primary outcome was microbiological success defined as negative blood cultures within 7 days of vancomycin initiation. Secondary outcomes included achievement of therapeutic target concentrations and incidence of nephrotoxicity.

Results: Microbiological success was achieved in 52/55 (95%) patients with TGD versus 50/51 (98%) patients with AGD (*P* = 0.619). In the TGD group, 24/55 (44%) patients achieved therapeutic target concentrations within 48 hours of initiation of vancomycin compared to 24/51 (47%) patients in the AGD group (*P* = 0.723). The median hospital length of stay was longer in the TGD group compared to the AGD group (16 days, IQR 11-27 days versus 13 days, IQR 9-24 days, respectively, P = 0.260). Nephrotoxicity occurred in 7/55 (13%) TGD patients versus 5/51 (10%) AGD patients during vancomycin therapy (*P* = 0.763).

Conclusions: AUC-guided dosing was non-inferior to trough-guided dosing at achieving microbiological success in patients with MRSA bacteremia and may lead to shorter lengths of hospital stay and lower rates of nephrotoxicity.

**BACKGROUND**

Vancomycin remains a mainstay of therapy for serious gram-positive infections, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Despite the longstanding widespread clinical use of vancomycin, the optimal strategy for dosing and monitoring remains controversial and continues to evolve. The first consensus guideline for therapeutic monitoring of vancomycin published in 2009 endorsed a 24-hour steady-state area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) ratio ≥ 400 as the primary pharmacokinetic/pharmacodynamic (PK/PD) predictor of efficacy in infections due to MRSA. The guideline recommended targeting serum trough concentrations of 15-20 mcg/mL in certain infections as a surrogate marker to achieve optimal AUC/MIC if the MIC was ≤ 1 mcg/mL in patients with normal renal function.1 These recommendations were primarily based on expert opinion and became common practice for the treatment of serious, invasive MRSA infections.2,3

Since publication of the 2009 guidelines, several studies have investigated the impact of these recommendations on the efficacy and safety of vancomycin. Vancomycin trough concentrations > 15 mcg/mL have been associated with increased nephrotoxicity, and recent pharmacokinetic data suggest most patients can achieve a target vancomycin AUC/MIC with trough concentrations < 15 mcg/mL.4-7 An AUC/MIC ≥ 400 has been associated with positive clinical outcomes, while an AUC/MIC > 600-700 has been associated with increased risk of nephrotoxicity. Thus, targeting vancomycin trough concentrations of 15-20 mcg/mL as previously recommended by the guidelines may result in unnecessary excess drug exposure and increased risk of nephrotoxicity. Based on emerging data supporting AUC-based dosing and the availability of new computer software programs (Bayesian modeling) that facilitate the calculation of an AUC, the 2020 vancomycin therapeutic drug guidelines now advocate an AUC/MIC target of 400-600.8

Two approaches for accurately estimating vancomycin AUC are described in the literature. The Bayesian model utilizes a computer software program to estimate the vancomycin AUC using probability distribution and minimal patient-specific PK sampling (e.g., a single non steady state concentration). The trapezoidal rule employs calculations using steady-state post-distribution peak and trough vancomycin concentrations to estimate the AUC.9 Studies employing these methods for vancomycin AUC estimation have demonstrated less nephrotoxicity and improved achievement of therapeutic target concentrations when compared to trough-based dosing; however, none of these studies evaluated efficacy outcomes.5-7 Therefore, the purpose of this observational study was to compare the clinical efficacy and safety of vancomycin using trough-guided versus AUC-guided dosing using the trapezoidal rule in patients with confirmed MRSA bacteremia.

**METHODS**

This was a single-center, retrospective, observational, quasi-experimental, non-inferiority study conducted at Eskenazi Health, a 333-bed safety-net, tertiary care, teaching hospital where vancomycin dosing is performed using a pharmacy-to-dose protocol. The original vancomycin pharmacy-to-dose protocol was based on trough-guided dosing but transitioned to AUC-guided dosing using the trapezoidal rule on October 14, 2019. The pre-implementation trough-guided dosing group (TGD) consisted of patients that were initiated on vancomycin using the trough-based dosing strategy between October 1, 2016 and September 30, 2018. The post-implementation AUC-guided dosing group (AGD) consisted of patients who were initiated on vancomycin using the AUC-based dosing strategy between October 14, 2019 and November 30, 2021. The date range selected for the pre-implementation group does not immediately precede the date range for the post-implementation group because some pharmacists were employing more conservative dosing based on available literature (targeting troughs <15 mcg/mL for gram positive infections caused by organisms other than MRSA) prior to the institution officially switching from trough-based dosing to AUC-based dosing. Therefore, the research team purposely included a washout period of one year between groups to minimize the impact on study results.

The pharmacy-to-dose protocol recommended an initial loading dose of 20 mg/kg followed by a maintenance dose of 15 to 20 mg/kg with a dosing interval selected based on the patient’s renal function and target serum concentrations or AUC/MIC ratio. For patients weighing ≤ 120 kg, actual body weight (ABW) was used to calculate the doses. For patients weighing >120 kg to 150 kg, a maintenance dose of 15 mg/kg based on the patient’s total body weight (TBW) was used. For patients >150 kg, a 3000 mg one time loading dose with 2 post-distribution serum concentrations were performed to determine subsequent dosing. In the TGD group, dosing regimens were adjusted to maintain a therapeutic target trough concentrations of 10-20 mcg/mL based on clinical indication, with trough concentrations of 15-20 mcg/mL recommended for patients with endocarditis, osteomyelitis, meningitis, and pneumonia. In the AGD, dosing regimens were adjusted to achieve a therapeutic target AUC/MIC of 400-600.

Hospitalized patients aged 18 years or older who received intravenous (IV) vancomycin for the treatment of MRSA bacteremia and had a minimum of one steady-state vancomycin trough concentration (TGD) or one set of steady-state vancomycin peak and trough concentrations (AGD) were included in the analysis. Patients were excluded from the study if they had an initial dosing interval greater than every 48 hours, were receiving continuous renal replacement therapy (CRRT) or intermittent hemodialysis (HD), were experiencing acute kidney injury (AKI) defined as an increase in serum creatinine (SCr) ≥ 0.5 mg/dL from baseline within 48 hours of the initiation of vancomycin and/or an increase by ≥ 50% from baseline, or weighed > 200 kg. Additional exclusion criteria included treatment of suspected or known central nervous system infection, vascular graft infection, infection due to MRSA with vancomycin MIC ≥ 2 mcg/mL, past medical history of cystic fibrosis, and administration of vancomycin by continuous infusion.

The primary outcome was microbiological success defined as the achievement of negative blood cultures within 7 days of vancomycin initiation. Microbiological failure was defined as persistently positive blood cultures on vancomycin therapy 7 days after the first positive blood culture or 7 days after achieving adequate source control, whichever occurred later. Infections that generally did not require additional intervention outside of antibiotic treatment to achieve adequate source control (e.g., pneumonia, cellulitis) were categorized as achieving source control, while those patients with infections requiring source control (e.g., abscesses prosthetic joint infections, etc.) that were not suitable surgical candidates were classified as not achieving source control.

Secondary outcomes included the number of patients who achieved therapeutic vancomycin concentrations with the first set of steady-state vancomycin serum concentrations (TGD: trough goal 10-20 mcg/mL; AGD: AUC/MIC goal 400-600), daily vancomycin dose, duration of vancomycin therapy (included total planned duration of vancomycin course inclusive of outpatient administration of antibiotics following discharge), the incidence of nephrotoxicity defined as an increase in SCr by ≥ 0.5 mg/dL from baseline or an increase by ≥ 50% of baseline SCr on two consecutive measurements that can be reasonably attributed to vancomycin (received minimum of 48 hours of vancomycin therapy)1, hospital length of stay, 30-day infection-related hospital readmission, and all-cause in-hospital mortality.

**Statistical Analyses**

Categorical variables were presented as the number of cases with corresponding percentages, and continuous variables were presented as the mean and standard deviation (SD) or median and interquartile range (IQR), depending on normality. Normality was assessed using the Anderson-Darling test. The primary outcome of microbiologic success was analyzed using the Chi-square test. Secondary outcomes were analyzed using Fisher’s Exact test or Chi-square test for nominal data, and 2-sample t-test (parametric data) or Mann-Whitney U test (nonparametric data) for continuous data. All statistical tests were performed using Minitab® 18 statistical software (Minitab LLC, State College, PA).

Lodise et al10 reported a 40% failure rate (60% success rate) in patients not achieving the target AUC/MIC exposure in the treatment of MRSA bacteremia, and a 20-25% treatment failure rate with achievement of exposure values above the CART-derived AUC/MIC threshold. Therefore, the anticipated success rate of vancomycin therapy for MRSA bacteremia using AGD was set at 75%, while the success rate in patients not achieving the target AUC/MIC exposure (the TGD group) was set at 60%. When applied to sample size calculation, this translated to a needed sample size of 152 patients in each group (304 patients total) to detect a 15% difference, with an anticipated success rate of 75% in the AGD group and 60% in the TGD group, based on an 80% power calculation. The research study was approved by the Indiana University Institutional Review Board.

**RESULTS**

Of the 207 patients who received IV vancomycin for MRSA bacteremia during the study period, 101 patients were excluded for the following reasons: 50 with AKI prior to vancomycin initiation, 36 receiving HD, 9 receiving CRRT, 3 weighing >200 kg, 2 with CNS infections, and 1 with vancomycin MIC ≥ 2 mcg/mL. For data analysis, the study cohort was comprised of 106 patients, 55 and 51 patients in the TGD and AGD groups, respectively.

Overall baseline characteristics were similar between groups (Table 1). More patients in the TGD group had Charlson Comorbidity Index scores ≥ 4 (17/55, 31%) compared to patients in the AGD group (7/51, 14%) (*P* = 0.029); however, the number of patients with APACHE II scores ≥ 20 (0/55, 0% TGD versus 3/51, 6% AGD, respectively, *P*  = 0.108) and Pitt Bacteremia scores ≥ 4 (3/55, 5% TGD versus 3/51, 6%, respectively, *P* = 1.0) were similar. In addition, 13/55 (24%) TGD patients required initial ICU management compared to 8/51 (16%) AGD patients (*P* = 0.3). Most of the patients in both groups had skin and soft tissue infections, while endocarditis was more common in AGD patients (13/51, 26%) compared to TGD patients (5/55, 9%) (*P* = 0.037). More patients in the TGD achieved source control compared to the AGD group. (41/55, 75% versus 31/51, 61%, respectively, *P* = 0.127). There were similar numbers of patients on concomitant nephrotoxic agents in the TGD group (49/55, 89%) and AGD group (44/51, 86%) (*P* = 0.660) with iodinated contrast and piperacillin/tazobactam being the most common.

**Primary Outcome**

Microbiologic success was achieved in 52/55 (95%) TGD patients compared to 50/51 (98%) AGD patients (*P* = 0.619) (Table 2). Time to first negative blood culture was similar between groups with a median of 3 days (IQR 2-5 days, *P* = 0.592).

**Secondary Outcomes**

Secondary outcomes data are listed in Table 2. Initial steady state vancomycin therapeutic targets were achieved by 24/55 (44%) TGD patients and 24/51 (47%) AGD patients (*P* = 0.723). The median trough was 11.9 mcg/mL (IQR 7.4-16.3 mcg/mL) in TGD versus 9.8 mcg/mL (IQR 6.6-13 mcg/mL) in the AGD group (*P* = 0.051). The median AUC/MIC was 423 (IQR 355-509) in the AGD group.

The average daily vancomycin dose was 32.9 mg/kg/day and 30.7 mg/kg/day in the TGD and AGD groups, respectively (*P* = 0.267), which corresponded to an average daily vancomycin dose of 2530 mg (TGD) and 2380 mg (AGD). Median duration of vancomycin therapy was 16 days for both groups (IQR 10-30 days for TGD and 10-42 days for AGD, *P* = 0.397). The median hospital length of stay was longer in the TGD group compared to the AGD group (16 days, IQR 11-27 days versus 13 days, IQR 9-24 days, respectively, *P* = 0.260). During vancomycin therapy, 7/55 (13%) TGD patients and 5/51 (10%) AGD patients experienced nephrotoxicity (*P* = 0.763). Rates of 30-day infection-related readmission were 17% (9/55 patients) and 10% (5/51 patients) in the TGD and AGD groups, respectively (*P* = 0.398). One patient receiving TGD died during their hospital stay compared to 2 deaths in the AGD group (*P* = 0.607).

**DISCUSSION**

Both dosing protocols resulted in similarly high rates of microbiological success and number of days to achieve clearance of blood cultures. Three patients in the TGD group and one patient in the AGD experienced microbiological failure. Of the three failures in the TGD group, two patients had endocarditis, and one patient had osteomyelitis. The first steady state trough concentrations in these failures were subtherapeutic, therapeutic, and supratherapeutic, respectively. The one microbiological failure in the AGD group had osteomyelitis with a subtherapeutic AUC/MIC with their first steady state concentrations. None of these failures were associated with in-hospital mortality or 30-day infection-related readmission. Although there were more initial ICU admissions and higher Charlson Comorbidity Index scores in the TGD group, APACHE II and Pitt bacteremia scores were comparable in both groups. In addition, the AGD group had more cases of endocarditis and failure of source control than the TGD group, yet the cure rates were similar and the hospital length of stay was shorter in the AGD group.

The results of this study add to the paucity of evidence evaluating clinical efficacy of AUC-guided dosing of vancomycin. Eads et al. 11 compared the efficacy and safety of IV vancomycin dosing using a trough-based (n=25) versus AUC/MIC-based (n=19) method in a veteran’s affairs hospital. Clinical failure was defined as persistent fever after 48 hours of therapy, deterioration of patient’s condition as assessed by attending physician, or escalation in prescribed antibiotic regimen, while safety was evaluated by the incidence of AKI defined by an acute increase in SCr ≥ 0.3 mg/dL over baseline over 48 hours and RIFLE criteria. Indications for vancomycin therapy included sepsis, pneumonia, osteomyelitis, and abscess. All patients in the study achieved clinical success, while only 2 patients experienced AKI (both in trough-based dosing group). When comparing the results to our study, clinical failure rates were slightly higher in our study, which is likely attributed to differences in clinical failure definition. The higher rate of nephrotoxicity observed in our study may be due to differences in AKI definitions, a larger sample size, and the inclusion of more severe infections

The PROVIDE trial 12 evaluated the impact of targeting vancomycin Bayesian-derived AUC/MIC above and below 650 on treatment failure rates in patients with MRSA bacteremia. Treatment failure was defined as death within 30 days of bacteremia or persistent bacteremia ≥ 7 days after initiation of vancomycin. There was no difference in treatment failure between the groups, but higher vancomycin exposures were associated with higher rates of nephrotoxicity prompting the authors to recommend targeting an AUC/MIC ≤ 515 with an unclear lower limit for the therapeutic range to maximize efficacy and minimize nephrotoxicity.Comparing results of our AGD group to the AUC/MIC < 650 group from the PROVIDE trial, lower rates of treatment failure were noted in our study (2% vs. 15.4%) along with lower rates of nephrotoxicity (9.8% vs. 22.6%). This could be related to the definition used for microbiological failure; we included the same definition of persistent bacteremia ≥ 7 days after vancomycin initiation but also added a caveat of ≥ 7 days from source control. Any patient that had persistent bacteremia 7 days from vancomycin initiation regardless of whether they achieved source control later in the treatment course would have been classified as microbiological failure in the PROVIDE trial. The lower rates of nephrotoxicity in our study might be explained by the high percentage of PROVIDE trial patients with an AUC ≥ 650 (44%) as well as our exclusion of patients with AKI prior to initiation of vancomycin.

Al-Sulaiti et al.13 conducted a randomized controlled trial comparing the clinical and pharmacokinetic outcomes of vancomycin trough-based dosing (target 10-20 mcg/mL) versus peak-trough-based dosing (target trough 10-20 mcg/mL and peak 20-40 mcg/mL) for infections due to Gram positive bacteria (e.g., central nervous system, bacteremia, skin and soft tissue, bone/joint, endocarditis, intra-abdominal). Cure was defined as the absence of signs and symptoms of infection without the need for additional antibiotic treatment and/or negative blood cultures at 5 days after vancomycin initiation. The patients who received vancomycin using peak-trough based dosing were significantly more likely to achieve cure compared to those who received vancomycin using trough-based dosing (23/30, 76.7% vs 17/35, 48.6%, *P* = 0.020). In comparison to our study, higher rates of clinical cure were noted with both dosing strategies in this study likely due to the definition of cure and the inclusion of any infection treated with vancomycin rather than just MRSA bacteremia, which was the focus of our study. In general, these studies evaluating the clinical efficacy of trough- versus AUC-based dosing of vancomycin have varying inclusion criteria and definitions of clinical success making it challenging to compare to our study results.

Several recent studies have compared the incidence of nephrotoxicity in patients receiving vancomycin using trough-guided versus AUC-guided dosing and have found a lower incidence of nephrotoxicity with AUC-guided dosing.5, 7, 14 When comparing nephrotoxicity rates using trough-guided versus AUC-guided vancomycin dosing, Finch et al.5 reported rates of 9.9% vs. 5.4% respectively (*P* = 0.107), and Meng et al.7 reported rates of 11% vs. 9.4%, respectively (*P* = 0.70). Similar to other studies, the patients in the AGD group in our study also experienced a lower rate of nephrotoxicity suggesting a potential benefit; however, the difference was not statistically significant perhaps due to the small sample size. The percentage of patients with nephrotoxicity was higher in our study (TGD 12.7%, AGD 9.8%) and the PROVIDE trial 12 (22.6%) when compared to other studies. One reason for these higher nephrotoxicity rates could be that the PROVIDE trial and our study included only patients with MRSA bacteremia, which may itself increase the risk of acute kidney injury.

For both groups of our study, a high percentage of patients (89% TGD and 86% AGD) received concomitant nephrotoxic agents while on vancomycin therapy including piperacillin/tazobactam, iodinated contrast, loop diuretics, thiazide diuretics, aldosterone antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aminoglycosides, and nonsteroidal anti-inflammatory drugs. A subgroup analysis on the potential contribution of each individual nephrotoxin on the incidence of nephrotoxicity was not performed due to small sample size. Several studies also collected data on concomitant nephrotoxins; however, specific reporting of individual agents was limited making it difficult to directly assess impact of nephrotoxins and compare rates of nephrotoxicity among studies.5, 7, 11, 12

In our study, therapeutic targets were achieved in a higher number of patients who received AGD compared to TGD (47.1% vs 43.6%, *P* = 0.723); however, the difference was not statistically significant in contrast to other studies.6, 7, 11 The achievement of therapeutic targets was higher in the AGD group even though a lower average total daily dose of vancomycin was used in this group (TGD 32.9 mg/kg/day versus AGD 30.7 mg/kg/day; *P* = 0.267). Additionally, in our study, 42% of the first steady-state serum trough concentrations in TGD patients were subtherapeutic compared to 39% in the AGD group (*P* = 0.785). This result was unexpected considering the TGD protocol was often targeting trough concentrations of 15-20 mcg/mL.

No statistically significant differences were noted for any of the outcomes investigated. The strengths of our study include the use of objective clinical outcome data, such as the clearance of blood cultures to determine microbiological success, which sought to eliminate the subjective evaluation of signs and symptoms of infection often included in clinical success definitions. Other strengths of this study include the pragmatic design and real-world application to maximize external validity, excluding AKI prior to vancomycin initiation, limiting inclusion to MRSA bacteremia infections, evaluating the primary outcome of microbiological success using objective data of clearance of blood cultures, and incorporating a washout period of one year leading up to the transition to AGD.

Limitations of this study include small sample size and those inherent to retrospective observational studies including confounding variables and selection bias. This study was performed at a single institution and may not be reproducible or generalizable elsewhere, limiting external validity. However, the beneficial findings of this study (non-inferior efficacy, decreased nephrotoxicity and shortened length of hospital stay) may support the implementation of AGD for vancomycin for those institutions considering the transition to AGD. In addition, evaluation of only first steady-state concentrations is a limitation since population-derived estimates were used for initial vancomycin dosing. The subsequent use of patient-specific pharmacokinetic estimates in the AGD group may result in a more accurate dosing regimen, which may lead to a higher rate of target attainment with subsequent concentrations. Finally, identification of infection-related readmissions was limited to those admissions within the Eskenazi Health system.

A larger, prospective, multicenter study comparing TGD and AGD should be performed to further evaluate the efficacy and safety of TGD versus AGD. In addition, a pharmacoeconomic analysis should also be performed to further evaluate the potential financial benefits of AGD.

**CONCLUSION**

AGD of vancomycin was non-inferior to TGD at achieving microbiological success in patients with MRSA bacteremia and may lead to shorter lengths of hospital stay and lower rates of nephrotoxicity.

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**Table 1.** Baseline Characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| **Demographics** | **TGD (n=55)** | **AGD (n=51)** | ***P* - value** |
| Age [years; median (IQR)] | 52 (38-63) | 45 (35-59) | 0.200 |
| Male sex [n (%)] | 35 (64) | 28 (55) | 0.359 |
| Actual body weight [kg; median (IQR)] | 74 (67-94) | 73 (64-89) | 0.862 |
| BMI [kg/m2; median (IQR)] | 25.7 (21.2-30.0) | 25.5 (22.6-29.9) | 0.533 |
| Baseline SCr [mg/dL; median (IQR)] | 0.70 (0.60-0.87) | 0.70 (0.60-0.90) | 0.717 |
| Vancomycin MIC \*  [mcg/mL; median (IQR)] | 1 (1-1) | 1 (1-1) | 0.463 |
| ID consult ordered [n (%)] | 49 (89) | 49 (96) | 0.273 |
| PWID [n (%)] | 21 (38) | 25 (49) | 0.258 |
| ICU admission [n (%)] | 13 (24) | 8 (16) | 0.300 |
| Concomitant nephrotoxic agents [n (%)]  ACEi/ARB/ARNI  Aldosterone antagonists  Aminoglycosides  Iodinated contrast  Loop diuretics  NSAID  Piperacillin/Tazobactam  Thiazide diuretics | 49 (89)  9 (16)  2 (4)  3 (5)  26 (47)  13 (24)  20 (36)  24 (44)  2 (4) | 44 (86)  10 (20)  0 (0)  3 (6)  27 (53)  7 (14)  24 (47)  17 (33)  2 (4) | 0.660 |
| Apache II score [n (%)]  <20  ≥20 | 55 (100)  0 (0) | 48 (94)  3 (6) | 0.108 |
| Charlson Comorbidity Index score [n (%)]  0-3  ≥4 | 38 (69)  17 (31) | 44 (86)  7 (14) | 0.029 |
| Pitt bacteremia score [n (%)]  <4  ≥4 | 52 (95)  3 (5) | 48 (94)  3 (6) | 1.000 |
| Indication/source of infection [n (%)]  Endocarditis†  Line infection  Osteomyelitis  Pneumonia  Prosthetic device  Septic arthritis  Skin/soft tissue infection | 5 (9)  8 (14)  6 (11)  8 (15)  1 (2)  7 (13)  20 (36) | 13 (26)  1 (2)  8 (15)  7 (14)  2 (4)  3 (6)  17 (33) | >0.050  0.037 |
| Achieved source control [n (%)] | 41 (75) | 31 (61) | 0.127 |

Abbreviations: ACEi – angiotensin-converting enzyme inhibitor; AGD – AUC-guided dosing; ARB – angiotensin receptor blocker; ARNI – angiotensin receptor/neprilysin inhibitor; AUC – area under the concentration-time curve; BMI – body mass index; ICU – Intensive Care Unit; ID – infectious diseases; IQR – interquartile range; MIC – minimum inhibitory concentration; NSAID – non-steroidal anti-inflammatory drug; PWID – persons who inject drugs; SCr – serum creatinine; SD – standard deviation; TGD – trough-guided dosing

\* MIC values derived using Vitek® technology

† Description of valvular involvement – TGD (5 patients – 2 native aortic, 1 native mitral, 2 native tricuspid); AGD (13 patients – 3 native aortic, 1 prosthetic mitral, 1 native pulmonary, 6 native tricuspid, 2 prosthetic tricuspid)

**Table 2.** Outcomes

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **TGD (n=55)** | **AGD (n=51)** | ***P* - value** |
| Microbiological success [n (%)]  Time to first negative culture [days; median (IQR)] | 52 (95)  3 (2-5) | 50 (98)  3 (2-5) | 0.619  0.592 |
| Incidence of nephrotoxicity [n (%)] | 7 (13) | 5 (10) | 0.763 |
| Steady state concentrations  Peak [mcg/mL; median (IQR)]  Trough [mcg/mL; median (IQR)]  AUC [mg\*h/L; median (IQR)] | N/A  11.9 (7.4-16.3)  N/A | 29.0 (24.8-34.4)  9.8 (6.6-13.0)  423 (355-509) | 0.051 |
| Achieved therapeutic target [n (%)] ‡  Subtherapeutic  Supratherapeutic | 24 (44)  23 (42)  8 (14) | 24 (47)  20 (39)  7 (14) | 0.723  0.785  0.904 |
| Daily Vancomycin dose - mg/kg/day [mean ± SD] | 32.9 ± 10.8 | 30.7 ± 9.3 | 0.267 |
| Duration of vancomycin therapy [days; median (IQR)] | 16 (10-30) | 16 (10-42) | 0.397 |
| Length of hospital stay [days; median (IQR)] | 16 (11-27) | 13 (9-24) | 0.260 |
| 30-day infection-related readmission in survivors [n (%)] | 9 (17) | 5 (10) | 0.398 |
| In-hospital mortality [n (%)] | 1 (2) | 2 (4) | 0.607 |

Abbreviations: AGD – AUC-guided dosing; AUC – area under the concentration-time curve; IQR – interquartile range; N/A – not applicable; SD – standard deviation; TGD – trough-guided dosing

‡ Therapeutic target defined as trough within 10-20 mcg/mL for TGD and AUC/MIC within 400-600 mg\*h/L for AGD