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Evaluating Vancomycin Clinical Outcomes Using Area under the Curve versus Trough Based Dosing Strategies

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Abstract

Background: The 2020 consensus guidelines recommend AUC guided dosing as the preferred monitoring method for vancomycin. AUC based dosing has shown to reduce incidence of acute kidney injury (AKI), utilize lower daily doses in obese patients, and maintain efficacy. Several institutions have adjusted their protocols to utilize AUC guided dosing. However, there are limited studies comparing the clinical outcomes of AUC versus trough monitoring. **Methods:** This was a retrospective, observational, single centered study. The primary outcome was to evaluate the clinical success of AUC dosing versus trough based dosing of vancomycin for MRSA infections using a composite outcome of afebrile post treatment (<100.4 for ≥48 hour as defined by the Centers for Disease Control and Prevention), decrease in white blood cell counts (WBC) to baseline, and culture clearance (negative cultures post treatment). Secondary outcomes included occurrence of AKI, number of patients that reached therapeutic goal, time to therapeutic goal, average total levels collected per course, and the average number of dose adjustments per course. **Results:** Forty-seven patients were included in this study, 17 in the AUC group and 30 in the trough group. The primary composite outcome showed a significant benefit of AUC dosing ($p = 0.04$). The composite component culture clearance showed the largest improvement for the AUC group when compared with the trough group ($p = 0.03$). More patients achieved therapeutic target attainment and reached the target sooner (3 days versus 4 days, $p = 0.2$) in the AUC group. Over the study course, 94.1% of patients in the AUC group were considered therapeutic compared to 63.8% in the trough group ($p = 0.03$). Vancomycin levels were collected less frequently in the AUC group (3 versus 4, $p = 0.2$). **Conclusion:** The outcomes of this study may suggest AUC guided dosing as a beneficial alternative to trough based

dosing. AUC based dosing may improve clinical success which can be further explored in larger prospective clinical trials.

Keywords

AUC, MRSA, Pharmacokinetics, Trough Based Dosing, Vancomycin

1. Introduction

Vancomycin is a glycopeptide antibiotic that has been used clinically in the treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA) for more than 61 years. Despite the historical use of this medication, experts now suggest an alternative optimal approach for monitoring vancomycin to optimize therapy while minimizing toxicity. The previous consensus guidelines in 2009 developed by the American Society of Health System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists recommended trough based monitoring (target 15 - 20 mg/L) as a surrogate marker of the AUC:MIC (target 400 mg*hour/L with an MIC up to 1.5 mg/L). However, since the implementation of these recommendations, there have been various reports of exposure related nephrotoxicity when achieving troughs of 15 - 20 mg/L, with no corresponding benefit in terms of efficacy [1] [2] [3] [4] [5]. Additionally, more recent pharmacokinetic/pharmacodynamic data revealed troughs <15 mg/L can achieve the recommended AUC24:MIC target [5]. Lodise *et al*., found a 5% risk of vancomycin induced kidney injury with troughs <10 mg/L compared to 21% with troughs 10 - 15 mg/L, 20% with troughs 15 - 20 mg/L, and 33% with troughs >20 mg/L [4]. Other studies have reported relatively similar risks of AKI with troughs ranging from 10 - 20 mg/L, concluding that targeting a trough concentration of 15 - 20 mg/L may result in unnecessary drug exposure and increase the risk of AKI [6]. The 2020 consensus guidelines recommend AUC based dosing as the preferred monitoring method [7]. Although, a target AUC24:MIC for therapeutic success was established to be 400 - 600 mg*h/L, institution specific guidelines may elect for a higher goal (500 - 600 mg*h/L) for more serious infections involving the central nervous system (CNS) or endocarditis.

Calculating an AUC:MIC ratio for vancomycin can be done by pharmacokinetic calculations after obtaining two levels within the same dosing interval (peak and trough) or it can be predicted using Bayesian Software and a single random level. When Bayesian Software is used, the timing of the level is irrelevant, as the software only needs to know the exact timing of the level in relation to the vancomycin doses. Levels cannot be drawn while vancomycin is infusing. Several Bayesian dose-optimizing software platforms are available and have been validated for clinical use [8] [9].

Numerous studies have shown AUC monitoring as an effective alternative to

trough based dosing in addition to lower therapeutic doses required in obesity [10] [11] [12] [13]. Evidence directly comparing clinical success of both dosing approaches is limited. This study aims to evaluate the clinical success of vancomycin AUC based dosing versus trough based dosing in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

2. Methods

This was a retrospective, observational, single centered study approved by the institutional review board at Mount Sinai Medical Center (MSMC) (FWA00000176). The study was conducted utilizing electronic healthcare records from September 1st, 2021, to October 31st, 2021 and included patients greater than or equal to 18 years of age, hospitalized with a confirmed MRSA infection, and treated with vancomycin. Patients were excluded if vancomycin was used for 72 hours or less, if the vancomycin MIC was greater than 1 mg/L, or if the patient had an acute kidney injury (AKI) at baseline, or were on any dialysis modality at baseline. The primary composite outcome of this study was to evaluate clinical success, which was defined using specific infection improvements measured pre and post treatment. The factors included in the composite were afebrile post treatment (<100.4 for ≥48 hour as defined by the Centers for Disease Control and Prevention), decrease in white blood cell counts (WBC) to baseline, and culture clearance (negative cultures post treatment). Secondary outcomes included occurrence of AKI, number of patients that reached therapeutic goal (therapeutic level attainment), time to therapeutic goal, average total levels collected per course, and the average number of dose adjustments per course. Baseline characteristics that were collected included age, sex, weight, comorbid conditions (diabetes, chronic obstructive pulmonary disease (COPD), CKD, malignancy, human immunodeficiency virus (HIV)), infection source (pneumonia, bacteremia, soft-skin tissue infection, osteomyelitis, central nervous system (CNS), endocarditis, diabetic foot infection, sepsis/septic shock, intra-abdominal infections), and concomitant medications (intensive care unit admission requiring vasopressors, concomitant anti-infectives, and nephrotoxic agents).

Initial levels were collected according to MSMC protocol: trough concentrations were measured at steady state (prior to 4th dose if on a 12 hr regimen, prior to the 3rd dose if on a 24 hr or 48 hr regimen) while AUC was predicted with DoseMeRx Bayesian software after obtaining one random vancomycin level after 2 doses were administered. The clinical pharmacist adjusted the dose to reach a therapeutic goal according to MSMC protocol (trough 10 - 20 mg/L, AUC24 of 400 - 600 mg*h/L, or AUC24 of 500 - 600 mg*h/L for CNS infections). Levels were repeated if the dose was changed to reach therapeutic target attainment or at the discretion of the pharmacist (*i.e.* fluctuating renal function, alteration in clinical status, or clinical judgement).

DoseMeRx predicts the AUC using one of their three models (1 compartment, 2 compartment, or an enhanced obese model). Patients were placed in the pri-

mary 1 compartment model, or into the enhanced obese model if their BMI >/= 35 kg/m^2, or they were greater than 200 kg, or if BMI >/= 30 kg/m^2 and the regression line was a "better fit". DoseMeRx best fit takes into account the serum concentration that aligns closest to the predicted individualized regression line graph. The 2 compartment model is not utilized at MSMC; however, was also available for patients that are assumed to have an altered volume of distribution (*i.e.* septic shock, amputation, etc.) or if the line fit did not correlate with the other models.

3. Statistical Analysis

Baseline demographics were determined using 2-sided Pearson's Chi Square. The primary composite outcome was evaluated using a meta-analysis for correlated proportions. The individual components of the composite primary outcome (afebrile post treatment (<100.4 for ≥48 hour as defined by the Centers for Disease Control and Prevention), decrease in white blood cell counts (WBC) to baseline, and culture clearance (negative cultures post treatment) were assessed with a test of proportions. Overall AKI was measured using Pearson Chi Square and target attainment was tested with Fisher's exact. Kruskal-Wallis ANOVA was used for time to therapeutic goal, number of levels collected, and number of dose adjustments required. All statistical tests were two-tailed, and a P value of less than 0.05 indicated significance.

4. Results

Forty-seven hospitalized patients were enrolled including 17 patients in the AUC group and 30 patients in the trough group (Table 1). Patient characteristics were similar among both groups except for those with COPD and pneumonia, which were more common in the trough group. Baseline renal function was similar among both groups. The majority indication for vancomycin utilization was skin and soft tissue infections (53%) which were more common in the AUC group.

5. Primary Outcome

The primary outcome of clinical success was a composite of variables (Table 2) and was statistically significant = 0.04. However, when examined individually, statistical significance was found only for culture clearance (p = 0.03). Individual components of the AUC versus trough groups for the composite were as follows: leukocytosis resolution was seen in 76.5% of the patients versus 76.7%, febrile resolution after vancomycin use was noted in 17.6% of patients versus 13.3%, and culture clearance 88.2% compared to 56.7%, respectively.

6. Secondary Outcomes

Secondary outcomes are shown in Table 3. Overall, more patients achieved therapeutic target attainment (Figure 1) and reached the goal target level sooner (3 days versus 4 days, p = 0.2) in the AUC group. Over the study course, 94.1% of

patients in the AUC group were considered therapeutic compared to 63.8% in the trough group (p = 0.03). Vancomycin levels were collected less in the AUC group (3 versus 4, p = 0.2) (Figure 2). The number of dose adjustments was similar in each group (Figure 2).

Table 1. Baseline characteristics.

Characteristics		AUC24 (n = 17)	Trough (n = 30)	P-value (98% Confidence Interval)
Demographic	Age (years) (median IQR)	63.5 (61, 66)	71.5 (70, 73)	0.3
	Weight (kg)	76	56	
	Female No. (%)	9 (50)	11 (37)	0.3
Comorbidities	Diabetes (%)	3 (17)	5 (17)	0.9
	COPD (%)	0	7 (23)	0.03
	CKD (%)	2 (11)	2 (7)	0.5
	Malignancy (%)	3 (17)	3 (10)	0.5
	HIV (%)	3 (17)	3 (10)	0.5
	Pneumonia	1	10	0.03
	Bloodstream	3	6	0.8
	Soft skin and tissue	9	7	0.04
	Osteomyelitis	2	6	0.5
	Central nervous system (CNS)	0	0	
	Endocarditis	0	0	
	Diabetic foot	1	0	0.2
	Septic shock	0	1	0.2
	Intra-abdominal	1	0	0.2
Medications	ICU/Vasopressor prior vancomycin (%)	2 (11.8)	4 (13.3)	0.5
	ICU/Vasopressor post vancomycin (%)	2 (12)	1 (3)	0.3
	Concomitant anti-infectives (%)	16 (89)	22 (73)	0.08
	Concomitant nephrotoxic agent (%)	12 (67)	21 (70)	1.0

Table 2. Primary outcome.

Primary Outcome	AUC	Trough	P-value
Primary Composite	31/51 (60.8)	44/90 (48.9)	0.04
Leukocytosis resolution	13/17(76.5%)	23/30(76.7%)	1.0
Fever resolution	3/17 (17.6%)	4/30 (13.3%)	0.7
Culture clearance	15/17 (88.2%)	17/30 (56.7%)	0.03

Table 3. Secondary outcomes.

Secondary Outcomes	AUC (n = 17)	Trough (n = 30)	P-value
Acute Kidney Injury	6/17 (35.3%)	8/30 (26.7%)	0.5
Therapeutic level attainment	16 (94.1%)	17 (63.8%)	0.03
Time to Therapeutic Goal	4 days	5 days	0.2
Total levels collected per course	3	4	0.2
Number of dose adjustments per course	2	2	0.4

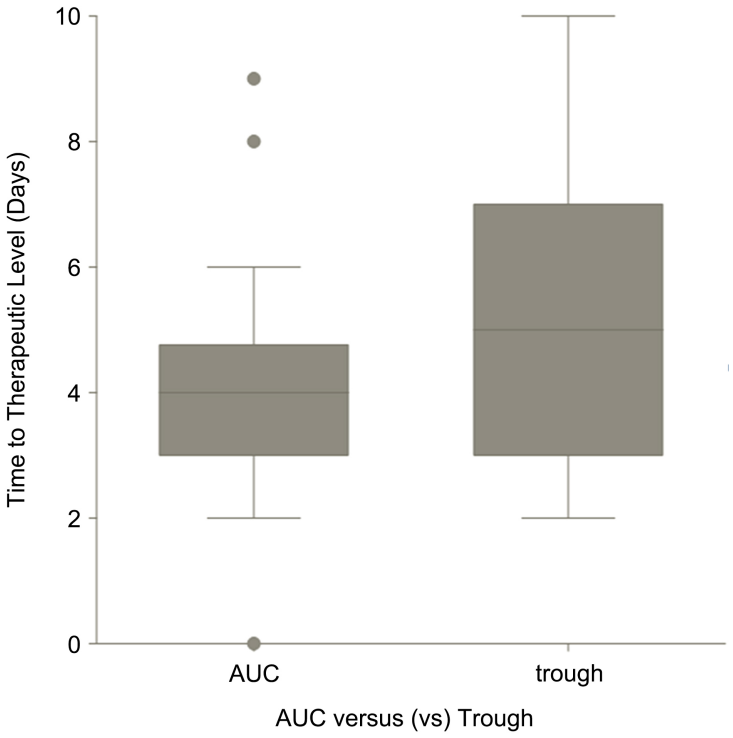

Figure 1. Time to therapeutic level.

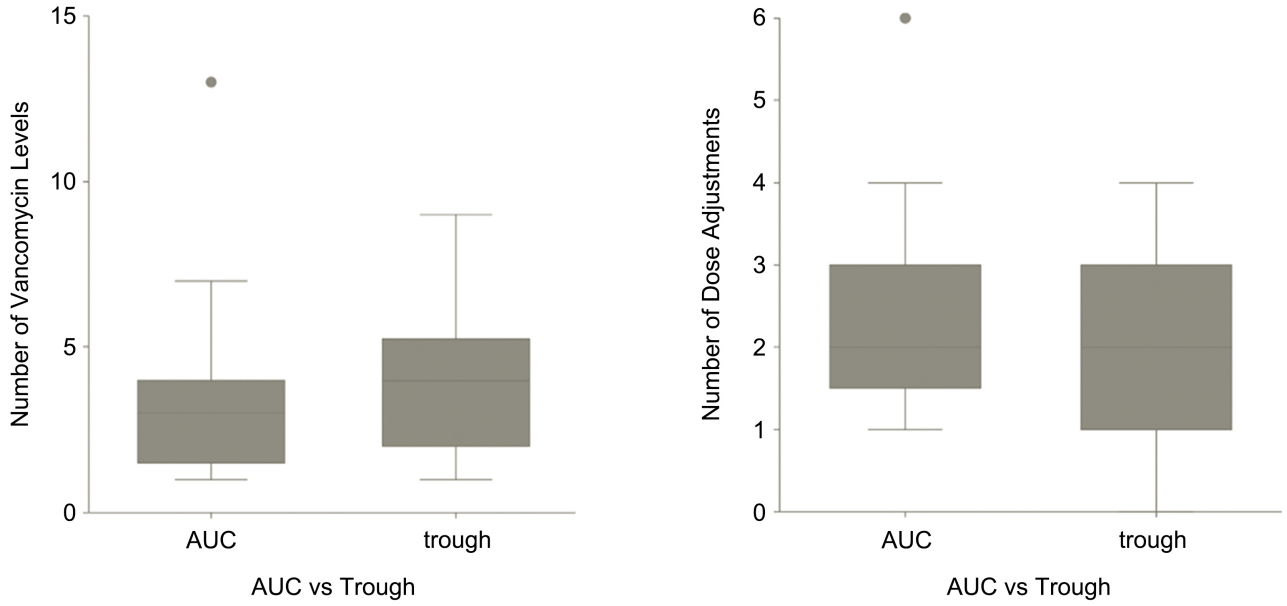

Figure 2. Number of levels acquired and number of dose adjustments.

7. Discussion

The results of this study's primary outcome further suggest that in hospitalized patients with a confirmed MRSA infection treated with vancomycin, the use of AUC monitoring represents a comparable alternative to trough monitoring. From an efficacy standpoint, this study found a statistically significant difference for clinical success with AUC based monitoring in regard to culture clearance. AUC dosing has demonstrated optimal efficacy outcomes in other studies as well [14] [15]. In this study, the primary outcome was comparable to other studies which also monitored culture clearance and symptoms resolution [16] [17] [18]. A systematic review and meta-analysis of 11 studies also assessed primary outcomes of 14-day or 30-day mortality to compare efficacy results [19].

Secondary outcomes revealing more patients achieving therapeutic target attainment in the AUC group has also been found in previously published literature [1]-[8]. This study was not able to accurately assess safety monitoring in terms of AKI, but this has been extensively reviewed throughout other studies [6] [20] [21] [22]. Although the authors in this study did not evaluate cost effectiveness between monitoring strategies, there were less lab draws per course. Data also supports the use of Bayesian software to generate greater cost savings [23].

The implementation of AUC monitoring at MSMC was a lengthy and arduous undertaking. However, the robust collaboration between pharmacy, the Infectious Disease Team, nursing, laboratory, and hospital administration, made this conversion implementation a streamlined process. Results of this study were shared with the Pharmacy & Therapeutics Committee members at MSMC. Further AKI validation was performed shortly after this study, which was followed by the approval of AUC monitoring for all patients with AKI and serum creati-

nine of 3 mg/dL or less at initiation of vancomycin. The new MSMC protocol will continue with trough based monitoring only for patients with serum creatinine > 3 mg/dL or receiving any hemodialysis modality.

The major limitations for the present study are those inherent in a single centered retrospective study and multiple factors which contributed to a small sample size. The DoseMeRx AUC software was a new practice implemented at the time of this study, which limited the sample size. In the future, more data can be collected and analyzed at our institution. Upon implementation, patients with an AKI at baseline when initiating vancomycin were excluded due to the institution's inability to validate recommendations. This further limited the sample size. Nevertheless, beyond the dates of this study, all patients with an AKI were eligible to receive vancomycin with AUC monitoring. Given the variety of infection sources included, the primary outcomes are not specific for each source. Future studies with a larger sample size can classify/distinguish each infection source and the outcome respectively.

8. Conclusion

In this study, AUC based dosing resulted in a statistically significant difference for culture clearance, one component of the composite outcome. This study also found that utilizing AUC guided monitoring leads to faster therapeutic target attainment, more frequently achieved target attainment, and fewer lab draws. These outcomes suggest AUC monitoring might provide a beneficial alternative to trough based monitoring. AUC based dosing may improve patient centered care and limit costs of pharmacokinetic monitoring.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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