Determination of the relationship between vancomycin trough concentrations and the area-under-the-curve/minimum inhibitory concentration (AUC/MIC) dosing

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Rationale: The recently revised guidelines for the therapeutic monitoring of vancomycin recommend targeting an AUC/MIC of 400-600 for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The feasibility of transitioning from trough-based dosing to dosing by AUC/MIC warrants further study as the latter method has been shown to require additional pharmacist training and increased costs secondary to laboratory monitoring and specialty software.

Methods: This was a prospective, non-randomized, single-centre trial conducted over eight months. Adult inpatients receiving vancomycin for greater than three days for the treatment of serious MRSA infections were included in the study. The AUC/MIC was calculated using two-point pharmacokinetic equations from peak and trough concentrations. The primary outcome was to determine the relationship between vancomycin trough concentrations and the AUC/MIC. Secondary objectives were to assess the difference in vancomycin doses and rates of acute kidney injury (AKI) between traditional trough-based dosing and AUC/MIC dosing.

Results: 234 patients received vancomycin over the study period and 32 patients met the inclusion criteria; 36 sets of vancomycin levels were obtained. Sites of infection included skin and soft tissue (31.2%), bacteremia (21.9%), pneumonia (18.8%), osteomyelitis (15.6%) and miscellaneous (12.5%). Vancomycin trough concentrations of 10.8-16.1 mg/L correlated to an AUC/MIC of 400-600 with 95% probability (r^2=0.75). The average total daily doses for trough-based and AUC/MIC dosing were 1590.28 mg and 1281.25 mg, respectively. The mean difference in dose between the two dosing strategies was 309 mg (p=0.179). There were no significant differences in the rates of AKI between trough-based dosing and dosing by AUC/MIC [OR=1.791; 95% CI (0.119,48.048)].

Conclusion: On average, vancomycin trough concentrations of approximately 11-16 mg/L correlated strongly with an AUC/MIC of 400-600, suggesting that adopting the cumbersome and costly strategy of AUC/MIC targeted dosing may be unnecessary, but further study is required. This correlation also suggests that aggressively targeting vancomycin troughs of 15-20 mg/L, as previously recommended, is unwarranted. Average daily doses and rates of AKI did not significantly differ between trough-based dosing and dosing by AUC/MIC.

Background

In 2009, the consensus guidelines for therapeutic monitoring of vancomycin in adult patients recommended that complicated infections with MRSA including bacteremia, pneumonia, meningitis, endocarditis, and osteomyelitis should be treated with vancomycin to maintain a steady-state serum trough level of 15-20 mg/L.[1] Although the area-under-the-curve/minimum inhibitory concentration (AUC/MIC) ratio was identified as the best marker of efficacy for vancomycin against *Staphylococcus aureus* infections including methicillin-resistant strains (MRSA), vancomycin trough concentrations were used a surrogate marker of AUC/MIC as obtaining multiple peak vancomycin concentrations was thought to be difficult to obtain in a clinical setting.[1,2] As a result, trough concentrations of 15-20 mg/L were thought to obtain an AUC/MIC of at least 400.[1]

Vancomycin serum trough concentrations of 15-20 mg/L were believed to be necessary to eradicate MRSA infections. Conversely, maintaining serum vancomycin trough concentrations of less than or equal to 10 mg/L demonstrated the development of resistance to vancomycin.[1] Recent literature has challenged these target concentration ranges; among patients with MRSA bacteremia, those patients with serum vancomycin trough concentrations of 15-20 mg/L had less microbiological success compared to patients with serum trough concentrations of less than 15 mg/L.[3] Additionally, there were greater rates of acute kidney injury (AKI) in those patients with serum trough concentration of 15-20 mg/L compared to patients with serum trough concentrations of less than 15 mg/L.[4]

Current consensus guidelines updated in 2019 for the therapeutic monitoring of vancomycin for serious MRSA infections have revised their recommendations for therapeutic monitoring of vancomycin. The impetus for these changes were the increasing number of studies indicating that vancomycin trough concentrations of 15-20 mg/L did not correlate to an AUC/MIC ≥ 400, were associated with increased rates of nephrotoxicity, and did not correlate with efficacy.[5] These new guidelines now recommend utilizing therapeutic drug monitoring to maintain an AUC/MIC ratio of 400-600 to maximize efficacy and improve patient safety.[5] This AUC/MIC ratio has demonstrated efficacy in the treatment of MRSA bacteremia, lower respiratory tract infections, and osteomyelitis.[2,6,7] Moreover, studies have demonstrated that targeting trough concentrations less than 15-20 mg/L can still provide therapeutic AUC/MIC ≥ 400.[8]

The two primary methods of calculating vancomycin doses based on the AUC/MIC ratio are using Bayesian equations or using two vancomycin levels, pre- and post-infusion concentrations.[5] The Bayesian model relies on generalized population parameters to calculate dose adjustments. The benefit of the Bayesian model is the requirement for only a single trough value to calculate vancomycin AUC and the ability to adapt to changes in the clinical status of patients.[5] Disadvantages of the Bayesian model are the use of population models that may not be reflective of the clinician's patient population, the requirement for expensive software, and the extensive training of pharmacists to utilize this software. Furthermore, the Bayesian model does not calculate an AUC as accurately as using pre- and post- infusion levels and has not been

validated for use with pediatric, obese, or critically ill patients or patients with unstable renal function.[5] Using pre- and post-infusion vancomycin concentrations are simple and can be easily adopted and calculated by common pharmacokinetic equations.[5] However, this method cannot readily adapt to changes in patient status, requires accurate workflow and documentation for precise vancomycin dose calculations and additional nursing and laboratory resources to obtain a post-infusion level.

A recent study conducted in the United States demonstrated that 23% of hospitals with 500-1000 beds have started dosing vancomycin using the AUC/MIC ratio.[9] Thus, the standard of care for vancomycin dosing is shifting towards use of the AUC/MIC ratio and adoption of this method will likely increase with the recent publication of the consensus guidelines. As a result, it is imperative to fully understand the logistics of converting to AUC/MIC monitoring and the relationship between these recommendations to our current dosing strategy of trough-based monitoring. In addition, the potential to characterize and potentially target a trough concentration that correlates to achieving an AUC/MIC ≥ 400 warrants additional study. Furthermore, there is a lack of evidence of utilizing this dosage methodology in patients in Canada. Therefore, the purpose of this study is to determine the relationship between vancomycin trough concentrations and AUC/MIC and the feasibility of adopting therapeutic monitoring of vancomycin by AUC/MIC ratio in a Canadian healthcare setting.

Methods

Study Design

The study was completed as a prospective, non-randomized, single-arm trial. Patients were recruited over an 8 month period from October 2019 to May 2020. Inclusion criteria for the study were adult inpatients with either complicated MRSA infections or MRSA skin and soft tissue infections and were expected to receive a minimum of 3 days of treatment with vancomycin. Patients with cystic fibrosis, admitted to the intensive care unit (ICU), experiencing AKI or unstable renal function within 48 hours of admission or starting treatment with vancomycin, using dialysis or having an allergy to vancomycin were excluded from the study. As the revised guidelines were set to become the standard of practice, informed consent from patients was not deemed to be required for inclusion in the study. The study was approved by the research ethics board at Windsor Regional Hospital.

Data Collection

The investigators collected patient data required for standard therapeutic drug monitoring of vancomycin and patient care including patient demographics, radiographic, laboratory and clinical data. Clinical data included age, height, weight, co-morbidities, allergies, site of infection, culture results, concurrent nephrotoxic medications, concurrent antibiotic regimens, vancomycin regimens including duration, dose, administration times and both peak and trough concentrations and baseline serum creatinine, blood urea nitrogen, white blood cell count, and platelet count. Efficacy and safety were monitored through white

blood cell count, culture results, serum creatinine, platelet count, clinical status of the patient and both vancomycin peak and trough concentrations.

Outcome Measures

The primary objective of this study was to determine the relationship between vancomycin AUC/MIC and trough concentrations. Secondary objectives were to assess the difference in dose and rates of AKI between traditional trough-based dosing and AUC/MIC dosing.

Dosing Strategies

Two sets of investigators were used when dosing patients for vancomycin. The first set of investigators treated patients with vancomycin for confirmed complicated MRSA infections to target steady-state trough concentrations of 15-20 mg/L. Patients with MRSA skin and soft tissue infections were treated to target steady state trough concentrations of 10-15 mg/L. Steady state trough concentrations were obtained within 30-60 minutes before the 4th dose of empiric vancomycin treatment which investigators used to propose doses of vancomycin. The first set of investigators were blinded to the peak concentration until after they proposed their dose.

Vancomycin peak concentrations were then drawn 1-3 hours after the end of infusion to allow for distribution. The second investigator utilized the peak and trough concentrations to calculate the AUC/MIC using 2-point pharmacokinetic equations. See Table 1. The vancomycin regimen was then modified to target an AUC/MIC of 400-600 and provided to the partially blinded first set of investigators for treatment. A comparison of the proposed dose based on the trough concentration and the dose ordered for the patient to target an AUC/MIC of 400-600 was used for the secondary outcome.

Table 1: Pharmacokinetic Equations.

Variable	Equation
Elimination Constant (k_e)	$k_e=\ln(C_1/C_2)/(t_2-t_1)$, where C_1 was the measured peak and C_2 was the measured trough
Half-life ($t_{1/2}$)	$t_{1/2}=0.693/k_e$
Volume of distribution (V_d)	$V_d= Dose*(1- e^{-k*t})/[t*k_e*(C_{max}-(C_{min}- e^{-k*t}))]$
Clearance (CL)	$CL= V_d*k_e$
True Peak Concentration after infusion (C_{max})	$C_{max}=C_1/e^{-k\Delta t}$, where Δt is time between end of infusion and time C_1 was measured
True Trough concentration (C_{min})	$C_{min}= C_{max}(e^{-k*(\tau-t)})$, where τ is the interval (hours) between doses and t is the duration of infusion (hours).
$AUC_{infusion}$	$AUC_{inf}=t*(C_{max} + C_{min})/2$
$AUC_{elimination}$	$AUC_{elim}=(C_{max}- C_{min})/ k_e$
AUC_{24}	$AUC_{24}= (AUC_{inf} + AUC_{elim})* 24/\tau$
Estimated total daily dose (TDD) to achieve AUC_{24}	New TDD= Current TDD* [(AUC_{24} desired)/ (AUC_{24} calculated)]
Predicted steady state C_{max} from new regimen	$C_{max}= [(New dose/(CL*t)]*[(1- e^{-k*t})/(1- e^{-k*\tau})]$

Statistical Analysis

Categorical variables including gender were reported using the total sample and percentage in each category. Continuous variables were reported with the mean, standard deviation and range. The Wilcox's rank sum test was used to compare the total daily doses of trough-based and AUC/MIC-based dosing strategies as the distribution of these doses were not symmetric. A linear regression model was used to determine the relationship between trough concentrations and AUC/MIC with an

estimated interval corresponding to an AUC/MIC of 400-600 estimated using 95% confidence limits for the mean AUC/MIC.

The comparison for rates of AKI in the current study to historical controls was completed using statistical matching. As the occurrence of AKI was not recorded for the historical sample and in order to limit the number of patient files to review for the AKI outcome, statistical matching was completed using based on coarsened exact matching (CEM).

Current study patients and historical controls were matched based on five potential five potential covariates: age, desired vancomycin trough (10-15 mg/L or 15-20 mg/L), total body weight, gender, and estimated creatinine clearance (CrCl). Current study patients and historical controls were divided into classes of estimated creatinine clearance of 20 mL/min and ages of 15 years but matched on gender, and desired vancomycin trough. Each subject in the current sample was matched to a minimum of two subjects in the historical sample. If a study patient was not matched to a historical control they were excluded from this objective.

Results

A total of 234 patients were screened with 32 patients meeting inclusion criteria; 2 patients had 2 sets of vancomycin levels drawn and 1 patient had 3 sets of vancomycin levels drawn for a total of 36 levels drawn. The average age was 67.8 ± 15.0 years, 43.8% were female, average total body weight was 75.9 ± 22.0 kg, and average creatinine clearance was 55.3 ± 28.3mL/min. Sites of infection included skin and soft tissues (31.2%), bacteremia (21.9%), pneumonia (18.8%), osteomyelitis (15.6%), and miscellaneous (12.5%). See Table 2.

Relationship between trough and AUC/MIC:

A linear relationship between trough concentrations and the AUC/MIC was demonstrated with a strong correlation (r^2=0.75). See Figure 1. It is estimated that trough levels of 10.8-16.1 mg/L lead to an average AUC/MIC of 400-600 with 95% probability.

Table 2: Baseline Patient Demographics

Characteristic (n=32)	Mean ± SD
Average age (years)	67.7 ± 15.0
Female (%)	14 (43.8)
Total Body Weight (kg)	75.9 ± 22.0
Baseline White Blood Cell Count (x10^9/L)	10.4 ± 4.8
Baseline Serum Creatinine (μmol/L)	112.1 ± 76.9
Baseline Creatinine Clearance (mL/min)	55.3 ± 28.3
Indication for Infection	**Value (%)**
Skin and soft tissue infection	10 (31.2)
Bacteremia	7 (21.9)
Pneumonia	6 (18.8)
Osteomyelitis	5 (15.6)
Other	4 (12.5)
Endocarditis	0 (0)
Meningitis	0 (0)
Comorbidities	**Value (%)**
Hypertension	19 (59.3)
Diabetes	17 (53.1)
Congestive Heart Failure	9 (28.1)
Chronic Kidney Disease	5 (15.6)

The average measured steady state peak and trough concentrations from initial vancomycin dosing were 31.3 ± 9.2 mg/L and 19.3 ± 8.1 mg/L, respectively. A corresponding AUC/MIC of 633.2 ± 201.3 was calculated using 2-point

pharmacokinetic equations. See Table 3. The predicted peak and trough concentrations after adjusting to a target AUC/MIC of 400-600 were 27.8 ± 7.4 mg/L and 13.2 ± 3.6 mg/L, respectively. After adjusting the AUC/MIC to target, the average AUC/MIC was 464.3 ± 60.8.

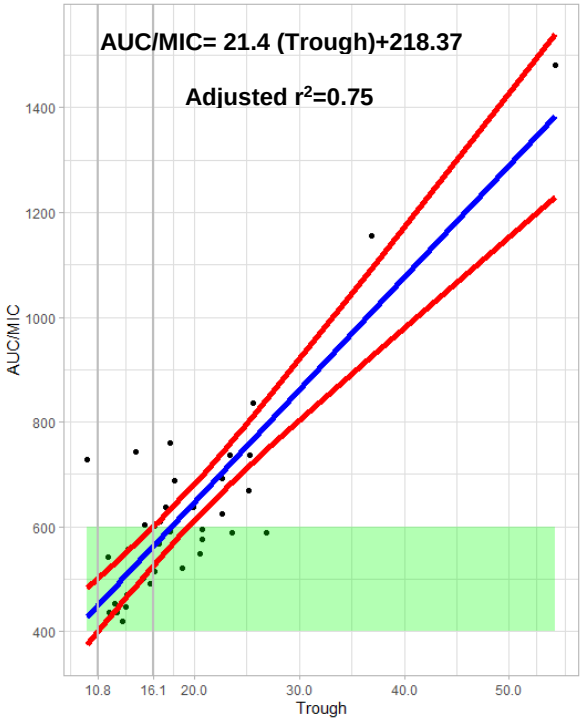

Figure 1. Relationship between vancomycin trough concentrations and AUC/MIC. The blue line represents the average AUC/MIC and the red lines indicate the 95% confidence intervals. The grey vertical lines indicate trough concentrations corresponding to an AUC/MIC range of 400-600 shaded in green.

A prediction confidence interval around the regression line was calculated to predict an individual's AUC/MIC from a given trough level. A lower limit of the trough concentration of 18.2 mg/L would guarantee an AUC/MIC of ≥400. However, an upper limit of the trough to guarantee an AUC/MIC ≤ 600 could not be calculated due to the wide prediction interval. See Figure 2.

Table 3: Comparison of Vancomycin Parameters for Trough-Based Dosing and Dosing by AUC/MIC

Vancomcin (n=36)	Mean ± SD
Trough-Based Dosing	
Peak (mg/L)	31.3 ± 9.2
Trough (mg/L)	19.3 ± 8.1
Average AUC/MIC	633.2 ± 201.3
AUC/MIC Dosing	
Peak (mg/L)	27.8 ± 7.4
Trough (mg/L)	13.2 ± 3.6
Average AUC/MIC	464.3 ± 60.8

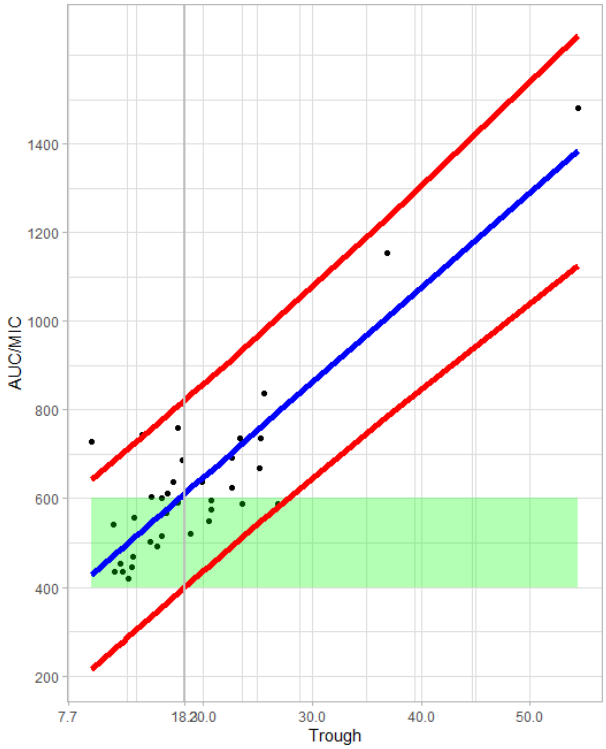

Figure 2. Individual prediction interval for AUC/MIC from vancomycin trough concentrations. The blue presents the average AUC/MIC for a given trough interval and the red lines in the show the 95% prediction intervals. The vertical grey line indicates the trough concentration corresponding to an AUC/MIC of ≥400. The green shaded region corresponds to an AUC/MIC range of 400-600.

Comparison of total daily doses between trough-based and AUC/MIC based dosing

The average total daily dose for traditional and AUC/MIC approaches were 1590.28 mg and 1281.25 mg, respectively. The mean difference between the approaches was approximately 309 mg (Wilcox's rank sum test statistics=529; p=0.179).

Comparison of rates of AKI

After applying the CEM algorithm and a logistic regression model, a total 11 patients in the current sample were matched to 22 patients in the historical control. See Table 4. A trend towards increased rates of AKI were found in the historical group using trough-based dosing compared to the study patients dosed using AUC/MIC but was not statistically significant (Odds Ratio=1.791; 95% CI (0.119, 48.048)).

Table 4: Comparison of Rates of Between Current Study Patients and Historical Controls

	Treatment Group	
AKI	**Trough-Based Dosing (n=22)**	**AUC/MIC Based Dosing (n=11)**
Yes	18	11
No	4	0

Discussion

To the knowledge of the investigators this is the first prospective study to investigate the relationship between AUC/MIC in a Canadian healthcare setting. A significant relationship between vancomycin trough concentrations and the AUC/MIC was demonstrated for the study population. The results suggest aggressively targeting trough concentrations of 15-20 mg/L is not justified and decreasing target trough concentrations to 10.8-16.1 mg/L could be used to obtain an AUC/MIC of 400-600. As a result, adopting an AUC/MIC dosing strategy may not be required for patients receiving vancomycin therapy for serious MRSA infections.

The relationship between vancomycin trough concentrations for the study population and AUC/MIC was similar to findings by Clark and colleagues where a strong correlation between vancomycin trough concentrations and AUC/MIC was found (r^2=0.731; p<0.001).[8] The relationship was also similar to the retrospective study by Neely *et al*, where the median trough concentration to achieve an AUC24 ≥ 400 was 11.9-13.3 mg/L.[10] This study and investigations by other researchers contrast findings from Pai *et al* where the relationship between trough concentrations and AUC was found to be moderate (N=5000, r^2=0.409).[11] However, their study used a Monte Carlo Simulation with a vancomycin regimen of 1 g every 8 hours using established pharmacokinetic models from 37 patients. Therefore, the results of their study may underestimate the relationship between vancomycin troughs and AUC/MIC that have been demonstrated in patients.

Despite a decreased total daily dose of vancomycin to target an AUC/MIC of 400-600 compared to traditional trough-based dosing, the difference was not significant. Targeting lower trough concentrations while still achieving an optimal AUC/MIC may allow for cost savings of therapy especially for patients on extended durations of vancomycin therapy. The introduction of dosing AUC/MIC for patient with MRSA infections will require additional training for pharmacists, nurses, physicians and laboratory staff. As a result, potential costs savings from decreased vancomycin doses

may be offset by the logistical costs of compounding non-standard doses of vancomycin, potential use of software to determine AUC/MIC for patients, and increased laboratory costs. The use of peak and trough based determination of AUC/MIC also requires additional blood samples from patients which may be unnecessary if targeting a reduced trough is implemented. Furthermore, the requirement of scheduling and obtaining peak and trough concentrations at specific times can be difficult when other procedures or tests for the patient must also be performed.

There was no significant difference in the rates of AKI between patients following AUC/MIC based dosing and trough-based dosing but this objective was likely underpowered for the sample size. However, the results are likely clinically significant for reduced rates of AKI by targeting decreased vancomycin trough goals to maintain an optimal AUC/MIC ratio.

The study has important limitations that should be considered for application of the results. As the relationship between vancomycin trough concentrations and AUC/MIC was found for a population, predicting individualized AUC/MIC from trough concentrations requires further study to find a narrower prediction interval for individuals. The short duration and resultant small sample size may overestimate the relationship between vancomycin trough concentrations and AUC/MIC. Similarly, the patients included in this study were not randomized and were recruited from a single healthcare organization. However, the consistency of the relationship found in this study in comparison with other similar studies provides confidence in the results.

The study excluded a number of patient groups including patients with cystic fibrosis, experiencing acute kidney injury or unstable renal function within 48 hours of admission or starting treatment with vancomycin, admission to the ICU, and/or using dialysis. Therefore additional investigations to understand the relationship between vancomycin trough concentrations and AUC/MIC will be required for these patient groups. However, the study with Clark and colleagues included patients primarily admitted to the ICU and demonstrated a similar relationship to the results of this study. Finally, the study did not include a group for comparison which limits the ability to assess clinical outcomes to similar patients treated with a trough-based approach.

Conclusion

To the knowledge of the investigators, this is the first investigation of the relationship between vancomycin trough concentrations and AUC/MIC in a Canadian healthcare institution. On average, vancomycin trough concentrations of approximately 11-16 mg/L correlated strongly with an AUC/MIC of 400-600, suggesting that adopting the cumbersome and costly strategy of AUC/MIC targeted dosing may not be necessary. This correlation also suggests that aggressively targeting vancomycin troughs of 15-20 mg/L, as previously recommended, is unwarranted. The use of lower doses of vancomycin to achieve the optimal AUC/MIC may result in a cost savings and decreased rates of AKI, however, the difference in both the dose and rates of AKI between the two strategies was not significant. Further investigations are required to predict individual AUC/MIC from trough concentrations.

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