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Evaluation of Target Attainment of Vancomycin Area Under the Curve in Children with Methicillin Resistant *Staphylococcus Aureus* Bacteremia

Andrea Hahn, MD¹, Robert W. Frenck Jr, MD^{2,3}, Mary Allen-Staat, MD, MPH^{2,3}, Yuanshu Zou, PhD⁴, and Alexander A. Vinks, PharmD, PhD^{3,5}

¹Division of Infectious Disease, Children's National Medical Center, Washington, DC, USA

²Division of Infectious Disease, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

³Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

⁴Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

⁵Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Abstract

Background—Vancomycin is often required to treat methicillin resistant *Staphylococcus aureus* (MRSA) bacteremia in children. Treatment failure occurs in up to 50% of adults and is associated with a 24 hour area under the curve/minimum inhibitory concentration (AUC_{24h}/MIC) <400. We sought to identify patient factors associated with vancomycin AUC and whether AUC_{24h}/MIC <400 was predictive of treatment failure in children.

Methods—Hospitalized children <18 years of age with MRSA bacteremia receiving vancomycin were included in a retrospective cohort study. AUC_{24h} was calculated using a validated PK model. Factors such as age, gender, underlying conditions, presence of foreign bodies, patient site of infection, and markers of illness severity were examined for an association with vancomycin AUC, and AUC_{24h}/MIC was evaluated for an association with treatment failure.

Results—Subjects requiring intensive care (ICU) support were significantly more likely to have higher vancomycin AUC_{24h} and AUC_{avg} than those subjects not needing ICU support. While vancomycin serum trough concentrations are predictive of vancomycin AUC, sub-optimal exposure of vancomycin occurred in almost 20% of subjects despite trough concentrations within the target range. A relationship between vancomycin AUC_{24h}/MIC and treatment failure could not be established.

Conclusions—To ensure optimal AUC/MIC pharmacodynamic index, especially in critically ill patients, estimation of the AUC is critical.

Due to an increase in multi-drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin is often used to treat children with serious infections. It has been shown that vancomycin dosing of 60 mg/kg/day divided every 6 hours typically achieves pre-dose trough concentrations of 15-20 µg/mL.[1-3] Serum vancomycin concentration troughs of 15-20 µg/mL often correlate with a 24 hour vancomycin concentration area under the curve (AUC_{24h}; equivalent to vancomycin daily dose/vancomycin clearance) over the minimum inhibitory concentration of vancomycin for the isolated bacteria (MIC) 400 in *S. aureus* isolates with an MIC 1 µg/mL.[3-6] More recent literature suggests that serum vancomycin troughs of 8-9 µg/mL may achieve AUC 400.[7, 8] Unfortunately, MICs for vancomycin are not always 1 µg/mL, which may complicate treatment.[9] Treatment failures for MRSA infections with vancomycin use are as high as 50% and have been associated with an AUC_{24h}/MIC < 400 in adults.[10, 11] Increasing drug exposure by increasing vancomycin concentrations can be associated with decreased renal function, especially with concomitant nephrotoxic agent use.[1, 3, 4, 11-13]

The purpose of our study was to determine what subject factors are associated with elevated vancomycin area under the curve in children treated with vancomycin for MRSA bacteremia and whether vancomycin AUC_{24h}/MIC was associated with patient outcomes. Using a validated pediatric pharmacokinetic model for vancomycin[14],[manuscript pending review], sparse sampling with Bayesian estimation was used to calculate AUC_{24h}.

Materials and Methods

Hospitalized children < 18 years of age with MRSA bacteremia treated with vancomycin therapy between January 1, 2010 and December 31, 2013 were evaluated for inclusion in the study. Subjects were identified through the Cincinnati Children's Hospital Medical Center's (CCHMC) infection control database. For sample size calculations, we used data from a previous study conducted over a 6 year period that found there were 365 children hospitalized with *S. aureus* bacteremia.[15] As approximately 50% of the *S. aureus* at our institution is MRSA, we expected to have about 30 subjects per year with MRSA bacteremia.

For this study, our objective was to identify factors associated with elevated vancomycin AUC in children with MRSA bacteremia and to evaluate whether an AUC_{24h}/MIC < 400 was associated with increased treatment failure (bacteremia 3 days, 30 day mortality, or recurrence of bacteremia within 30 days of end of treatment). Secondary outcome measures included increased intensive care unit (ICU) admissions, increased total length of hospitalization (LOS), higher use of synergistic antimicrobials (specifically gentamicin and rifampin), and increased incidence of renal toxicity (defined by a creatinine increase by 50% or 0.5 mg/dL, whichever was greater). Subjects were included in the study if they had MRSA bacteremia, were treated with vancomycin for at least three days, and had a complete electronic medical record available for review. Subjects were excluded from the study if they did not have a vancomycin concentration or serum creatinine documented in the medical record or they received a concurrent antibiotic to which the MRSA was susceptible.

Medical records for each subject were reviewed for demographic data, past medical history, clinical information about the MRSA infection, vancomycin peak and trough concentrations, serum creatinine concentrations, bacterial blood cultures, other bacterial cultures, and minimum inhibitory concentration (MIC) of vancomycin for MRSA isolates. Due to the retrospective nature of this study collection of blood cultures was not standardized, but in most cases they were obtained daily. Susceptibility testing was performed using Vitek 2 (BioMerieux, Inc., Durham, NC) with MICs ≥ 2 confirmed by E-test (BioMerieux, Inc., Durham, NC).

To calculate AUC_{24h} for each subject, we entered the subject's age, weight, serum creatinine, vancomycin doses and times of administration, and all measured vancomycin concentrations and times they were obtained for the first 72 to 120 hours of therapy into the relevant sections of the MW/Pharm program (Version 3.60, Mediware, Groningen, The Netherlands).[16] Bayesian estimation was performed using the validated pediatric population pharmacokinetic model and the AUC for the first 24 hours of therapy was estimated (AUC_{24h}).[17] As prior studies have looked at both the first 24 hours of therapy and an average of AUC over time, we also evaluated the average 24 hour AUC over the first 72 hours of therapy ($AUC_{24h \text{ average}}$) for comparison.

Descriptive statistics were used to characterize the study population. Inferential statistics performed included Pearson correlation, Mann-Whitney Rank Sum Test, Multiple Linear Regression, and ANOVA on Ranks for continuous variables, with data reported as medians and 25th and 75th interquartile ranges (IQR). Categorical variables were compared using the Fisher's exact test. These tests were performed using SigmaPlot (SPSS Science, San Rafael CA).

This study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center. As it was a retrospective study, a waiver of consent was obtained.

Results

Overall, there were 83 children with MRSA bacteremia receiving vancomycin during the study period. Of these, 59 (71%) were eligible for the study. Of those excluded, six subjects were excluded due to not receiving vancomycin for the initial three days of infection, one because vancomycin concentrations were not available, and 17 due to concurrent receipt of antibiotics to which the MRSA was susceptible.

The median age of study subjects was 2.95 (1.2, 9.3) years, median vancomycin AUC_{24h} was 321.4 (246.4, 459.6) and median vancomycin AUC_{avg} was 417.7 (340.6, 537.5) mg*hr/L. No correlation between age and vancomycin AUC was found (AUC_{24h} $p=0.333$, AUC_{avg} $p=0.686$). There was also no statistical association between gender, underlying conditions, or sites of infection and vancomycin AUC. Demographic, clinical characteristics of the subjects, including the presence of foreign bodies, and sites of infection are shown in Table 1.

Markers of illness severity and vancomycin AUC were also evaluated, specifically looking at the need for ICU support, shock or hypotension at presentation, renal insufficiency at

presentation ($\text{CrCl} < 75 \text{ ml/min/1.73m}^2$), or the development of renal failure during the hospitalization (serum Cr increased by 50% from admission baseline for two occurrences). The results are shown in Figure 1 and Table 2. The need for ICU care was statistically associated with vancomycin AUC at both 24 hours and as an average over the first 72 hours of therapy. Importantly, the increased AUC was not simply a function of increased starting dose in those children admitted to the ICU, as there was no difference in starting dose between the two groups (median starting dose 45 mg/kg/day for both groups, $p=0.574$). This was also true when standardizing the AUC by dividing by the starting dose for each subject (standardized $\text{AUC}_{24\text{h}}$ median 8.8 (6.2, 13.1) versus 6.2 (5.1, 7.6), $p=0.007$ and standardized AUC_{avg} median 10.1 (7.9, 14.2) versus 8.5 (6.9, 9.5), $p=0.025$ for ICU and no ICU, respectively). No statistical association was found with the other markers of illness severity measured, although there was a trend toward increased renal insufficiency at presentation for children in the ICU ($p=0.076$ for $\text{AUC}_{24\text{h}}$).

A comparison was performed between early trough values (first vancomycin serum trough concentration obtained after receiving more than one dose of vancomycin) to both vancomycin $\text{AUC}_{24\text{h}}$ and $\text{AUC}_{24\text{h}}/\text{MIC}$, which are shown in Figure 2 and Table 3. Serum trough concentrations were predictive of both vancomycin $\text{AUC}_{24\text{h}}$ and $\text{AUC}_{24\text{h}}/\text{MIC}$ for all trough cut-offs measured, and the area under an ROC curve was 0.863 (95% confidence interval 0.749 to 0.939, $p<0.001$), confirming the relationship. However, 17% of subjects with a trough > 10 did not achieve an $\text{AUC}_{24\text{h}}/\text{MIC} > 400$ while 52% of subjects with a trough < 15 and 46% with a trough < 10 achieved an $\text{AUC}_{24\text{h}}/\text{MIC} > 400$. Additionally, the coefficient of determination (R^2) of initial vancomycin serum trough concentrations and $\text{AUC}_{24\text{h}}$ was only 50%.

Lastly, the relationship between vancomycin $\text{AUC}_{24\text{h}}/\text{MIC}$ and patient outcome was evaluated and is shown in Figure 3. While the study was underpowered to fully answer this question, there were no statistically significant differences in either primary or secondary outcomes between the two groups, although there was a trend toward renal toxicity in the children with an $\text{AUC}_{24\text{h}}/\text{MIC} < 400$. Thirty six percent of children with an $\text{AUC}_{24\text{h}}/\text{MIC} < 400$ experienced treatment failure, while 38% experienced treatment failure in children with an $\text{AUC}_{24\text{h}}/\text{MIC} \geq 400$ ($p=1.000$). Twenty eight percent of subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} < 400$ had prolonged bacteremia as compared to 32% of subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} \geq 400$ ($p=0.781$). Recurrence of bacteremia occurred in 8% of the subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} < 400$ compared to 6% of subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} \geq 400$ ($p=1.000$). Due to lack of events, MRSA related death could be evaluated. There was no statistical difference in the use of gentamicin or rifampin ($p=1.000$ for both). Renal toxicity occurred in 4% of subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} < 400$ and 24% of subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} \geq 400$ ($p=0.065$). The median LOS and the percentage of subjects hospitalized in the ICU was not significantly different between the groups (20 days and 32% of subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} < 400$ as compared to 14 days and 56% of subjects with an $\text{AUC}_{24\text{h}}/\text{MIC} \geq 400$; $p=0.304$ and $p=0.112$).

Discussion

In our study, we found that subjects ill enough to require ICU care for management during their infection with MRSA were significantly more likely to have higher vancomycin AUC_{24h} and vancomycin AUC_{avg} than those subjects who did not require such intensive support. This was independent of their starting dose of vancomycin, as no statistical difference was noted in the starting vancomycin dose between the two groups or the AUC_{24h} standardized by starting dose. This is most likely reflective of renal impairment affecting vancomycin clearance, although change in serum creatinine was not sensitive enough to detect this as there was no significant difference of AUC_{24h} detected in those with or without renal insufficiency at presentation or those with or without the development of renal failure during hospitalization. However, the inability to detect a difference in AUC_{24h} between those subjects with and without shock, renal insufficiency, and/or renal failure may be related to low subject numbers ($n < 10$) having those presenting features and outcomes.

While this study did find that vancomycin serum trough concentrations are predictive of AUC, they do not capture between patient variability and leave many subjects either under- or over-dosed on their vancomycin to achieve an $AUC_{24h}/MIC > 400$ (Figure 2 and Table 3). Almost 20% of subjects with a vancomycin serum trough concentration > 10 needed more vancomycin exposure to achieve an $AUC_{24h}/MIC > 400$. It is worth noting that the lower vancomycin MICs for MRSA at our institution helped account for increased numbers of subjects achieving an $AUC_{24h}/MIC > 400$. Only 34% of subjects had a vancomycin AUC > 400 at 24 hours, so at an institution where vancomycin MICs for MRSA are higher than the susceptibility cut-off of $1 \mu g/mL$ there would be an even larger proportion of patients receiving insufficient vancomycin exposure. Even though population pharmacokinetic models suggest that as a group children can easily achieve $AUC/MIC > 400$ with a dosing regimen of 60 mg/kg/day [5], our findings suggest that this may be more difficult to achieve in clinical practice[18]. Likewise, vancomycin serum trough concentrations of < 10 may be sufficient when the MIC is $1 \mu g/mL$, but would not be indicative of sufficient vancomycin exposure when MICs are $> 1 \mu g/mL$. [7, 8]

Several studies in adults have found an association between the vancomycin AUC_{24h}/MIC and treatment failure or success in MRSA bloodstream infections.[11, 19-22] No outcome studies looking at pharmacodynamic indices such as the AUC_{24h}/MIC ratio have been reported to date in children. While we had hoped to also identify whether AUC_{24h}/MIC is associated with treatment failure or success in children by this study, our patient numbers were insufficient to achieve the desired power to detect a difference.

Limitations to the present study are inherent to its retrospective nature, which accounts in part for possible selection, confounding and confirmation biases. In addition, the data derived from the study comes from a single center, which could limit the generalizability of the results. Another limitation is that outcome measures in pediatric subjects may not be comparable to adults. In the Kullar study, vancomycin treatment failure was defined as bacteremia > 7 days, recurrence of bacteremia within 30 days, or 30 day mortality.[11] In our study, no subjects died, none had recurrence of bacteremia, and we had to decrease days of bacteremia because no subjects had bacteremia > 7 days. This limits the comparability of

our data to previously performed adult studies. Questions may arise about the generalizability of our validation results as a significant proportion of the children had underlying diseases, particularly cancer. A study by Chang found that children with a malignancy had increased vancomycin clearance compared to those without, but had a similar volume of distribution.[23] This could lead to less precision and a negative bias in predicting trough concentrations and ultimately lead to a lower predicted AUC. With that said, we found there was no significant difference in precision and bias between the Lamarre validation data and our validation results.[14, 25] Therefore we concluded the Lamarre model could be used in our general pediatric population to reliably predict the AUC. Another limitation is use of Vitek 2 to define MIC for the MRSA isolates, as prior studies have shown inconsistency among different methods of measurement.[24] However, our institution routinely uses Vitek 2 to measure MIC, and it is important to look at how measuring AUC/MIC would be implemented in clinical practice. A potential limitation was assessing kidney function using serum creatinine. Other markers, such as serum cystatin C, better predict glomerular filtration rate. However, serum cystatin C values were not checked for most subjects which is why serum creatinine measurements were used. Lastly, there is the potential for type II error in this study given we did not meet our desired sample size. However, in addition to not being statistically significant there was no significant numeric difference in the rate of children with prolonged bacteremia between the two groups.

Conclusion

Vancomycin exposure in children requiring ICU support for MRSA bacteremia should be monitored closely, as their renal function based on serum creatinine measurements may not be completely reflective of their vancomycin clearance. In addition, while vancomycin serum trough concentrations clearly correlate with vancomycin AUC, this information is not enough to predict true vancomycin exposure for all pediatric patients. Thus, to ensure optimal pharmacodynamic index which incorporate the vancomycin MIC for *S. aureus*, especially for more critically ill patients, knowing the AUC is imperative. The use of sparse D-optimal sampling techniques, e.g. by obtaining vancomycin concentrations at the end of the-infusion, during drug distribution (e.g. at 40-45 min post-infusion) and at either 12 hours post-infusion or as a pre-dose trough, whichever is more convenient, would be most informative to predict AUC using Bayesian estimation. [25]

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Figure 1. Markers of illness severity and vancomycin AUC_{24h}. Figure 1A. AUC_{24h} ICU versus No ICU. 1B. AUC_{24h} Shock versus No Shock . 1C. AUC_{24h} Renal Insufficiency (RI) at presentation versus None . 1D. AUC_{24h} Renal Failure (RF) during hospitalization versus None. Box plots show the median, 10th, 25th, 75th, and 90th percentiles as vertical boxes with error bars.

Figure 2.
Scatter plot of initial vancomycin serum trough concentrations and AUC_{24h}.

Figure 3. Primary and Secondary Outcomes, AUC_{24h}/MIC. No significant differences were noted in any outcome measures.

Table 1
Relationship between Vancomycin Area Under the Curve and Subject Demographics, Underlying Conditions and Site of Infection

Gender*	n	AUC 24h (mg [*] h/L)	P value	AUC avg (mg [*] h/L)	P value
Male	39	328.5 (234.3, 466.7)	0.879	427.3 (355.4, 564.6)	0.383
Female	20	305.3 (260.0, 451.7)		408.7 (329.6, 452.4)	
Underlying Conditions/Foreign Bodies [†]					
Cancer	4	252.5 (228.9, 562.2)	0.214	414.0 (326.9, 582.4)	0.385
Prior Transplant	5	451.1 (365.5, 546.3)	0.679	564.6 (383.8, 640.0)	0.917
Immunodeficiency	1	451.1	0.944	564.6	0.870
Renal Disease	1	306.4	0.983	384.5	0.867
Cardiac Disease	5	281.9 (168.9, 484.4)	0.111	355.4 (263.6, 597.3)	0.234
GI Disease	13	345.5 (216.4, 439.7)	0.142	417.0 (311.5, 503.1)	0.094
Lung Disease	8	295.6 (207.7, 444.0)	0.298	355.2 (310.3, 715.7)	0.577
Neurologic Disease	8	332.7 (298.3, 476.0)	0.581	378.7 (327.8, 502.1)	0.556
Genetic/Metabolic Disease	7	336.9 (306.4, 397.4)	0.968	384.5 (342.8, 518.2)	0.648
Indwelling Line	29	345.5 (252.5, 486.3)	0.073	417.7 (349.1, 568.6)	0.381
Tracheostomy/ET tube	5	306.4 (229.0, 379.7)	0.690	356 (328.3, 461.0)	0.409
Orthopedic Hardware	2	273.9	0.352	321.3	0.542
Patient Site of Infection [‡]					
Disseminated	4	332.3 (245.5, 493.2)	0.606	416.9 (381.3, 591.5)	0.386
Bone and Joint	12	292.3 (204.8, 412.2)		436.4 (200.3, 512.4)	
Lung	6	295.6 (231.4, 350.5)		349.4 (322.9, 422.7)	
SSTI/Deep Tissue	8	294.2 (212.3, 435.8)		381.2 (303.8, 449.7)	
CNS	2	400.6		556.9	
Primary Bacteremia	27	373.6 (258.6, 543.1)		436.3 (375.9, 587.9)	

* Mann Whitney Rank Sum Test

[†] Multiple Linear Regression

[‡] ANOVA on Ranks

Table 2
Association Between Vancomycin Area Under the Curve and Markers of Illness Severity

Need for ICU	n	AUC 24h (mg* μ h/L)	P value	AUC avg (mg* μ h/L)	P value
Yes	27	373.6 (297.8, 543.8)	0.011	447.5 (372.9, 626.5)	0.047
No	32	286.0 (225.8, 394.7)		406.4 (311.0, 467.9)	
Shock/Hypotension at Presentation					
Yes	6	316.8 (277.5, 557.3)	0.607	445.4 (407.8, 605.5)	0.275
No	53	321.4 (241.5, 455.4)		416.5 (328.2, 534.9)	
Renal insufficiency at presentation (CrCl<75 ml/min/1.73m ²)					
Yes	3	1091.0 (476.8, 1094.8)	0.076	1175.7 (532.2, 1292.5)	0.125
No	56	458.9 (269.4, 673.5)		561.6 (406.8, 837.5)	
Renal failure (serum Cr increased by 50% from admission baseline for two occurrences)					
Yes	9	451.1 (260.9, 524.8)	0.317	463.5 (333.2, 684.7)	0.297
No	50	307.4 (244.0, 430.4)		416.7 (338.1, 528.3)	

Mann Whitney Rank Sum Test

Table 3
Comparison of Vancomycin AUC24h and AUC24h/MIC to Early Vancomycin Serum Trough Concentrations

	Trough < 5	Trough > 5	Trough < 10	Trough > 10	Trough < 15	Trough > 15
AUC 24h < 400 (n)	19	20	35	4	39	0
AUC 24h > 400 (n)	2	18	6	14	11	9
P value		0.004		<0.001		<0.001
AUC 24h/MIC < 400 (n)	13	12	22	3	24	0
AUC24h/MIC > 400 (n)	8	26	19	15	26	9
P value		0.031		0.01		0.008

Fisher's exact test