Vancomycin Treatment Failure in Children With Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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OBJECTIVES Limited data exist regarding clinical outcomes of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in children treated with vancomycin. Treatment success in adults correlates best with an area under the curve/minimum inhibitory concentration (AUC_{24}/MIC) ratio ≥ 400 . It is unknown if this relationship is useful in children.

METHODS Charts of children who received vancomycin ≥ 5 days for MRSA bacteremia with a steady state trough were reviewed. AUC_{24}/MIC ratios were estimated using 2 different vancomycin clearance equations. Vancomycin treatment failure was defined as persistent bacteremia ≥ 7 days, recurrent bacteremia within 30 days, or 30-day mortality.

RESULTS There were 67 bacteremia episodes in 65 patients. Nine (13.4%) met failure criteria: persistent bacteremia ($n = 6$), recurrent bacteremia ($n = 2$), 30-day mortality ($n = 1$). There were no differences between patients receiving < 60 mg/kg/day and ≥ 60 mg/kg/day of vancomycin in median trough (11.9 versus 12.3 mg/L, $p = 0.1$). Troughs did not correlate well with AUC_{24}/MIC ratios ($R^2 = 0.32$ and 0.22). Patients receiving ≥ 60 mg/kg/day had greater probability of achieving ratios ≥ 400 . There were no significant differences in median dose ($p = 0.8$), trough ($p = 0.24$), or AUC_{24}/MIC ratios ($p = 0.07$ and $p = 0.6$) between patients with treatment success and failure.

CONCLUSIONS Treatment failure was lower than previously reported in children. AUC_{24}/MIC ratios ≥ 400 were frequently achieved but were not associated with treatment success, dose, or troughs. Prospective studies using standard definitions of vancomycin treatment failure are needed to understand treatment failure in children with MRSA bacteremia.

ABBREVIATIONS AUC, area under the curve; AUC_{24} , area under the curve at 24 hours; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*

KEYWORDS area under the curve; bacteremia; children; MRSA; vancomycin

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Introduction

Limited data exist regarding clinical outcomes of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in children treated with vancomycin.^{1–7} Studies in adults suggest that vancomycin treatment success correlates best with an estimated area under the curve/minimum inhibitory concentration (AUC_{24}/MIC) ratio ≥ 400 , but this relationship has not been established in children.^{6,8–10} Guidelines suggest that higher trough concentrations increase the probability of achieving a target AUC_{24}/MIC ratio ≥ 400 , but this also has not been validated in children.^{3,11,12} Pharmacokinetic models suggest that ratios ≥ 400 may be achievable in pediatric patients with lower trough concentrations than in adults.^{13–15} However, trough concentrations have not been shown to correlate well with AUC_{24}/MIC ratios in the pediatric population.^{3,15–17}

In a study of 22 children with MRSA bacteremia treated with vancomycin, Welsh et al² reported a treatment failure of 50%, but vancomycin trough concentrations and estimated AUC_{24}/MIC ratios were not reported. Treatment failure was reported to be 35% in a multicenter study of children with MRSA bacteremia treated with vancomycin with a measured steady state vancomycin trough concentration ($n = 174$). While trough concentrations and risk factors for treatment failure were evaluated, AUC_{24}/MIC ratios were not. In their study, treatment failure was associated with critical illness and source of infection (musculoskeletal and endovascular) but not with vancomycin MICs or troughs.⁴ For 59 children with MRSA bacteremia, treatment failure (37%) was not associated with AUC_{24}/MIC ratios.¹ The primary objective of our study was to evaluate the rate of vancomycin treatment failure in children with primary or secondary MRSA bacteremia. Secondary objectives

assessed the correlation between vancomycin trough concentrations and the corresponding estimated AUC_{24}/MIC ratios as well as the relationship of dose, trough, and estimated AUC_{24}/MIC ratio with vancomycin treatment failure.

Materials and Methods

Study Population. This was a single-center, retrospective study of children with MRSA bacteremia who received vancomycin from February 2005 through January 2015 at Le Bonheur Children's Hospital in Memphis, TN. Patients with a blood culture positive for MRSA were identified through the electronic medical record and microbiology records. Patients were included if they were 2 months to 17 years of age, had a confirmed diagnosis of MRSA bacteremia, and had at least 1 appropriately drawn steady state vancomycin trough concentration. Trough concentrations were considered appropriately drawn if the trough level was drawn within 1 hour of administration of the next vancomycin dose. Patients were excluded if they received vancomycin therapy for fewer than 5 days, received non-weight-based dosing, were treated while admitted to the neonatal intensive care unit (due to variability of pharmacokinetics and renal function), or complete medical records were unable to be located. Patients who were excluded for non-weight-based dosing were adult sized and received doses, such as 1000 or 1500 mg, which were less than traditional pediatric weight-based dosing of 10 to 15 mg/kg/dose. This study was approved by the Institutional Review Board at the University of Tennessee Health Science Center.

Data Collection. We collected demographic and clinical data including gender, race, age, weight, height, primary source of infection, source control documentation, if applicable (e.g., intravenous catheter removal, surgical debridement, drainage of abscess), vancomycin dosing (dose per kilogram and duration), and any additional antimicrobials for the treatment of MRSA. We collected laboratory data that included time of blood cultures, time to culture positivity, source (central venous catheter [CVC] versus peripheral blood) of positive blood culture, and vancomycin MIC. Episodes were defined as the initial positive MRSA blood culture during the patient's hospital admission; whereas, recurrence of bacteremia was defined as a new positive MRSA blood culture within 30 days of the end of vancomycin therapy.

MICs were obtained by broth microdilution using an automated susceptibility testing instrument (Vitek 2, bioMérieux, Marcy-l'Étoile, France). Prior to March 2009, our microbiology laboratory reported MIC values as ≤ 1 and 2 mg/L. After a laboratory reporting change, MIC values were reported as ≤ 0.5 , 1, and 2 mg/L. For the purpose of consistency, this latter set of values was used for calculations, and organisms with vancomycin MICs reported as ≤ 1 mg/L were grouped with those

reported as 1 mg/L.

Additional laboratory parameters collected included steady state vancomycin trough concentrations and serum creatinine. The first steady state trough concentration following the optimal vancomycin dose was recorded and used for evaluations. The optimal vancomycin dose was defined as the final dose requiring no further adjustment. If a dose change was made but no corresponding steady state trough concentration was available, then the preceding vancomycin dose and corresponding trough was used for analysis. Troughs between 10 and 20 mg/L were considered within the traditional therapeutic range, and undetectable trough concentrations (<5 mg/L) were reported as zero.

AUC_{24} was calculated using the following equation: $AUC_{24} = \text{vancomycin total daily dose} / \text{vancomycin clearance}$. There is variability in pharmacokinetic models estimating AUC_{24}/MIC ratios. We used 2 methods to estimate vancomycin clearance. Neither the Chang¹⁸ nor Le et al¹⁴ method require repeat vancomycin trough concentrations for calculations making them practical for implementing in practice.⁶ Thus, our study chose to compare both of these methods of determining clearance for all patients. Chang¹⁸ developed the following equation in pediatric patients with malignancies: $\text{vancomycin clearance (mL/min)} = \text{creatinine clearance} \times 0.7099 + 1.4084$. Le et al¹⁴ produced the following equation: $\text{vancomycin clearance (L/hr)} = 0.248 \times \text{weight (kg)}^{0.75} \times (0.48/\text{serum creatinine})^{0.361} \times [\ln(\text{age})/7.8]^{0.995}$. For patients younger than 1 year of age, the Schwartz et al¹⁹ equation was used to estimate creatinine clearance, and the modified Schwartz and Work²⁰ equation was used for patients ≥ 1 year of age.^{6,21}

Outcomes. The primary outcome, rate of vancomycin treatment failure, was defined as persistent bacteremia ≥ 7 days while receiving vancomycin therapy, recurrence of bacteremia within 30 days of the end of vancomycin therapy, or 30-day all-cause mortality.^{1,2,4} Secondary outcomes included correlation between vancomycin trough concentrations and their corresponding estimated AUC_{24}/MIC ratios. Additionally, the relationship of vancomycin treatment failure with vancomycin dose, vancomycin trough concentration, and estimated AUC_{24}/MIC ratio was evaluated.

Statistical Analysis. Descriptive statistics were reported as frequencies and medians with IQRs. Associations between categorical variables were assessed using the χ^2 test. Correlations between continuous variables were evaluated using Spearman rank correlation and reported as an R^2 value. The relationship of vancomycin treatment outcome (success or failure) with vancomycin dose, trough concentration, and estimated AUC_{24}/MIC ratio was analyzed using the Mann-Whitney U test. A p value < 0.05 indicated statistical significance.

Results

Patient Characteristics. There were 215 episodes of

Figure. Patient selection.

MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit.

MRSA bacteremia during the study period. Sixty-seven episodes of infection in 65 patients met inclusion criteria; 1 patient had 3 separate episodes of MRSA bacteremia associated with a CVC. Most episodes were excluded for absence of a measured trough concentration ($n = 40$, 27%) and lack of vancomycin administration ($n = 36$, 24.3%) (Figure). Patient demographics and clinical characteristics are shown in Table 1. Thirty-nine patients (58%) were African-American, and 64% of patients were male. The median age of the patients was 4 years (IQR, 1.4–12 years). Musculoskeletal infections accounted for 43% ($n = 29$) of bacteremia episodes, while 28% ($n = 19$) of patients had a central line-associated bloodstream infection (CLABSI).

Vancomycin Therapy and Associated MICs. The median dose of vancomycin was 60 mg/kg/day (IQR, 45–60 mg/kg/day), and the median duration of therapy was 11 days (IQR, 7–14 days) for the 55 patients who completed therapy in the hospital. Twelve patients were discharged home on vancomycin therapy. Twenty-nine patients (43%) initially received <60 mg/kg/day of vancomycin. Forty patients (60%) experienced vancomycin dosing changes following their initial dose and associated trough concentration, most of which ($n = 36$) involved increasing the dose. MRSA isolates for 64 episodes (96%) had an MIC of ≤ 0.5 mcg/mL ($n = 11$) or 1 mcg/mL ($n = 53$). Three isolates (4%) had an MIC of 2. For the 9 patients (13.4%) classified as treatment failure, the associated MIC values were as follows: ≤ 0.5 mg/L ($n = 1$), 1 mg/L ($n = 7$), and 2 mg/L ($n = 1$).

Vancomycin Treatment Failure. Nine of 67 (13.4%; 95% CI, 6%–22%) episodes of bacteremia were clas-

sified as vancomycin treatment failure. Six patients had persistent bacteremia ≥ 7 days while receiving vancomycin therapy, 2 had recurrence of bacteremia within 30 days of the end of vancomycin therapy, and 1 patient died within 30 days of MRSA isolation. Among the 6 patients with persistent bacteremia ≥ 7 days, 4 presented with a primary musculoskeletal infection requiring repeated incision and drainage procedures. Primary bacteremia and CLABSI were the other 2 sources associated with persistent bacteremia. In the latter, the CVC was removed, and linezolid was initiated after the patient was believed to have failed vancomycin therapy. The 2 patients who experienced recurrent bacteremia within 30 days both had a CLABSI. Of these, 1 patient had their original CVC removed followed by the removal of the replacement CVC after continued MRSA infection. The other patient received 16.5 days of continuous vancomycin therapy without removal of the CVC. The single patient who died within 30 days of infection onset presented with pneumonia and septic shock requiring extracorporeal membrane oxygenation support. Six of the 9 patients (67%) who met treatment failure criteria were ≤ 2 years of age; however, larger studies are warranted to determine if there is clinical significance regarding this relationship.

Comparisons of Dose, Trough Concentrations, and Estimated AUC_{24}/MIC Ratios. For the analysis of vancomycin trough concentrations and estimated AUC_{24}/MIC ratios (Table 2), patients were grouped according to vancomycin daily dosing regimens of <60 mg/kg/day and ≥ 60 mg/kg/day. Fifteen patients (22%) experienced dose changes but did not have a new

Table 1. Patient Demographics and Clinical Characteristics

	Treatment Success (n = 58)	Treatment Failure (n = 9)
Median age, yr (IQR)	5 (1.5–13)	2 (1–7)
Median weight, kg (IQR)	19.3 (9.7–41)	12.6 (8.3–23.8)
Gender, males (%)	37 (63.8)	6 (66.7)
Race, n (%)		
African-American	32 (55.2)	7 (77.8)
Caucasian	24 (41.4)	2 (22.2)
Other	2 (3.4)	0
Primary site of infection, n (%)		
Musculoskeletal	25 (43.1)	4 (44.4)
CLABSI	16 (27.5)	3 (33.3)
Primary bacteremia (no CVC)	3 (5.2)	1 (11.1)
Pneumonia	3 (5.2)	1 (11.1)
Abscess (non-musculoskeletal)	3 (5.2)	0
CNS (postoperative or shunt)	3 (5.2)	0
Mediastinitis	3 (5.2)	0
Cellulitis (without abscess)	1 (1.7)	0
Endocarditis	1 (1.7)	0

CLABSI, central line-associated bloodstream infection; CNS, central nervous system; CVC, central venous catheter

vancomycin trough concentration drawn appropriately. The median trough concentration for the 29 patients (43%) receiving <60 mg/kg/day of vancomycin was 11.9 mg/L (IQR, 7.6–15.6) compared with a median trough of 12.3 mg/L (IQR, 9.9–15.6, $p = 0.1$) for the 38 patients (57%) receiving ≥ 60 mg/kg/day. There were no differences in the proportion of patients achieving trough values in the 10 to 20 mg/L range (62% for <60 mg/kg/day versus 74% for ≥ 60 mg/kg/day, $p = 0.6$) or in the 15 to 20 mg/L range (35% for <60 mg/kg/day versus 26% for ≥ 60 mg/kg/day, $p = 0.5$).

The Chang¹⁸ and Le et al¹⁴ methods to estimate vancomycin clearance for determination of AUC_{24} yielded differing results for AUC_{24}/MIC ratios. Six patients were not included in the analyses using the Chang¹⁸ method as no height was documented. The Chang¹⁸ method produced a broader range of AUC_{24}/MIC ratio values than the Le et al¹⁴ method (Table 2). Median AUC_{24}/MIC ratios for the 2 vancomycin dosing groups, using the Chang¹⁸ method, did not differ significantly [<60 mg/kg/day, 388 (IQR, 230–801); ≥ 60 mg/kg/day, 591 (IQR, 430–793); $p = 0.1$]; whereas, the medians did differ significantly using the Le et al¹⁴ method [<60 mg/kg/day, 456 (IQR, 288–576); ≥ 60 mg/kg/day, 609 (IQR, 483–727); $p = 0.001$] (Table 2). There was a higher proportion of children with AUC_{24}/MIC ratios ≥ 400 in the high dose versus the low dose group for both the Chang¹⁸ (84% versus 48%, $p = 0.002$) and the Le et al¹⁴ methods (100% versus 52%, $p < 0.001$). There was weak correlation between vancomycin trough concentrations

and estimated AUC_{24}/MIC ratios using both the Chang¹⁸ method ($R^2 = 0.32$; $p = 0.009$) and the Le et al¹⁴ method ($R^2 = 0.22$; $p = 0.07$).

Correlations With Treatment Success or Failure.

Comparisons of vancomycin dose, trough concentrations, and estimated AUC_{24}/MIC ratios between treatment successes and failures are shown in Table 3. There were no differences in the median daily dose or median trough concentrations between treatment successes and failures. In addition, the differences between the median estimated AUC_{24}/MIC ratios were not significantly different between treatment successes and failures for either the Chang¹⁸ method [median AUC_{24}/MIC ratio, 591 (IQR, 385–793) for successes compared with 245 (IQR, 90–728) for failures ($p = 0.07$)] or the Le et al¹⁴ method [median AUC_{24}/MIC ratio, 540 (IQR, 446–681) for successes versus 523 (IQR, 250–772) for failures ($p = 0.6$)].

Discussion

Our study estimates AUC_{24}/MIC ratios and evaluates their relationship with not only vancomycin dose and trough concentrations, but also treatment outcomes in children with MRSA bacteremia treated with vancomycin. To our knowledge, this is the first study to report relationship of AUC_{24}/MIC ratios, trough concentrations, vancomycin doses, and treatment outcomes in pediatric patients who have received vancomycin for a duration of therapy greater than 72 hours. Previous studies ei-

Table 2. Vancomycin Daily Dose and Corresponding Vancomycin Trough Concentrations and Estimated AUC₂₄/MIC Ratios

	Vancomycin, <60 mg/kg/day (n = 29)	Vancomycin, ≥60 mg/kg/day (n = 38)	p value
Median trough, mg/L (IQR)	11.9 (7.6–15.6)	12.3 (9.9–15.6)	0.1
Median AUC ₂₄ /MIC ratio (IQR) using the Chang ¹⁸ method*	388 (230–801)	591 (430–793)	0.1
Median AUC ₂₄ /MIC ratio (IQR) using the Le et al ¹⁴ method	456 (288–576)	609 (483–727)	0.001

AUC₂₄, area under the curve at 24 hours; MIC, minimum inhibitory concentration

* n = 26 and 35 for <60 and ≥60 mg/kg/day, respectively, as 6 patients did not have a documented height with which to calculate area under of the curve.

ther partially assessed these relationships or included patients with vancomycin durations too short to attribute outcomes.^{1,2,4} We found that higher vancomycin doses, ≥60 mg/kg/day, were not associated with higher trough concentrations but were associated with higher median AUC₂₄/MIC ratios. While the median estimated AUC₂₄/MIC ratio was higher in patients receiving ≥60 mg/kg/day, using the Le et al¹⁴ method, we did not find a statistically significant difference between dosing groups using the Chang¹⁸ method.

While several studies have examined the relationship between vancomycin dosing and pharmacokinetics, the available data addressing clinical outcomes of invasive MRSA infections in children in relation to vancomycin dose and achievable trough concentrations are more limited.^{1,2,4,5,7,22} These studies have assessed a mix of healthcare-associated and community-acquired infections. In addition, there is no standard definition for treatment failure in children making comparisons across studies difficult.^{1,2,4,7,23–25} We used a definition similar to that used in 3 pediatric studies.^{1,2,4} In the first, Welsh et al² evaluated 22 children with MRSA bacteremia treated with vancomycin for at least 5 days. Both community-acquired and healthcare-associated cases were included in their analysis. Treatment failure, which occurred in 50% of patients, included persistent bacteremia ≥7 days. They did not report dosing, trough concentrations, or AUC₂₄/MIC ratios. The second study, by Hamdy et al,⁴ was a retrospective review of 232 episodes of MRSA bacteremia in which treatment failure was defined as persistent bacteremia >3 days. With this less stringent definition, treatment failure was documented in 35% of children (n = 174) who had a steady state trough concentration available within the first 3 days of therapy. In the third study, Hahn et al¹ defined MRSA bacteremia ≥3 days as failure and evaluated 59 children receiving vancomycin for at least 3 days. Treatment failure was reported as 36% for patients with an AUC₂₄/MIC ratio < 400 (n = 25) and 38% for those with a ratio ≥400 (n = 34). Yoo et al²² analyzed mortality in 46 cases of healthcare-associated MRSA bacteremia. All-cause mortality and recurrence of bacteremia in their

study population were substantially higher than in our patient cohort at 11.1% and 15.2%, respectively, versus 1% and 3%. They concluded that initial vancomycin trough concentrations are not predictive of 30-day mortality or recurrent bacteremia in children. While we used a definition of treatment failure similar to the Welsh et al² study, persistent bacteremia ≥7 days, community-acquired infections comprised the majority of episodes in our patients, which may explain the lower mortality and recurrence rates compared with nosocomial infections in these other studies. The lack of a standard definition of treatment failure clearly contributes to variability in treatment failure rates.

The Infectious Diseases Society of America¹¹ recommends 60 mg/kg/day (15 mg/kg/dose every 6 hours) of vancomycin for the treatment of severe invasive MRSA infections in children and adults. Additionally, they consider 15 to 20 mg/L to be the target vancomycin trough concentration; however, this dose may not be sufficient to achieve target trough concentrations in children.^{3,11,13,26,27} In 1 study of 94 patients receiving vancomycin 60 mg/kg/day, fewer than 15% of patients achieved a trough concentration within the range of 15 to 20 mg/L.²⁶ Chhim et al³ reported similar findings for 60 mg/kg/day dosing regimens with only 16.5% of patients (n = 102) achieving concentrations of 15 to 20 mg/L, 43% of whom had concentrations <10 mg/L.³ Both Hamdy et al⁴ and Yoo et al²² concluded that initial vancomycin trough concentrations ≤10 mg/L were not predictive of vancomycin treatment failure although, in the Hamdy et al⁴ study, troughs <10 mg/L were associated with a longer duration of MRSA bacteremia.⁵ Our study further exposes difficulties in achieving trough concentrations above 15 mg/L in children and lack of association of trough concentrations with vancomycin dose and outcome of infection. While 74% of our patients receiving ≥60 mg/kg/day had a trough between 10 and 20 mg/L, only 26% achieved a trough of 15 to 20 mg/L. For patients receiving <60 mg/kg/day, 35% achieved a trough of 15 to 20 mg/L (p = 0.5).

In adults, treatment success appears to correlate best with an estimated AUC₂₄/MIC ratio ≥400.^{8–10,12}

Table 3. Correlation of Treatment Outcomes With Vancomycin Doses, Trough Concentrations, and Estimated AUC₂₄/MIC Ratios

	Treatment Success (n = 58)	Treatment Failure (n = 9)	p value
Median dose, mg/kg/day (IQR)	60 (45–60)	56 (46–80)	0.8
Median trough, mg/L (IQR)	11.8 (9.6–15.2)	13.7 (10.6–18.2)	0.24
Median AUC ₂₄ /MIC ratio (IQR) using the Chang ¹⁸ method*	591 (385–793)	245 (90–728)	0.07
Median AUC ₂₄ /MIC ratio (IQR) using the Le et al ¹⁴ method	540 (446–681)	523 (250–772)	0.6

AUC₂₄, area under the curve at 24 hours; MIC, minimum inhibitory concentration

* n = 54 and 7 for treatment success and failure, respectively, as 6 patients did not have a documented height with which to calculate area under the curve.

Vancomycin troughs of 15 to 20 mg/L are suggested to increase the probability of achieving this target ratio.^{12,25} However, modeling studies suggest that lower vancomycin trough concentrations, which are more easily achieved, may produce ratios ≥ 400 in children.^{13,14} Frymoyer et al¹³ predicted that lower trough concentrations of 7 to 10 mg/L may achieve ratios ≥ 400 in children receiving 15 mg/kg/dose every 6 hours when the MIC is 1. AUC₂₄/MIC ratios ≥ 400 were achieved via Monte Carlo simulation with trough concentrations of 8 to 9 mg/L in patients receiving vancomycin 60 to 70 mg/kg/day at varying dosing intervals.¹⁴ In a retrospective study of 40 children, a mean trough of 11 mg/L was associated with a mean AUC₂₄/MIC ratio of 489.¹⁵ For our entire population, the median vancomycin trough concentration was 12.2 mg/L, and the median estimated AUC₂₄/MIC ratio was 598 using the Chang¹⁸ method and 529 using the Le et al¹⁴ method to estimate vancomycin clearance. Correlation between trough concentration and estimated ratio was low, reinforcing that trough concentrations may be poor surrogates for AUC₂₄/MIC ratios in children.

A major issue confounding all these studies is that AUC₂₄ is being estimated rather than measured. Both the Le et al¹⁴ and Chang¹⁸ equations for vancomycin clearance were derived using population pharmacokinetic simulation. These methods are attractive as they do not require additional trough concentration monitoring; however, we question their use in clinical practice due to finding widely differing results for each method.^{6,14,18} Similarly, when Kishk et al⁶ determined AUC₂₄/MIC ratios using 3 pharmacokinetic methods, trapezoidal, Chang¹⁸ and Le et al,¹⁴ the likelihood of achieving an AUC₂₄/MIC > 400 varied from 16% to 91% depending on the method used. They concluded that the trapezoidal method (which required 2 trough values) had the highest correlation with trough concentrations ($R^2 = 0.59$), and the Le et al¹⁴ method was most likely to produce ratios > 400 .⁶ In our analysis, we found that neither the Chang¹⁸ nor Le et al¹⁴ methods correlated well with trough levels (Chang¹⁸: $R^2 = 0.32$; Le et al¹⁴: $R^2 = 0.22$), similar to Kishk et al.⁶ This indicates a

need for studies to prospectively validate the methods used to estimate vancomycin AUC₂₄.

In the absence of a prospectively validated method for estimating vancomycin AUC₂₄ practical for use in routine clinical practice, examining the association between vancomycin dose, trough concentration, and outcome of infection should be the best way to determine optimal vancomycin dosing for invasive MRSA infections. In our patient population, comprising entirely MRSA infections, we observed treatment failure in 13.4% of patients. Median daily vancomycin doses did not differ significantly between treatment failures and successes (56 versus 60 mg/kg/day, $p = 0.8$) nor did median vancomycin trough concentration (13.7 versus 11.8 mg/L, $p = 0.24$). Although the median AUC₂₄/MIC ratio was greater for successes than for failures using the Chang¹⁸ method (591 versus 245), the difference was not significant and was not replicated using the Le et al¹⁴ method. This, again, highlights the problem of the validity of these equations and the difficulty of determining the optimal vancomycin dose in children to achieve treatment success while minimizing the risk of toxicity.

This study has several limitations as a result of its retrospective design. Although we reviewed 10 years of bacteremia episodes after exclusions, we were left with a relatively small sample (with few treatment failures), which limited the statistical power to detect differences between patient groups. We could not control timing of repeat cultures, which leads to inaccuracies in predicting duration of bacteremia. In addition, vancomycin trough concentrations were not always collected after changes in dosing, limiting our ability to assess the effect of the dose change. Additionally, attribution of treatment failure directly to antibiotic failure is fraught with uncertainty as there are factors outside of antibiotic therapy that contribute to treatment success such as source control. Source control is crucial to the successful treatment of many infection sites, such as CLABSI and infections with abscess formation (complicated skin and soft tissue infections or bone and joint infections). Finally, we cannot assess the accuracy of AUC₂₄

estimates as it is not routine practice in pediatrics to repeatedly measure vancomycin concentrations to accurately calculate AUC_{24} .

Conclusions

Vancomycin treatment failure occurred in 13.4% of children in this study, a much lower rate than previously reported. Vancomycin trough concentrations did not correlate well with estimated AUC_{24}/MIC ratios in our population of children with MRSA bacteremia no matter the method of AUC_{24} estimation. Vancomycin treatment failure was not associated with vancomycin daily dose, vancomycin trough concentration, or estimated AUC_{24}/MIC ratios. Large prospective studies using standard definitions of treatment failure and repeated vancomycin trough measurements are needed to predict failure in children with MRSA bacteremia treated with vancomycin. Methods to estimate vancomycin AUC_{24} , such as those by Chang¹⁸ and Le et al,¹⁴ require validation of appropriate pharmacokinetic studies in children in order to be used in future studies.

ARTICLE INFORMATION

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