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BRIEF REPORT

# Association Between Vancomycin Trough Concentrations and Duration of Methicillin-Resistant *Staphylococcus aureus* Bacteremia in Children

**Alice J. Hsu,[1] Rana F. Hamdy,[2] Yanjie Huang,[3] Jared A. Olson,[4] Shahira Ghobrial,[5] Jeffrey S. Gerber,[6,7] Adam L. Hersh,[8] and Pranita D. Tamma[9]**

[1]Department of Pharmacy, The Johns Hopkins Hospital, Baltimore, Maryland; [2]Department of Pediatrics, Children's National Health System, Washington, DC; [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [4]Department of Pharmacy, Primary Children's Hospital, Salt Lake City, Utah; [5]Department of Pharmacy, MedStar Georgetown University Hospital, Washington, DC; [6]Department of Pediatrics, Children's Hospital of Philadelphia, Pennsylvania; [7]Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia; [8]Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Utah, Salt Lake City; and [9]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland

In a multicenter retrospective study, we sought to determine the optimal vancomycin trough concentration that would impact the duration of methicillin-resistant *Staphylococcus aureus* bacteremia in children. We found that a median vancomycin trough concentration of <10 μg/mL within the first 72 hours may be associated with a longer duration of bacteremia compared to a median trough concentration of ≥10 μg/mL.

**Keywords.** pediatrics; methicillin-resistant *Staphylococcus aureus*; therapeutic drug monitoring; vancomycin troughs.

Studies in adults with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia have demonstrated treatment failures when vancomycin area under the concentration–time curve over minimum inhibitory concentration (AUC/MIC) ratios are <400 [1]. Pharmacokinetic modeling in adults has suggested that a trough concentration of 15 μg/mL is needed to achieve an AUC/MIC of ≥400 at a vancomycin MIC of 1 μg/mL [2]. It remains unclear if vancomycin trough concentrations of ≥15 μg/mL are needed in children with MRSA bacteremia. This question is of particular importance because children have enhanced renal elimination, which makes it challenging for them to obtain a trough concentration of ≥15 μg/mL, and attempts to reach this goal often require higher doses and an increased frequency of administration [3]. In addition, trough concentrations of >15 μg/mL are associated with an increased risk of nephrotoxicity [4].

Previous pharmacokinetic modeling in children has suggested that a trough concentration of 7 to 10 μg/mL may be adequate to achieve an AUC/MIC of ≥400 for >90% of children who receive vancomycin 60 mg/kg per day [5]; however, subsequent studies did not find the same results [6–9]. Because of the uncertainty of whether trough concentrations of ≥15 or ≥10 μg/mL should be targeted in children with MRSA bacteremia, we conducted a multicenter cohort study to determine if there is an optimal vancomycin trough cutoff value that would impact the duration of bacteremia.

## METHODS

Patients aged <18 years admitted between 2007 and 2014 to The Johns Hopkins Hospital (Baltimore, Maryland), Children's Hospital of Philadelphia (Philadelphia, Pennsylvania), or Primary Children's Hospital (Salt Lake City, Utah) with documented monomicrobial MRSA bacteremia were included. To meet eligibility criteria, the children had to have received intravenous vancomycin within 48 hours of the onset of bacteremia and have at least 1 steady-state vancomycin trough concentration measured. For each patient, only the first episode of bacteremia was included.

Baseline demographic, microbiologic, treatment, and clinical outcomes data were collected from medical records and entered into a REDCap database. The duration of MRSA bacteremia was calculated as the time between the first and the last positive blood culture. It is the practice at all 3 institutions to collect daily blood cultures from patients with MRSA bacteremia until clearance has been demonstrated. The dates and times of vancomycin administration were collected from medication-administration records. Trough concentration was defined as a level obtained within 60 minutes of the next scheduled dose, with appropriate timing of each previous dose (defined as no more than a 2-hour deviation from the scheduled time of administration). Due to changes in therapeutic drug-monitoring practices over the years, steady-state trough concentrations were classified as steady-state before the third dose or steady-state before at least the fourth dose of the same vancomycin regimen. All steady-state trough concentrations

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Correspondence: A. J. Hsu, PharmD, BCPS, AQ-ID, 600 N Wolfe Street, Carnegie 180, Baltimore, MD 21287 (ajenh1@jhmi.edu).

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measured during the first 72 hours of bacteremia were used for each patient, and the median value was calculated to estimate vancomycin exposure.

The primary exposure was median steady-state vancomycin trough concentration within the first 72 hours of MRSA bacteremia. The primary outcome was MRSA bacteremia that lasted for >3 days. Secondary outcomes included 30-day attributable death and 30-day significant sequelae from day 1 of MRSA bacteremia (eg, septic emboli, endocarditis, increase in size of existing vegetation, new or progressive venous thrombosis, new stroke, amputation, need for extracorporeal membrane oxygenation, metastatic foci of infection, or extension of existing focus of infection). Attributable death was defined as death in a patient whose blood culture was positive for MRSA at the time of death, death within 14 days of the onset of MRSA bacteremia without another explanation, or death in a patient with MRSA infection listed as the cause of death in the autopsy report. All patients were assessed by 2 infectious diseases clinicians to determine if adequate source-control interventions were undertaken within 3 days of the onset of MRSA bacteremia. Appropriate source control was defined as the removal of infected hardware, drainage of infected fluid collections, and/or debridement of devitalized bone, as appropriate.

Patient demographic and clinical characteristics were summarized using descriptive statistics. Comparisons were made using the Fisher exact test for categorical data and the Wilcoxon rank-sum test for continuous data. A receiver operating characteristic (ROC) curve was used to determine the trough cutoff value that would best discriminate between patients who developed bacteremia that lasted for >3 days versus those who did not. Logistic regression was used to estimate the association between median trough concentration and the outcome of bacteremia that lasted for >3 days. All analyses were performed using Stata 13.1 (StataCorp LP, College Station, Texas). A 2-sided *P* value of < .05 was used to determine statistical significance.

## RESULTS

During the 8-year study period, 232 children with MRSA bacteremia at the 3 institutions were evaluated, and 143 of these patients met the eligibility criteria. Patients were excluded if they did not have vancomycin initiated within the first 48 hours of bacteremia (n = 20), did not have steady-state vancomycin trough concentrations measured (n = 24), or had steady-state trough concentrations measured but not within the first 72 hours of bacteremia (n = 45). Ninety-six (53%) of the steady-state trough concentrations included were obtained before at least the fourth dose, and 86 (47%) were obtained before the third dose.

Thirty percent of the children had a median trough of <5 μg/mL, 43% had a median trough of 5 to <10 μg/mL, 19% had a median trough of 10 to <15 μg/mL, and 8% had a median trough of ≥15 μg/mL. The median durations of bacteremia were 2 days (interquartile range [IQR], 1–4 days) for those with a median trough of <5 μg/mL, 2 days (IQR, 1–4 days) for those with a median trough of 5 to <10 μg/mL, 1 day (IQR, 1–3 days) for those with a median trough of 10 to <15 μg/mL, and 2 days (IQR, 1–2 days) for those with a median trough of ≥15 μg/mL. Twenty-eight percent of the children with a median trough of <5 μg/mL, 32% with a median trough of 5 to <10 μg/mL, and 19% with a median trough of 10 to <15 μg/mL experienced bacteremia for >3 days. No child with a median trough of ≥15 μg/mL experienced bacteremia for >3 days (*P* = .097). ROC curve analysis revealed that a median trough cutoff of 10 μg/mL within the first 72 hours was most predictive of developing bacteremia that lasted for >3 days (AUC, 0.59 [95% confidence interval (CI), 0.52–0.66]; sensitivity, 87%; specificity, 31%).

Baseline characteristics of children with a median trough of <10 μg/mL and those with a median trough of ≥10 μg/mL are compared in Table 1. Children with a median trough of <10 μg/mL were less likely to be immunocompromised (7.6% vs 21.1%, respectively; *P* = .035) compared to children with a median trough of ≥10 μg/mL, and they had a lower baseline serum creatinine (0.3 vs 0.4, respectively; *P* = .002). Although not statistically significantly different, we found a higher frequency of osteoarticular infection in those with a median trough of <10 μg/mL (40% vs 29%, respectively) and a lower frequency of catheter-related infection (21% vs 39.5%, respectively) compared to those with a median trough of ≥10 μg/mL.

Based on a logistic regression model, a median vancomycin trough of <10 μg/mL within the first 72 hours was associated with an approximately 3-fold higher odds of developing MRSA bacteremia that lasted for >3 days when compared to a median trough of ≥10 μg/mL (unadjusted odds ratio [OR], 2.9 [95% CI, 1.1–9.0]; *P* = .043). After we adjusted for immunocompromised state and delayed source control, the adjusted OR was 2.7 (95% CI, 0.9–7.9) (*P* = .069).

Two children died as a result of MRSA bacteremia, and both of them had a median trough of <10 μg/mL. Nineteen percent of the children with a median trough of <5 μg/mL, 29% of those with a median trough of 5 to <10 μg/mL, 26% of those with a median trough of 10 to <15 μg/mL, and 0% of those with a median trough of ≥15 μg/mL experienced significant sequelae due to MRSA bacteremia (*P* = .154), including septic emboli (n = 11), endocarditis (n = 1), new venous thrombosis (n = 12), need for extracorporeal membrane oxygenation initiation (n = 1), metastatic foci of infection (n = 11), and extension of existing focus of infection (n = 12).

## DISCUSSION

This multicenter study of 143 children with MRSA bacteremia addressed the impact of median steady-state vancomycin trough concentrations on the duration of MRSA bacteremia.

**Table 1. Demographic and Clinical Characteristics of 143 Children With MRSA Bacteremia**

| Characteristic | Median Steady-State Vancomycin Trough Concentration <10 μg/mL During the First 72 h (n = 105) | Median Steady-State Vancomycin Trough Concentration ≥10 μg/mL During the First 72 h (n = 38) | *P* |
|---|---|---|---|
| Age (median [IQR]) (y) | 4.6 (1–9.4) | 6.3 (0.7–12.2) | .763 |
| Sex, female (n [%]) | 43 (41) | 13 (34.2) | .562 |
| Race (n [%]) | | | |
| Black | 39 (37.1) | 17 (44.7) | .018 |
| White | 25 (23.8) | 15 (39.5) | |
| Other | 41 (39.1) | 6 (15.8) | |
| Institution (n [%]) | | | |
| Children's Hospital of Philadelphia | 68 (64.8) | 10 (26.3) | <.001 |
| The Johns Hopkins Hospital | 21 (20) | 18 (47.4) | |
| Primary Children's Hospital | 16 (15.2) | 10 (26.3) | |
| Baseline serum creatinine (mg/dL) | 0.3 (0.2–0.4) | 0.4 (0.3–0.6) | .002 |
| Previously healthy with no underlying medical conditions (n [%]) | 44 (41.9) | 10 (26.3) | .118 |
| Immunocompromised (n [%])[a] | 8 (7.6) | 8 (21.1) | .035 |
| Primary source of MRSA bacteremia (n [%]) | | | |
| Osteoarticular | 42 (40) | 11 (29) | .473 |
| Catheter related | 22 (21) | 15 (39.5) | |
| Skin or soft tissue | 12 (11.4) | 5 (13.2) | |
| Pneumonia | 10 (9.5) | 2 (5.3) | |
| Suppurative thrombophlebitis | 5 (4.8) | 1 (2.6) | |
| Central nervous system infection | 3 (2.9) | 1 (2.6) | |
| Pyomyositis | 3 (2.9) | 0 (0) | |
| Other hardware | 2 (1.9) | 1 (2.6) | |
| Endocarditis | 2 (1.9) | 0 (0) | |
| Intra-abdominal | 0 (0) | 1 (2.6) | |
| Suppurative focus of infection (n [%]) | 84 (80) | 32 (84.2) | .637 |
| Source control intervention performed (n/N [%]) | 71/84 (84.5) | 26/32 (81.3) | .780 |
| Delayed source control intervention for >3 days or no source control (n/N [%]) | 28/84 (33.3) | 12/32 (37.5) | .669 |
| Intensive care unit stay on day 1 of MRSA bacteremia (n [%]) | 36 (34.3) | 16 (42.1) | .434 |
| Vancomycin MIC from first positive blood culture (n [%]) | | | |
| 0.5 μg/mL | 35 (33.3) | 14 (36.8) | .882 |
| 1 μg/mL | 54 (51.4) | 19 (50) | |
| 2 μg/mL | 9 (8.6) | 4 (10.5) | |
| Combination therapy within the first 72 h of MRSA bacteremia (n [%]) | 26 (24.8)[b] | 14 (36.8)[c] | .205 |

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Includes primary immunodeficiency, human immunodeficiency virus infection, absolute neutrophil count of <500 cells/mm$^3$, solid organ transplantation, immunomodulator therapy or >14 days of systemic corticosteroid use, chemotherapy within previous 6 months, and hematopoietic stem cell transplantation within previous 12 months.

[b]Gentamicin (n = 18), clindamycin (n = 11), rifampin (n = 2), and linezolid (n = 1).

[c]Gentamicin (n = 8), clindamycin (n = 7), rifampin (n = 2), and linezolid (n = 1).

ROC curve analysis revealed that a median trough concentration cutoff of 10 μg/mL within the first 72 hours was most predictive of developing MRSA bacteremia that lasted for >3 days. Children with a median trough concentration of <10 μg/mL had an approximately 3-fold higher odds of developing bacteremia that lasted for >3 days.

Similar to our study, Yoo et al [10] published a single-center retrospective study of 46 children with healthcare-associated MRSA bacteremia and found that initial trough concentrations of <10 μg/mL were associated with a higher odds of developing bacteremia that lasted for ≥2 days (unadjusted OR, 7 [95% CI, 1.02–47.97]), but on multivariable analysis, the effect did not remain significant.

Although our findings suggest that a median trough concentration of <10 μg/mL is associated with a longer duration of MRSA bacteremia, it remains unclear if trough concentrations of ≥15 μg/mL provide an additional benefit over trough concentrations of ≥10 μg/mL. Our study had few patients (n = 11) with a median vancomycin trough concentration of ≥15 μg/mL within the first 72 hours, which is likely a reflection of different monitoring practices at the 3 sites (only 1 site routinely targeted trough concentrations of ≥15 μg/mL). It also is likely reflective of the difficulty attaining trough concentrations of ≥15 μg/mL in children because of their enhanced renal elimination [3, 11, 12]. Because of our limited power, we were unable to perform logistic regression analysis for trough concentrations of <15 versus those of ≥15 μg/mL.

However, no child with a median trough concentration of ≥15 μg/mL experienced bacteremia that lasted for >3 days, attributable death, or significant sequelae as a result of MRSA bacteremia.

Two previous studies did not find a benefit in those with trough concentrations of ≥15 μg/mL [13, 14]. McNeil et al [13] evaluated 54 children with healthcare-associated MRSA bacteremia and found no association between the highest trough concentration achieved within 96 hours and duration of bacteremia or attributable death. A second study evaluated 35 children with MRSA bacteremia due to osteoarticular infection, and found no difference in the duration of bacteremia between the low- and high-trough groups [14]. Few children in either study had trough concentrations of ≥15 μg/mL (15 and 7, respectively), which limits the power of the studies to detect differences in outcomes, if they exist.

Our study had several limitations. First, because of the retrospective design, our data collection was limited to what was documented in the medical records. Second, we did not estimate AUC/MIC exposure for our patients. Third, we included trough concentrations obtained before the third dose because it was standard practice before 2009; however, trough concentrations before the third dose may not be representative of true steady state for some patients depending on the frequency of drug administration and age of the patient. Finally, there may have been inconsistencies with data collection across the study centers. To maintain consistency, the investigators participated in weekly telephone calls to review patient cases and adhered to a detailed data dictionary.

In summary, our data suggest that a median steady-state vancomycin trough concentration of <10 μg/mL within the first 72 hours may be associated with developing MRSA bacteremia that lasts for >3 days in children. Previously published data from our cohort suggest that each additional day of bacteremia increases the odds of developing serious subsequent sequelae such as septic emboli and metastatic disease [15]. Targeting trough concentrations of ≥10 μg/mL can potentially decrease the duration of bacteremia and these subsequent sequelae. We were unable to demonstrate an additional benefit with trough concentrations of ≥15 μg/mL because of the limited statistical power. Future studies powered to assess this relationship will be highly informative.

## Notes

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