의학석사 학위논문

메티실린 내성 황색포도알균 균혈증 소아에서 베이지안 유도 투여 소프트웨어로 추정한 최적의 혈중 반코마이신 곡선하면적

Optimal vancomycin area under the concentration-time curve target estimated by Bayesian-guided dosing software in children with methicillin-resistant *Staphylococcus aureus* bacteremia

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이 논문을 의학석사 학위 논문으로 제출함

2024년 2월

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Abstract

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Title: Optimal vancomycin area under the concentration-time curve target estimated by Bayesian-guided dosing software in children with methicillin-resistant *Staphylococcus aureus* bacteremia

Background: Despite the widespread use of vancomycin in methicillin-resistant *Staphylococcus aures* (MRSA) infections, evidence for the target of the area under the concentration-time curve (AUC) for pediatric population is lacking. This study was conducted using Bayesian-based software to derive the target of vancomycin AUC, aiming to provide optimal outcomes for pediatric patients with MRSA bacteremia.

Methods: From September 2013 to December 2021, all hospitalized patients with MRSA bacteremia aged ≥ 3 months and < 19 years were analyzed retrospectively. The AUC of vancomycin over 168 hours after the first dose was simulated using Bayesian-guided dosing software, incorporating individual patient data, including age, sex, height, weight, serum creatinine, and all measured vancomycin trough concentrations (C_{trough}). Outcomes included persistent bacteremia (≥ 48 hours), recurrence, and 30-day all-cause mortality. Acute kidney injury (AKI) was investigated for 14 days after initiating vancomycin therapy. To identify an appropriate AUC target for anticipating optimal outcomes, I initially examined whether the AUC/minimum inhibitory concentration (MIC) ratio of ≥ 400, as per recent guidelines, demonstrated clinical benefits. In cases where this target was considered inappropriate, alternative AUC targets were explored through receiver operating characteristic (ROC) analysis. In addition, factors potentially influencing outcomes, such as intensive care unit stay, immunocompromised state, clinical severity, polymicrobial bloodstream infection, MIC, source of infection, and conducted interventions, were collectively analyzed.

Results: During the study period, 79 cases of MRSA bacteremia were identified. Cases that had received vancomycin 72 hours before the onset of MRSA bacteremia (n=5), had a treatment period of vancomycin <72 hours (n=10), or were receiving renal replacement therapy at baseline (n=8) were excluded, leaving 56 cases finally included in the study. Persistent bacteremia, recurrence, 30-day all-cause mortality, and AKI were observed in 10 (17.9%), 8 (14.8%), 2 (3.7%), and 4 (7.1%) cases, respectively. AUC over the

second 24 hours ($AUC_{24\text{-}48}$) ≥ 400 did not demonstrate clinical benefit in the outcomes. On the contrary, persistent bacteremia was frequently observed in patients with higher AUCs. $AUC_{24\text{-}48}$ was a more statistically significant parameter than AUC over the first 24 hours ($AUC_{0\text{-}24}$) in predicting persistent bacteremia. $AUC_{24\text{-}48}$ ≥ 528.2 mg·h/L was associated with persistent bacteremia ($P < 0.01$). $AUC_{24\text{-}48}$ ≥ 536.8 mg·h/L was associated with AKI ($P = 0.01$). Variables associated with mortality and recurrence could not be identified. The group with persistent bacteremia exhibited a significantly higher $AUC_{24\text{-}48}$ compared to the group with resolved bacteremia, along with a higher frequency of the presence of noneradicable or not eradicated focus and a higher occurrence of AKI.

Conclusion: I suggest that an $AUC_{24\text{-}48}$ < 528.2 mg·h/L is the optimal target for non-dialysis pediatric patients aged ≥ 3 months with MRSA bacteremia. The lower limit of the target range indicating subtherapeutic levels has not been identified. A large-scale multicenter study is necessary to generalize this finding for pediatric patients with MRSA bacteremia.

Keywords: MRSA, bacteremia, vancomycin, Bayesian, pediatric

차 례

표 및 그림 차례

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the major health concerns in both healthcare-associated and community-acquired infections in children, and clinical outcomes of MRSA bacteremia are considered to be worse than cases caused by methicillin-susceptible *S. aureus* (MSSA) [1, 2]. Vancomycin is an important treatment option for invasive MRSA infections [1]. Traditional therapeutic drug monitoring (TDM) of vancomycin has been relied primarily on measuring the vancomycin trough concentration (C_{trough}). However, trough level monitoring does not consistently reflect the area under the concentration-time curve (AUC), which is considered a surrogate marker for therapeutic efficacy [3, 4]. Moreover, several studies have shown inconsistent correlations between C_{trough} and clinical outcomes [5-8]. In addition, a meta-analysis study has suggested that monitoring AUC may decrease the incidence of acute kidney injury (AKI) compared to measuring C_{trough} [9]. The study found that the incidence of AKI increased when the AUC over the first 24 hours (AUC_{0-24}) or AUC over the second 24 hours (AUC_{24-48}) exceeded 650 mg·h/L. The 2020 revised vancomycin TDM guidelines recommend adjusting the vancomycin dose based on AUC measurement prefer to use Bayesian-guided software [10]. Bayesian method can easily estimate the AUC using the vancomycin population pharmacokinetic (PK) model and individual patient information [10, 11].

In pediatric patients, a C_{trough} of 7-15 mg/L, roughly equivalent to an AUC of 400-600 mg·h/L [10, 12], has been considered optimal target for treating MRSA bacteremia. Although elevated nephrotoxicity has been reported at $C_{trough} > 15$ mg/L without demonstrating clinical benefits [13], vancomycin $C_{trough} < 10$ mg/L did not show a significant difference in treatment failure for MRSA bacteremia among children [14]. Despite differences in AUC estimation methods and limitations in retrospective studies, previous studies on adults with MRSA infection have indicated that an AUC/minimum inhibitory concentration (MIC) ratio of ≥ 400 is indicative of higher therapeutic efficacy [4, 15, 16]. However, there is a lack of clinical data in children with MRSA bacteremia to determine the optimal AUC. Two retrospective studies have investigated differences in clinical outcomes with an AUC/MIC of 400 as the cut-off point in pediatric patients [17, 18]. One study evaluated both AUC_{0-24} and the average 24-hour AUC over the first 72 hours using Bayesian estimation [17], while the other evaluated the steady-state AUC/MIC using

two different equations [18]. However, both studies did not find statistically significant differences in the incidence of mortality, recurrence, persistent bacteremia, or AKI based on the AUC/MIC of 400. However, another retrospective study in children observed a statistically significant increase in persistent bacteremia at 48-72 hours at AUC/MIC < 300, where AUC was derived using an equation [19].

There is relative inconsistency in the relationship between vancomycin exposure and clinical efficacy in children. Considering that pediatric patients with MRSA bacteremia may have different clinical severity, prognosis, and physiological responses to medication, it remains uncertain whether the AUC/MIC target recommended for adults can be directly extrapolated to pediatric patients [20], particularly given the potential variability of MIC results depending on the measurement method [21, 22]. Therefore, this study aims to explore the optimal target range of AUC in pediatric patients with MRSA bacteremia using the Bayesian-guided dosing software, taking into consideration clinical outcomes including persistent bacteremia, 30-day all-cause mortality, recurrence, and AKI.

2. Methods

2.1 Study population and design

This retrospective study reviewed the medical records of all patients aged 3 months to 18 years diagnosed with MRSA bacteremia at Asan Medical Center Children's Hospital, a tertiary referral center in Seoul, between September 2013 and December 2021. All cases were reviewed for a period of 3 months from the onset of bacteremia. The following cases were excluded: administration of vancomycin within 72 hours prior to the onset of MRSA bacteremia, duration of vancomycin treatment < 72 hours, and receiving renal replacement therapy at baseline.

Patient's demographic and clinical characteristics, including underlying diseases, primary source of MRSA infection, source control history, vancomycin administration data (each injection time, dose, and interval), inotropic use, ventilator care, extracorporeal membrane oxygenation (ECMO), renal replacement therapy, and intensive care unit (ICU) stay were examined. Laboratory data, including blood culture, vancomycin MIC, vancomycin C_{trough}, serum creatinine, were extracted. Estimated glomerular filtration rate (GFR) was calculated using Schwartz equation [23].

2.2 Outcomes

As a microbiological outcome, persistent bacteremia defined as positive blood culture at ≥ 48 hours since vancomycin was initiated after onset of MRSA bacteremia. Recurrence was defined as a positive MRSA blood culture at least 7 days after two consecutive negative blood cultures or within 30 days after discontinuation of anti-MRSA therapy. Recurrence was not counted as separate case. However, cases of MRSA bacteremia occurring more than 30 days after discontinuing anti-MRSA therapy were considered as new MRSA infections and included as separate one. As a clinical outcome, death within 30 days after onset of MRSA bacteremia (referred to as 30-day all-cause mortality) or the recurrence of MRSA bacteremia were reviewed, any of which were defined as clinical failure.

2.3 Definitions

AKI was defined as either an increase in serum creatinine of ≥ 50% or ≥ 0.5 mg/dL, whichever was greater, compared to the patient`s baseline value (as determined by the initial laboratory finding) [24] or the need for renal replacement therapy within 14 days after administering vancomycin. Immunocompromised state was defined as those with primary immune deficiency, a history of hematopoietic stem cell transplantation within one year, and those receiving immunosuppressant or corticosteroid therapy with prednisone or its equivalent at doses of ≥ 20 mg/day (≥ 2 mg/kg/day for patients weighing less than 10 kg) for at least 14 days within 30 days prior to MRSA bacteremia. Severe presentation at onset of MRSA bacteremia was defined as the following cases: patients who required new ICU care for the management of sepsis or septic shock, mechanical ventilation, ECMO, or inotropic drugs use within 24 hours before or after onset of MRSA bacteremia. The definitions of healthcare–associated infection, central line-associated bloodstream infection (CLABSI), specific primary site definition of secondary bacteremia, and catheter-related bloodstream infection (CRBSI) were based on the respective references [25-27]. The category of "uncertain focus" encompassed cases in which the definition of CRBSI was not met among CLABSI and instances where there is no identifiable focus at all. An "eradicable focus" was inclusive of CRBSI, peripheral catheter infection, surgically removable infections, and drainable abscess. The term "eradicated focus" was defined as the removal of infected device removal or incision and drainage performed within 3 days for conditions falling under the eradicable focus category. A "noneradicable focus," treated solely with antibiotics without surgery or intervention for the primary focus, included pneumonia, infective endocarditis, and osteomyelitis, which posed challenges for removal considering the high mortality associated with these conditions [28, 29].

2.4 Microbiological data

Bacterial cultures were performed using the BACTEC FX automated incubation system (Becton Dickinson, NJ, USA). Automated susceptibility testing was performed using MicroScan WalkAway (Siemens, CA, USA), and methicillin-resistance was defined as oxacillin MIC > 2 mg/L in accordance

with the Clinical and Laboratory Standards Institute (CLSI) guidelines [30]. In cases where multiple MRSA strains with different vancomycin MICs were detected in a single episode of MRSA bacteremia from the same patient, the highest MIC value was selected for the analysis.

2.5 Estimation of vancomycin AUC

The estimation of vancomycin AUC was conducted using the Bayesian-guided dosing software, PrecisePK software trials (PrecisePK, CA, USA). For each case, the vancomycin AUC value for 168 hours after vancomycin administration was simulated by software. For cases with a creatinine level < 0.9 mg/dL, the basic pharmacokinetic (PK) model for AUC estimation was automatically selected in the PrecisePK web application's set model by Le et al. [12]. Alternatively, for cases with a creatinine ≥ 0.9 mg/dL, another PK model specifically designed for children with renal insufficiency was automatically selected [31].

2.6 Receiver operating characteristic (ROC) analysis for the optimal threshold of vancomycin AUC

Firstly, in accordance with recently presented guidelines and studies [8], an analysis was conducted to determine whether AUC ≥ 400 mg·h/L (assuming an MIC of 1.0 mg/L) demonstrates clinical benefits. Similar to previous studies [6, 32], $AUC_{24\text{-}48}$, representing the time when vancomycin concentration is primarily obtained, was selected for analysis. If benefits were not identified at $AUC_{24\text{-}48}$ ≥ 400 mg·h/L, ROC analysis was employed to explore alternative AUC values demonstrating optimal outcomes.

ROC analysis was conducted to determine the vancomycin AUC target range for predicting persistent bacteremia at > 48 hours after vancomycin administration (hereafter referred to as persistent bacteremia at > 48 hours), clinical failure, and AKI. The corresponding maximized Youden index (J = sensitivity + specificity – 1) for each of the two vancomycin AUC values measured during different periods ($AUC_{0\text{-}24}$, $AUC_{24\text{-}48}$) was calculated to assess the predictive performance of vancomycin AUC for the specified

outcomes and to identify optimal threshold values for each period.

2.7 Statistical analysis

To analyze the correlation between vancomycin C_{trough} and AUC, Pearson`s correlation coefficient was used. For comparison between two groups, Fisher's exact test was employed for categorical data, and the Mann-Whitney test or independent sample t-test was used for numerical data. The following covariates were included in logistic regression analysis of risk factors associated with outcomes: age, estimated GFR, immunocompromised state, ICU stay at baseline, polymicrobial bloodstream infection, infection source control (uncertain focus, eradicated focus, noneradicable or not eradicated focus), and severe presentation at onset. Variables associated with outcomes at $P < 0.1$ in univariate analysis were considered for inclusion in a multivariate model for persistent bacteremia, clinical failure and AKI. All analyses were two-tailed, and $P < 0.05$ was considered statistically significant.

3. Result

3.1 Study population and clinical characteristics

A total of 79 cases of MRSA bacteremia were observed between September 1, 2013, and December 31, 2021. Among these cases, 23 were excluded for the following reasons: (1) administration of vancomycin since 72 hours before the onset of MRSA bacteremia (n=5); (2) duration of vancomycin treatment < 72 hours (n=10); and (3) receiving renal replacement therapy at baseline (n=8).

A total of 56 cases of MRSA bacteremia were included in this study, with a median age of 2.4 (interquartile range [IQR]: 0.7-6.5) years (Table 1). Most of the cases occurred in patients with underlying diseases (92.9%) and were healthcare–associated infections (96.4%). Additionally, 35.7% of the cases occurred during the patients` stay in the ICU. A severe presentation at the onset of bacteremia was observed in 11 cases (19.6%). Except for one, all cases were secondary bacteremia, with 40 cases being CLABSI, of which 20 met the criteria for CRBSI. Other primary focus included peripheral phlebitis (n=4), deep-seated infections (n=6), pneumonia (n=4), and osteomyelitis (n=1). Eradicable focus comprised 30 cases (53.6%), with 15 cases being eradicated and 15 cases not eradicated. Uncertain focuses and noneradicable focuses accounted for 21 (37.5%) and 5 cases (8.9%), respectively. The majority of MRSA isolates exhibited a vancomycin MIC ≥ 1.0 mg/L (n = 55; 98.2%), with MIC values of 1.0 mg/L (n = 42) or 2.0 mg/L (n =13), and one remaining isolate had an MIC of 0.5 mg/L.

3.2 Outcomes and comparison between the two groups stratified by $AUC_{24\text{-}48}$ of 400 mg·h/L

Overall, persistent bacteremia at > 48 hours was observed in 17.9% (10/56). The rates of recurrence and 30-day all-cause mortality were 14.8% (8/54) and 3.7% (2/54), respectively (Table 1).

When comparing the two groups based on $AUC_{24\text{-}48}$ of 400 mg·h/L, demographics and clinical characteristics were similar, except that the group with higher AUC had a higher median age (2.8 years vs. 1.0 years, $P < 0.01$) and a tendency to have a higher frequency of immunocompromised state (44.0% vs. 19.4%, $P = 0.08$). Persistent bacteremia at > 48 hours was observed more frequently in the group

with $AUC_{24\text{-}48} \geq 400$ mg·h/L without statistical significance (28.0% vs. 9.7%, $P = 0.09$). Recurrence rate was comparable between the two groups.

3.3 Acute kidney injury

AKI was observed in 7.1% (4/56) and was exclusively observed in the group with $AUC_{24\text{-}48} \geq 400$ mg·h/L. In the group with AKI, $AUC_{24\text{-}48}$ and initial C_{trough} were higher (572.1 mg·h/L and 17.3 mg/L for AKI vs. 374.1 mg·h/L and 7.4 mg/L for non-AKI, $P = 0.01$ and $P < 0.01$, respectively) even though they received a slightly lower initial vancomycin dose (30.6 mg/kg/day for AKI vs. 42.6 mg/kg/day for non-AKI; $P = 0.06$). The median duration from the initiation of vancomycin to the occurrence of AKI was 64.8 hours (IQR: 56.8-73.4).

Table 1. Demographics, clinical characteristics, outcomes and comparison between the two groups separated by AUC_{24-48} of 400 mg·h/L

Characteristics	Overall (n=56)	AUC_{24-48}, mg·h/L [a]		*P*- value
	No. (%)	< 400 (n=31)	≥ 400 (n=25)	
Age, median (IQR), years	2.4 (0.7-6.5)	1.0 (0.5-5.7)	2.8 (2.2-10.0)	< 0.01 ¶
Male	29 (51.8)	19 (61.3)	10 (40.0)	0.18
Initial estimated GFR, median (IQR), mL/min/1.732m^2	154.3 (106.1-211.4)	137.1 (105.7-180.0)	163.0 (107.4-229.2)	0.18 ¶¶
Presence of underlying disease	52 (92.9)	29 (93.5)	23 (92.0)	> 0.99
Hemato-oncologic diseases	11 (19.6)	3 (9.7)	8 (32.0)	0.05
Congenital heart diseases	12 (21.4)	7 (22.6)	5 (20.0)	> 0.99
Chronic gastrointestinal diseases	10 (17.9)	6 (19.4)	4 (16.0)	> 0.99
Chronic lung diseases	9 (16.1)	7 (22.6)	2 (8.0)	0.17
Neuromuscular diseases	3 (5.4)	1 (3.2)	2 (8.0)	0.58
Other genetic diseases [b]	6 (10.7)	5 (16.1)	1 (4.0)	0.21
Primary immunodeficiency	1 (1.8)	0	1 (4.0)	0.45
Immunocompromised state [c]	17 (30.4)	6 (19.4)	11 (44.0)	0.08
ICU stay at baseline	20 (35.7)	13 (41.9)	7 (28.0)	0.40
Healthcare-associated infection	54 (96.4)	30 (96.8)	24 (96.0)	> 0.99
Polymicrobial BSI [d]	12 (21.4)	7 (22.6)	5 (20.0)	> 0.99
Source of bacteremia infection				
Without a focus	1 (1.8)	0	1 (4.0)	0.45
CLABSI except CRBSI	20 (35.7)	11 (35.5)	9 (36.0)	> 0.99
Definite CRBSI	20 (35.7)	10 (32.3)	10 (40.0)	0.59
Peripheral phlebitis	4 (7.1)	3 (9.7)	1 (4.0)	0.62
Deep-seated infection [e]	6 (10.7)	4 (12.9)	2 (8.0)	0.68
Pneumonia	4 (7.1)	2 (6.5)	2 (8.0)	> 0.99
Osteomyelitis	1 (1.8)	1 (3.2)	0	> 0.99
Infection source control				
Uncertain focus	21 (37.5)	11 (35.5)	10 (40.0)	0.79
Eradicated focus [f]	15 (26.8)	8 (25.8)	7 (28.0)	> 0.99

Noneradicable or not eradicated focus [g]	20 (35.7)	12 (38.7)	8 (32.0)	0.78
Severe presentation at onset [h]	11 (19.6)	5 (16.1)	6 (24.0)	0.51
Vancomycin MIC of 2.0 mg/L	13 (23.2)	8 (25.8)	5 (20.0)	0.75
Persistent bacteremia [i]	10 (17.9)	3 (9.7)	7 (28.0)	0.09
Recurrence [j]	8 (14.8)	4 (13.8)	4 (16.0)	> 0.99
30-day all-cause mortality [k]	2 (3.7)	0	2 (8.0)	0.21
AKI [l]	4 (7.1)	0	4 (16.0)	0.03

Abbreviations: AKI, acute kidney injury; AUC_{24-48}, area under the curve over the second 24 hours; BSI, bloodstream infection; CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; GFR, glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration.

Data were analyzed with Fisher's exact test except ¶ and ¶¶: The data marked with ¶ were analyzed using Mann-Whitney test and ¶¶ were analyzed using independent samples t-test.

[a]: As the broth microdilution method was not used for MIC measurement, AUC was used as the parameter instead of AUC/MIC (assuming an MIC of 1 mg/L).

[b]: Mitochondrial disease (n=2), congenital insensitivity to pain with anhidrosis, SLC7a7 mutation, arthrogryposis multiplex congenita, Miller-Dieker syndrome.

[c] Congenital immuno-deficiency (n=1), History of hematopoietic stem cell transplantation within one year (n=6), Receiving immunosuppressive drugs within 30 days before onset (n=10)

[d]: 12 cases in which two or more common commensal or any pathogenic microorganisms other than MRSA were identified in blood culture: *Enterococcus faecalis* (n=4), *Streptococcus pneumoniae* (n=2), *Staphylococcus epidermidis* (n=2), *Candida albicans* (n=2), *Enterococcus faecium* (n=2), *Burkholderia* spp. (n=1), *C. glabrata* (n=1), *Acinetobacter baumannii* (n=1), *Micrococcus spp.* (n=1).

[e]: Mediastinitis after cardio-surgery (n=3), mediastinitis associated with tracheostomy site infection (n=1), retropharyngeal abscess with mediastinitis (n=1), suspicious osteomyelitis associated with coccyx sore (n=1)

[f]: Eradicated focus included CRBSI (n=9), peripheral phlebitis (n=3), and deep-seated infection (n=3).

[g]: Not eradicated focus included CRBSI (n=11), deep-seated infection (n=3), and thrombophlebitis with skin and subcutaneous abscess (n=1).

[h]: Extracorporeal membrane oxygenation (n=2), mechanical ventilator (n=4), transfer to intensive care unit (n=2) and receiving inotropic agent for hypotension (n=3)

[i]: Cases of positive blood culture at ≥ 48 hours

[j]: Cases of MRSA bacteremia that recurred at least 7 days after two consecutive negative blood cultures or within 1 month after the discontinuation of MRSA treatment. Two cases were excluded due to loss of follow-up.

[k]: Two cases were excluded due to loss of follow-up.

[l]: Cases within 14 days after the first vancomycin dose for MRSA bacteremia.

3.4 Vancomycin pharmacokinetic/pharmacodynamic parameters

The median time of measuring initial C_{trough} was 30.8 hours (IQR: 19.8-50.3) after the initiation of vancomycin. Vancomycin concentrations were measured twice or more within 72 hours in 19 cases (33.9%). The median value (IQR) of the initial vancomycin dose, initial C_{trough}, AUC_{0-24}, and AUC_{24-48} were 41.1 (40.0-59.2) mg/kg/day, 9.5 (5.7-12.8) mg/L, 323.1 (256.7-408.1) mg·h/L, and 382.2 (294.0-479.1) mg·h/L, respectively. Pearson`s correlation coefficient showed a moderate correlation between the average vancomycin C_{trough} within the first 72 hours and AUC_{24-48} ($r = 0.646$, $P < 0.01$) (Figure 1).

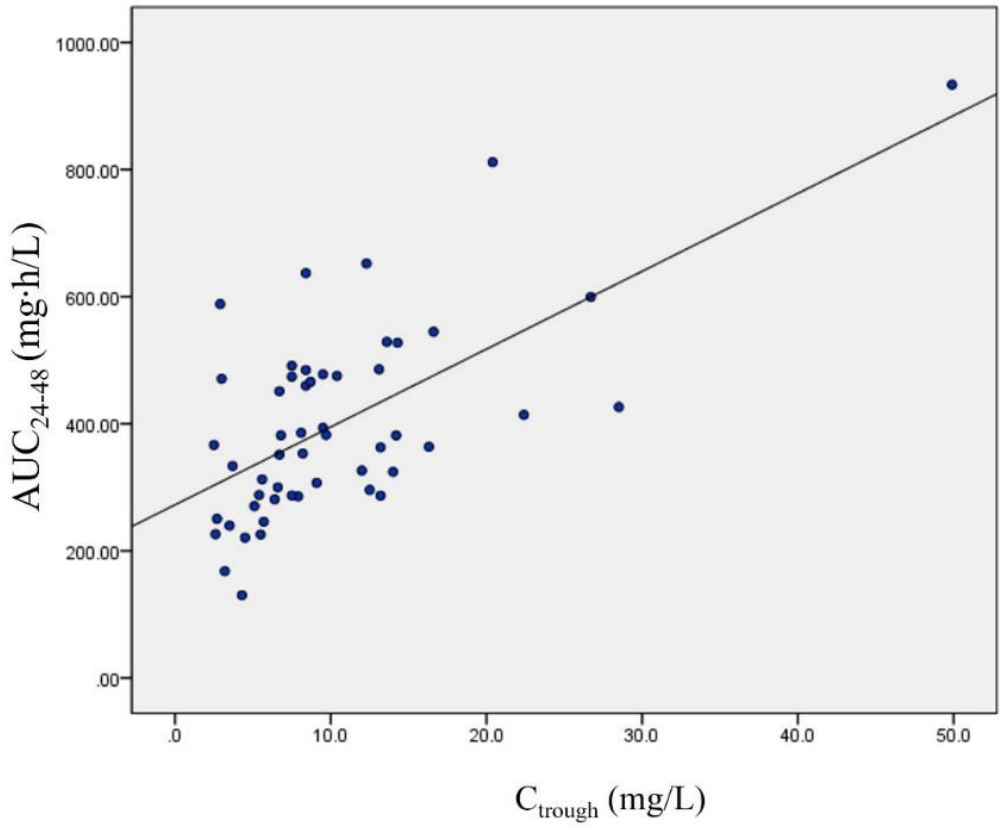

Figure 1. The correlation between average vancomycin trough concentration (C_{trough}) within the first 72 hours and AUC_{24-48} (Pearson coefficient=0.646, *P* < 0.01). The median time of measuring of all C_{trough} within the first 72 hours was 42.0 hours (IQR: 31.9-45.9) after initiation of vancomycin.

Table 2. Vancomycin pharmacokinetic/pharmacodynamic parameters

Characteristics	Overall (n=56)	AUC_{24-48}, mg·h/L [a]		*P* value
		< 400 (n=31)	≥ 400 (n=25)	
Initial vancomycin dose, mg/kg/day	41.1 (40.0-59.2)	40.2 (39.2-41.1)	59.5 (50.6-60.3)	< 0.01
Initial C_{trough}, mg/L	7.5 (5.2-12.2)	6.4 (4.4-9.6)	10.7 (7.2-14.3)	0.01
AUC_{0-24}, mg·h/L	323.1 (256.7-408.1)	259.4 (236.8-294.0)	419.6 (392.6-465.1)	< 0.01 ¶
AUC_{24-48}, mg·h/L	382.2 (294.0-479.1)	300.0 (260.4-358.0)	484.6 (465.9-588.5)	< 0.01

Data are presented as median value (IQR).

Abbreviations: AUC, area under the curve; AUC_{0-24}, AUC over the first 24 hours; AUC_{24-48}, AUC over

the second 24 hours; CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; C_{trough}, trough concentration; IQR, interquartile range.

All categorical data were analyzed by Fisher's exact test. Continuous data were analyzed by Mann-Whitney test except ¶: The data marked with ¶ were analyzed using independent samples t-test.

[a]: As the broth microdilution method was not used for MIC measurement, AUC was used as the parameter instead of AUC/MIC (assuming an MIC of 1.0 mg/L).

3.5 Determining vancomycin AUC cut-off points using ROC analysis

For predicting persistent bacteremia, vancomycin $AUC_{24\text{-}48}$ showed a statistically significant higher area under the ROC curve with a value of 0.735 ($P = 0.02$) between the two vancomycin AUC values ($AUC_{0\text{-}24}$, $AUC_{24\text{-}48}$) (Table 3). I established a significant cutoff for predicting persistent bacteremia: a vancomycin $AUC_{24\text{-}48}$ value of 528.2 mg·h/L, which resulted in a maximized Youden index of 0.535, with a sensitivity of 60% and specificity of 93.5%. The incidence of persistent bacteremia in the group with a vancomycin $AUC_{24\text{-}48} \geq 528.2$ mg·h/L was significantly higher than in the group with $AUC_{24\text{-}48} <$ 528.2 mg·h/L (66.7% vs. 8.5%, respectively, $P < 0.01$).

None of vancomycin AUC values ($AUC_{0\text{-}24}$, $AUC_{24\text{-}48}$) demonstrated statistically significant performance as a classifier for predicting clinical failure.

For predicting AKI, vancomycin $AUC_{24\text{-}48}$ showed a statistically significant higher area under the ROC curve with a value of 0.861 ($P = 0.02$) between the two vancomycin AUC values ($AUC_{0\text{-}24}$, $AUC_{24\text{-}48}$). Youden index was maximized (0.654, along with a sensitivity of 75% and specificity of 90.4%) at a vancomycin $AUC_{24\text{-}48}$ of 536.8 mg·h/L. The incidence of AKI was significant higher in the $AUC_{24\text{-}48} \geq$ 536.8 mg·h/L group compared to the $AUC_{24\text{-}48} <$ 536.8 mg·h/L group (37.5% vs. 2.1%, respectively, $P = 0.01$).

Table 3. Vancomycin AUC for predicting outcomes of MRSA bacteremia

Vancomycin AUC	Persistent bacteremia		Clinical failure		AKI	
	Vancomycin AUC [a] (*J*)	Area under the ROC curve (*P*-value)	Vancomycin AUC [a] (*J*)	Area under the ROC curve (*P*-value)	Vancomycin AUC [a] (*J*)	Area under the ROC curve (*P*-value)
AUC_{0-24}	478.2 (0.378)	0.659 (0.12)	N.A.	0.443 (0.58)	417.3 (0.558)	0.784 (0.06)
AUC_{24-48}	528.2 (0.535)	0.735 (0.02)	458.8 (0.282)	0.507 (0.95)	536.8 (0.654)	0.861 (0.02)

Abbreviations: AKI, acute kidney injury; AUC, area under the curve; AUC_{0-24}, AUC for the first 24 hours; AUC_{24-48}, AUC over the second 24 hours; N.A., not applicable; ROC, Receiver operating characteristic.

[a]: Vancomycin AUC values and their corresponding maximized Youden index (*J*) for predicting each specific outcome.

3.6 Risk factors associated with outcomes of MRSA bacteremia

In the univariate logistic regression analysis, persistent bacteremia at > 48 hours was associated with noneradicable or not eradicated focus (vs. uncertain focus [reference], odds ratio [OR] 10.77, $P = 0.04$), and $AUC_{24\text{-}48} \geq 528.2$ mg·h/L (OR 21.50, $P < 0.01$) (Table 4). After adjusting variables with $P < 0.1$ in univariate analysis, only vancomycin $AUC_{24\text{-}48} \geq 528.2$ mg·h/L (aOR 15.38, $P < 0.01$) was associated with persistent bacteremia.

For clinical failure, which includes 30-day all-cause mortality and recurrence, there were no statistically significant risk factors observed. Multivariate analysis for clinical failure, which includes 30-day all-cause mortality and recurrence, could not conducted due to the lack of significant statistical associations at $P < 0.1$ in univariate analysis among all variables.

Logistic regression analysis for AKI was not conducted due to the low occurrence.

Table 4. Risk factors associated with persistent bacteremia

Variables	Persistent bacteremia	
	OR (95% CI)	**Adjusted OR (95% CI) [a]**
Age < 12 months [b]	0.52 (0.10-2.74)	N.A.
Initial estimated GFR	1.00 (0.99-1.01)	N.A.
Immunocompromised state	0.21 (0.02-1.79)	N.A.
ICU stay at baseline	0.73 (0.17-3.21)	N.A.
Polymicrobial BSI	0.35 (0.04-3.11)	N.A.
Infection source control		
Uncertain focus	1 [Reference]	1 [Reference]
Eradicated focus	3.08 (0.25-37.48)	2.24 (0.15-33.71)
Noneradicable or not eradicated focus	10.77 (1.18-98.03)	6.16 (0.56-67.53)
Severe presentation at onset	1.03 (0.19-5.70)	N.A.
Vancomycin MIC of 2.0 mg/L	2.74 (0.64-11.80)	N.A.
Vancomycin $AUC_{24\text{-}48} \geq 528.2$ mg·h/L	21.50 (3.84-120.49)	15.38 (2.54-93.12)

Abbreviations: AUC, area under the curve; $AUC_{24\text{-}48}$, AUC over the second 24 hours; BSI, blood stream infection; CI, confidence interval; GFR, glomerular filtration rate; ICU, intensive care unit; MIC, minimum inhibitory concentration; N.A., not applicable.

[a]: Variables associated with outcomes at $P < 0.1$ in univariate analysis were considered for inclusion in a multivariate model for persistent bacteremia. Only variables included in the final model are presented, displaying adjusted odds ratios (aOR). Nagelkerke $R^2 = 0.422$, Hosmer-Lemeshow goodness-of-fit test $P = 0.278$

[b]: In children and adolescents, the mortality rate is likely to be higher in S. aureus patients aged <12 months [29].

3.7 Characteristics of group with persistent bacteremia

In the group with persistent bacteremia, noneradicable or not eradicated focus was observed more frequently (70% vs. 28.3%, P = 0.03) (Table 5). AKI was also more frequently associated with the persistent bacteremia group (30% vs. 2.2%, P = 0.02) and 30-day all-cause mortality was exclusively observed in the persistent bacteremia group. Statistical differences were not observed between the two groups in terms of initial vancomycin dose, initial C_{trough}, and $AUC_{0\text{-}24}$. However, in the persistent bacteremia group, $AUC_{24\text{-}48}$ exhibited significantly higher values compared to the group without persistent bacteremia (536.8 mg·h/L vs. 374.1 mg·h/L [P = 0.02]).

Table 5. Characteristics of the group with persistent bacteremia

Characteristics	Persistent bacteremia (n=10)	Non-persistent bacteremia (n=46)	*P* value
Age, median (IQR), years	3.5 (2.4-12.9)	2.2 (0.7-6.2)	0.16
Initial eGFR, median (IQR), mL/min/1.732m^2	130.9 (56.1-192.1)	158.9 (109.5-213.6)	0.36
Immunocompromised state	1 (10.0)	16 (34.8)	0.25
ICU stay at baseline	3 (30.0)	17 (37.0)	> 0.99
Polymicrobial BSI	1 (10.0)	11 (23.9)	0.67
Infection source control			
Uncertain focus	1 (10.0)	20 (43.5)	0.07
Eradicated focus	2 (20.0)	13 (28.3)	0.71
Noneradicable or not eradicated focus	7 (70.0)	13 (28.3)	0.03
Severe presentation at onset	2 (20.0)	9 (19.6)	> 0.99
Recurrence	2 (20.0)	6 (13.6)	0.63
30-day all-cause mortality	2 (20.0)	0	0.03
AKI	3 (30.0)	1 (2.2)	0.02
Vancomycin MIC of 2.0 mg/L	4 (40.0)	9 (19.6)	0.22
Initial vancomycin dose, median (IQR), mg/kg/day	40.5 (31.5-56.5)	41.6 (40.0-60.0)	0.22
Initial vancomycin C_{trough}, median (IQR), mg/L	8.2 (5.0-13.5)	7.2 (5.3-12.0)	0.58
AUC_{0-24}, median (IQR), mg·h/L	379.0 (270.7-530.3)	316.2 (252.4-397.3)	0.12
AUC_{24-48}, median (IQR), mg·h/L	536.8 (352.0-627.6)	374.1 (289.9-464.4)	0.02

Abbreviations: AKI, acute kidney injury; AUC, area under the curve; AUC_{0-24}, AUC over the first 24 hours; AUC_{24-48}, AUC over the second 24 hours; BSI, bloodstream infection; CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; C_{trough}, trough concentration; GFR, glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration.

All categorical data were analyzed by Fisher's exact test. Continuous data were analyzed by Mann-Whitney test.

4. Discussion

In this retrospective study involving pediatric MRSA bacteremia cases with a 30-day all-cause mortality rate of 3.7%, I investigated the optimal target of vancomycin AUC simulated by Bayesian dosing software. Vancomycin $AUC_{24\text{-}48} \geq 400$ mg·h/L did not demonstrate benefits in persistent bacteremia, recurrence, and 30-day all-cause mortality. In the exploration to identify the optimal target, $AUC_{24\text{-}48} \geq 528.2$ mg·h/L was identified as a statistically significant risk factor associated with persistent bacteremia.

The utilization of Bayesian-guided dosing for vancomycin optimization is more adaptive to the patient's dynamic physiologic changes and has the advantage of requiring relatively fewer restrictions on the timing or number of samplings needed, even before steady-state is achieved. Furthermore, depending on the size of the institution, Bayesian dosing may be cost-effective [33]. This approach, despite being in its evolving stages, shows promise in tailoring dosing strategies for optimal patient outcomes. Moreover, Bayesian dose optimization software programs offer a practical solution for implementing such approaches [34].

My study`s analysis of AUC values, shed light on potential thresholds for optimal dosing, with an $AUC_{24\text{-}48} \geq 528.2$ mg·h/L being predictive of persistent bacteremia. After approximately 48 hours following antibiotic administration, it is an essential juncture to evaluate both clinical response and the identification of causative bacteria. This time window is corroborated by a recent multicenter prospective study, which indicated that persistence at day 3 marked an inflection point for increased mortality [35].

There are no studies demonstrating clinical efficacy based on Bayesian-derived AUC in pediatric patients with MRSA bacteremia. This study, conducted with a Bayesian dosing program for vancomycin TDM, aims to bridge this gap. A recent multicenter prospective observational study in adults suggested that an $AUC_{24\text{-}48}$ of ≤ 515 mg·h/L by Bayesian estimation is the optimal target for favorable outcomes in terms of mortality and AKI, though without proposing a lower bound [32]. The finding that treatment failure and mortality rates did not decrease but were rather higher at AUC > 515 mg·h/L is particularly noteworthy. This finding can be interpreted in a similar context to another pediatric study, which

observed frequent nephrotoxicity without clinical benefits when C_{trough} > 15 mg/L [13]. In my study, the AUC_{24-48} was significantly higher in the group with persistent bacteremia despite the initial dosage of vancomycin being slightly lower. The outcome of this "soaring AUC group" became a major factor affecting the overall outcome.

Study by Yoo *et al.* [19], employing an equation model, suggested an association between an AUC/MIC < 300 and persistent bacteremia at 48-72 hours. However, as this study solely relied on the equation derived from trough concentration to estimate AUC, there's a potential for inaccuracies in AUC estimation. Additionally, variations in MIC measurement methods (MicroScan) could result in discrepancies in AUC/MIC values compared to those from other institutions. Regarding MIC determination for S. aureus isolates, my study used the MicroScan method, which tends to overcall MIC compared to the broth microdilution method (BMD) [21, 22]. The discrepancies in inter-institutional MIC results due to measurement methods [6, 32] pose challenges in applying AUC/MIC as a target parameter for TDM. Consequently, my study suggests that AUC alone could be a more reliable monitoring target.

The absence of a discernible association between AUC and clinical outcomes is presumed to be due to the relatively low mortality rate among pediatric patients with MRSA bacteremia. My study was unable to assess the impact of vancomycin PK/PD on mortality, as only two fatal cases were observed during the study period. No patients were diagnosed with infective endocarditis in this study. This aligns with findings from other pediatric studies, which indicated infective endocarditis rates of 0% to 2.1% among children with MRSA bacteremia [14, 17, 18, 29], while in adults, this rate can be as high as 29% [32]. Such disparities might contribute to the differing clinical courses and prognoses between pediatric and adult patients, emphasizing the need to prioritize safety over aggressively high vancomycin exposure in pediatric patients.

Despite the majority being healthcare-associated infections, the incidence rate of AKI in this study was relatively lower compared to other previous pediatric studies [13, 17], likely attributed to dosage reduction in patients vulnerable to nephrotoxicity from the initial vancomycin administration and TDM through repeated concentration measurements. However, it was noted that a higher incidence of AKI

was observed in higher AUC.

There are limitations in this study. The single-center, small sample size and retrospective nature of the study may limit the generalizability of the findings. This was a study of non-dialysis patients with mostly healthcare-associated infections and relatively few musculoskeletal infections, making it difficult to represent patients with community-acquired infection or patients on dialysis. In addition, the BMD method was not performed simultaneously when measuring MIC, which labor intensive and has limitation to clinical microbiological lab handling lots of specimens compared to automated MIC measuring system. Patients younger than 3 months had to be excluded because of the inconsistency of AUC estimation method, although a higher mortality rate in this age among pediatric patients with MRSA bacteremia has been reported [36, 37]. However, since this age group, which can include many preterm infants in the neonatal intensive care unit, may have very different characteristics from pediatric patients over that age, it would be more appropriate to investigate it as a separate study. Prior studies [12, 31] utilized by the Bayesian software to estimate AUC primarily involved Hispanic and Caucasian race/ethnicities, with Asians constituting a minority (3-4%). Since most of the patients in this study were East Asians, differences in pharmacokinetics might exist, potentially leading to discrepancies between the estimated AUC and the actual values. Finally, this study had limited representation of infective endocarditis, central nervous system infections, and pneumonia, which are known for high mortality and treatment failure rates. Caution is warranted in applying the target AUC < 528.2 mg·h/L solely based on the results of this study to patients with those disease. However, I believe that this target can be applied to most other disease groups in pediatric patients (≥ 3 months) with MRSA bacteremia.

Conclusion

While $AUC_{24\text{-}48} \geq 400$ mg·h/L did not demonstrate clinical benefits, $AUC_{24\text{-}48} < 528.2$ mg·h/L was an appropriate surrogate marker predicting less persistent bacteremia without statistically significant disadvantages in mortality and recurrence. Therefore, $AUC_{24\text{-}48} < 528.2$ mg·h/L can be considered as the upper bound of the optimal target of AUC for children aged > 3 months with MRSA bacteremia. AKI was associated with $AUC_{24\text{-}48} \geq 536.8$ mg·h/L. The lower bound of the target range indicating subtherapeutic levels was not identified.

A large-scale multicenter study is needed that includes a sufficient number of pediatric patients with MRSA bacteremia from infective endocarditis, pneumonia, central nervous system infections, and community-acquired infections to generally apply the findings in this study.

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국문요약

제목: 메티실린 내성 황색포도알균 (MRSA) 균혈증 소아에서 베이지안 유도 투여 소프트웨어로 추정한 최적의 반코마이신 혈중 농도 곡선하 면적

배경: 메티실린 내성 황색포도상구균(MRSA) 감염증에서 반코마이신의 광범위한 사용에도 불구하고 현재 소아 집단에서의 농도-시간 곡선 아래 면적(area under the concentration-time curve, AUC) 목표에 대한 근거 자료는 부족한 실정이다. 이 연구는 소아 MRSA 균혈증 환자에게 최적의 결과를 제공하는 반코마이신 AUC의 목표를 도출하기 위해 수행되었다.

방법: 2013년 9월부터 2021년 12월까지, 3개월 이상 및 19세 미만의 MRSA 균혈증이 있는 모든 입원 환자를 후향적으로 분석하였다. 반코마이신 투여 후 168시간 동안의 AUC는 베이지안 기반 소프트웨어를 사용하여 각 환자의 나이, 성별, 신장, 체중, 혈중 크레아티닌 및 모든 측정된 반코마이신 최저 농도를 포함한 개별 환자 데이터를 이용하여 시뮬레이션 되었다. 결과에는 48 이상의 지속 균혈증, 재발, 30일 사망률이 포함되었다. 급성 신부전(acute kidney injury, AKI)은 반코마이신 투약 시작 후 14일간 조사되었다. 적절한 AUC 목표를 식별하기 위해, 우선 최근 지침에서 제시된 AUC/최소억제농도(MIC)비 ≥ 400이 임상적 이득이 있는지 조사했다. 이 목표가 부적절하다고 판단된 경우 Receiver Operating Characteristic (ROC) 분석을 통해 대안적인 AUC 목표를 탐색했다. 또한 최소억제 농도 (MIC), 면역 저하 상태, 중환자실 재원 여부, 임상적 중증도, 복합 혈류 감염, 감염 원인, 실시된 중재 등 결과에 영향을 미칠 수 있는 요인을 함께 분석했다.

결과: 연구 기간 동안 79건의 MRSA 균혈증이 확인되었다. MRSA 균혈증 발병 72시간 전에 반코마이신을 투여받은 사례(n=5), 반코마이신 치료 기간이 72시간 미만인 사례(n=10), 기준시점에 신대체요법을 받고 있던 사례(n=8)는 제외되었다. 최종적으로 56개의 사례가 연구에 포함되었다. 지속 균혈증 (≥ 48시간), 30일 내 모든 원인으로 인한 사망, 재발 및 급성 신장 손상이 각각 10례(17.9%), 2건(3.7%), 8건(14.8%), 4건(7.1%)에서 관찰되었다. 반코마이신 투약 후 24-48시간 시점의 AUC (AUC_{24-48}) ≥ 400 mg·h/L는 결과에 있어서 임상적 이득을 보여주지 못했다. 지속 균혈증은 오히려 높은 AUC_{24-48} 환자에서 빈번하게 관찰되는 경향성을 보였다. AUC_{24-48}은 지속 균혈증을 예측하는 데 반코마이신 투약 후 첫 24시간 동안의 AUC (AUC_{0-24}) 보다 통계적으로 더 유의미한 지표였다. AUC_{24-48} ≥ 528.2 mg·h/L는 지속 균혈증과 관련이 있었다 (P < 0.01). AUC_{24-48} ≥ 536.8 mg·h/L는 급성 신부전과 관련이 있었다 (P = 0.01). 사망률이나 재발과 관련된 변수는 확인할 수 없었다. 지속 균혈증 군은 균혈증이 호전된 군에 비해 반코마이신 투약 후 AUC_{24-48}가 유의하게 높았으며, 근절할 수 없거나 근절되지 않은 감염원이 남아있는 빈도 및 급성 신부전 발생 빈도도 높게 관찰되었다.

결론: MRSA 균혈증이 있는 3개월 이상의 비투석 소아 환자에 대한 반코마이신 AUC의 최적 목표치로 AUC_{24-48} < 528.2 mg·h/L 를 제시한다. 본 연구에서는 치료 수준 미만을 의미하는 목표 범위의 하한선은 식별할 수 없었다.

중심단어: 메티실린 내성 황색포도알균, 균혈증, 반코마이신, 베이지안, 소아