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Population Pharmacokinetics of Vancomycin and Dose Optimization in Pediatric Patients with Sepsis or Septic Shock

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Article Info	ABSTRACT
Received: November 14, 2024 Accepted: May 14, 2025 Published: August 1, 2025 Keywords: Pediatrics, Population pharmacokinetics, Sepsis, Septic shock, Vancomycin.	Objectives: This study aimed to develop a population pharmacokinetic model for vancomycin in pediatric patients with sepsis or septic shock and to propose tailored initial dose recommendations based on the model's findings. Methods: We conducted a retrospective analysis of pediatric patients with sepsis or septic shock who received vancomycin treatment from January 2017 to December 2019. A population pharmacokinetic model was developed using NONMEM. Monte Carlo Simulations were performed using Crystal Ball software to determine the probability of target attainment (PTA) for different vancomycin dosage regimens based on the target PK/PD index of $AUC_{24hr}/MIC > 400$. Results: Analyzing 580 vancomycin concentrations from 228 patients (median age 4.1 years; 33.8% with septic shock), we determined that a one-compartment model best described the pharmacokinetics, estimating clearance (CL) at 1.8 L/hr and volume of distribution (Vd) at 15.8 L. Body weight (BW) significantly influenced both CL and Vd, while serum creatinine (SCr) and blood urea nitrogen (BUN) affected only CL. The optimal doses adjusted by SCr and BW to achieved PTA range from 60 mg/kg/day (SCr 0.1–0.3 mg/dL) decreasing to 20–30 mg/kg/day (SCr 0.7–1.0 mg/dL) when the $MIC \leq 0.5$ mg/L. For $MIC = 1$ mg/L, higher doses up to 90 mg/kg/day are needed in patients with low SCr. A loading dose of 25–35 mg/kg was necessary to reach PTA within 24 hours. No regimen achieved target PTA at $MIC > 1$ mg/L. Conclusions: Customized vancomycin dosing based on BW and renal function may improve target AUC attainment for <i>S. aureus</i> in sepsis or septic shock children. Caution is warranted for $MIC > 1$ mg/L or $SCr > 1$ mg/dL due to limited data.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA), are a major contributor to sepsis and septic shock in pediatric patients, with MRSA-associated mortality nearly twice as high as methicillin-susceptible infections (20.9% vs 9%).¹ Vancomycin remains a cornerstone in the treatment of serious MRSA infections across all age groups. Its pharmacodynamic (PD) efficacy is best assessed by the ratio of the 24-hour area under the concentration-time curve (AUC_{24hr}) to the minimum inhibitory concentration (MIC) (AUC_{24hr}/MIC). Current pediatric guideline recommends an AUC_{24hr} target of 400-600 mg·h/L (assuming MIC of 1 mg/L) to optimize efficacy while minimizing nephrotoxic risk, particularly when AUC_{24hr} exceeds 800 mg·h/L or minimum concentrations (C_{min}) exceed 15 mg/L.²

In pediatric populations, vancomycin pharmacokinetics (PK) are influenced by dynamic physiological changes across age, including variations in body water, protein binding, and renal function. These changes are further compounded in critically ill children—especially those with sepsis or septic shock—where altered drug distribution and clearance are frequently observed.^{3,4} Importantly, studies report that fewer than 50% of children receiving standard vancomycin dosing achieve the recommended AUC_{24hr}/MIC target.^{5,6}

Though the current dosing regimen for children is based on body weight (BW) and renal function, several additional factors—such as sepsis⁷, augmented renal clearance (ARC)⁸, malignancies⁹⁻¹¹, cardiac arrest¹², or extracorporeal devices^{13,14}—can significantly impact vancomycin PK. This study aimed to develop a PopPK model of vancomycin in pediatric patients with sepsis or septic shock, and to propose initial dosing recommendations for *S. aureus* infections based on model-derived simulations.

Materials and Methods

A retrospective study chart review was conducted at a university hospital in southern Thailand from January 2017 to December 2019 on children aged 1 month to 18 years diagnosed with sepsis or septic shock, per the International Pediatric Surviving Sepsis Campaign (IPSSC) 2005 guidelines.¹⁵ Inclusion criteria included receiving intravenous vancomycin and having at least one monitored plasma concentration (Cp). Patients undergoing renal replacement therapy were excluded. Baseline characteristics, including sex,

age, BW, height, underlying diseases, and vital signs at the time suspected sepsis or shock were gathered. Data on vancomycin dosing and monitoring profiles, blood urea nitrogen (BUN), serum creatinine SCr, and the use of vasoactive, inotropic, and nephrotoxic agents (listed in footnote of **Table 1**) within 7 days before and during treatment were documented. Ethical approval was granted by the Human Research Ethics Unit, Faculty of Medicine, Prince of Songkla University (REC.63-185-19-2). Details of vancomycin bioassays are provided in **Supplementary 1**.

PopPK analyses

PK parameters and variabilities were analyzed using NONMEM version 7.4.3 (Icon Development Solutions, Columbia, MD, USA) with the first-order conditional estimation method with interaction (FOCE-I). Model fit was evaluated using a likelihood ratio test, employing changes in the objective function value (ΔOFV). Initial covariates like BW for CL and Vd were considered during base model development.¹⁶ Model refinement followed a stepwise process involving forward addition (ΔOFV decrease > 3.84 , $p < 0.05$) and backward elimination (ΔOFV increase > 10.83 , $p < 0.001$), guided by physiological plausibility, parameter estimate precision, and diagnostic goodness-of-fit (GOF) scatterplots, including population predicted and individual predicted versus detected values (PPRED vs. DV and IPRED vs. DV) and conditional weighted residuals (CWRES) versus PPRED and time. Model uncertainty was assessed via bootstrapping 1000 datasets, validating reliability if bootstrap estimates fell within 95% CI. Tools such as Pirana (version 3.0.0, Certara, USA), Perl-Speaks-NONMEM (PsN, version 5.2.6), and R (version 4.1.0) with Xpose4 packages supported data preparation, diagnostics, and visualization.

Dose optimization

The study aimed to optimize vancomycin dosing by calculating the PTA, defined as the proportion of patients achieving an AUC_{24hr}/MIC ratio above 400. Crystal Ball® (Oracle Corporation, CA, USA) was used to analyze Monte Carlo Simulation (MCS) in a simulated population of 10,000 patients, considering a range of MIC values from 0.5 to 2 mg/L¹⁷. The regimen was based on our institution's practice, where a loading dose of 25-35 mg/kg is administered, followed by a maintenance dose every six hours with a 2-hour infusion time. We evaluated maintenance doses of 20-100 mg/kg/day, adjusted

Table 1. Baseline Characteristics

Characteristics	Patients (N=228)	Treatment episodes (n=287)
Male, n (%)	137 (60.1)	
Age (years), median (range; IQR)	4.1 (0.1-16.8; 1.2-9.7)	
1 month-1 year, n (%)	52 (22.9)	
1-6 years, n (%)	87 (38.2)	
6-12 years, n (%)	53 (23.2)	
12-18 years, n (%)	36 (15.8)	
Weight (kg), median (range; IQR)	13.8 (2-92; 8-26.3)	
2-10 kg, n (%)	73 (32.0)	
10-25 kg, n (%)	94 (41.2)	
25-50 kg, n (%)	49 (21.5)	
> 50 kg, n (%)	12 (5.3)	
Height (cm), median (range; IQR)	99 (42-165; 71-130)	
Initial serum creatinine (mg/dL), median (range; IQR)	0.3 (0.08-4.76; 0.22-0.45)	
0.1-0.3 mg/dL, n (%)	119 (52.2)	
0.3-0.5 mg/dL, n (%)	66 (28.9)	
0.5-0.7 mg/dL, n (%)	20 (8.8)	
0.7-1.0 mg/dL, n (%)	10 (4.4)	
> 1.0 mg/dL, n (%)	13 (5.7)	
Initial blood urea nitrogen (mg/dL), median (range; IQR)	7.7 (1.5-128.4; 5.3-11.8)	
Cancer (co-morbidities)		
Solid tumors, n (%)	57 (25.0)	
Hematologic malignancies, n (%)	46 (20.2)	
Diagnosis		
Sepsis, episodes (%)		190 (66.2)
Septic shock, episodes (%)		97 (33.8)
Undergoing cardiac surgery, episodes (%)		33 (11.5)
Concurrent use of vasoactive drugs, episodes (%)		110 (40.4)
Concurrent use of inotropic drugs, episodes (%)		63 (22.0)
Concurrent use of nephrotoxic drugs*, episodes (%)		235 (81.9)
Vancomycin administration		
Loading dose (mg/kg), mean ± SD		29.6 ± 3.4
Maintenance dose (mg/kg/dose), mean ± SD		15.0 ± 2.0
Infusion time (hr), mean ± SD		2.1 ± 0.6

*Concurrent use of nephrotoxic drugs was defined as the administration of any of the following medications within 7 days before or during vancomycin therapy: aminoglycosides, colistin, amphotericin B, furosemide, radiocontrast media, NSAIDs, sirolimus, tacrolimus, cyclosporine A, cisplatin, carboplatin, ifosfamide, and high-dose methotrexate (> 500 mg/m²).

according to renal function, both with and without the loading dose. The AUC_{24hr} was segmented into AUC₀₋₂₄ and AUC₄₈₋₇₂, calculated using the following equation.¹⁸

$$AUC_{0-t} = (C_{SOR} - C_{min})/k_e$$

where t represents the dosing interval, C_{SOR} denotes the back-extrapolated concentration at the start of infusion, C_{min} indicates the minimum concentration at time t, and k_e signifies the elimination constant. We also assessed the risk of nephrotoxicity for AUC_{24hr} ≥ 800 mg·h/L and C_{min} ≥ 15 mg/L, based on current therapeutic drug monitoring (TDM) guideline² and prior study.¹⁹

Results

A total of 580 vancomycin samples from 228

children undergoing 287 treatment courses were analyzed. The children's median age was 4.1 years, ranging from one month to 16.8 years, with an interquartile range (IQR) of 1.2 to 9.7 years. Median BW was 13.8 kg, with a range of 2 to 92 kg and an IQR of 8 to 26.3 kg. **Table 1** provides an overview of the demographic and clinical characteristics of the patients. Notably, one-third of these courses were for patients with septic shock. Additionally, 25% had solid tumors, and 20.2% had hematologic malignancies. The median initial SCr level was 0.3 mg/dL, IQR of 0.22 to 0.45 mg/dL, with a range from 0.08 to 4.76 mg/dL.

The mean loading dose was 29.6 ± 3.4 mg/kg, and the mean maintenance dose was 15.0 ± 2.0 mg/kg with an average infusion time of 2.1 ± 0.6

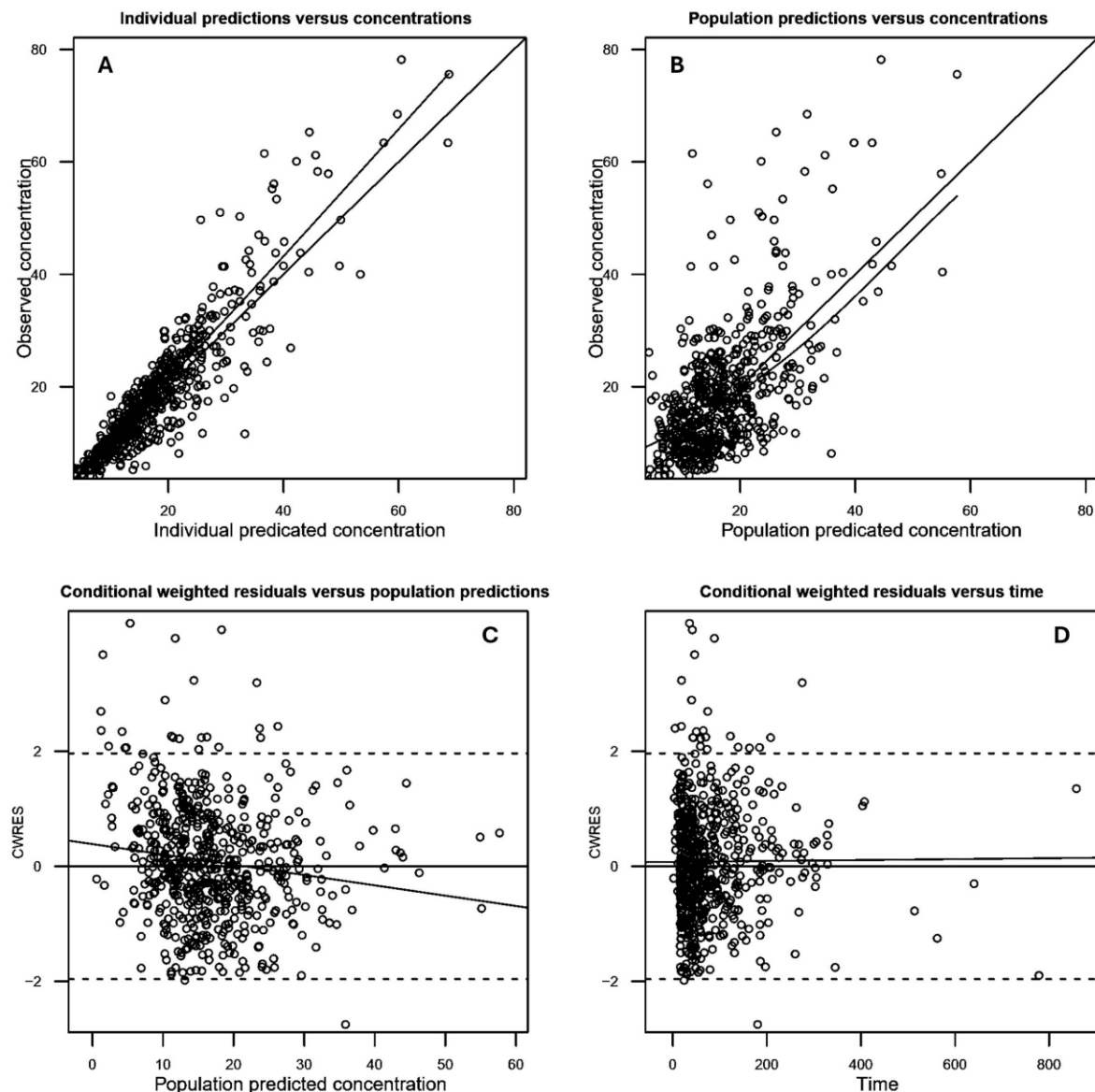


Figure 1. Diagnostic plots of the final pharmacokinetic model show observations versus population predictions (A) and individual predictions (B), marked by the identity line. Conditional weighted residuals (CWRES) versus population predictions (C) and time post-dose (D) are also displayed, with lines indicating zero residuals.

hours. Of the total vancomycin Cp analyzed, approximately 87% were C_{min} , which were collected at an average of 5.75 hours after the dose. More than 90% of patients utilized vancomycin for empirical therapy. The relationship between vancomycin concentration and the time elapsed after drug administration is depicted in **Figure S1**.

PopPK analyses

Vancomycin PK data were best described by a one-compartment model with a proportional residual error model. Details of the model development process are summarized in **Table S1** and **Table S2**. During the structural and covariate modeling process, the power covariate model with the normalized covariate of BW on CL and BW on Vd,

diverging from traditional allometric scaling, was employed due to a significantly lower OFV (3203.401 vs 3427.972, Δ OFV -224.571). In addition to BW's impact on CL and Vd, only SCr and BUN were identified as covariates significantly influencing CL. No other covariates significantly impacted Vd. High correlations between age and BW ($r^2 = 0.82$) and between height and BW ($r^2 = 0.94$), shown in **Figure S2**, precluded their inclusion to avoid multicollinearity. The population values of CL and Vd are derived as follows:

$$CL = 2.05 \times (BW/13.8)^{1.11} \times (SCr/0.3)^{-0.592} \times \exp^{(-0.131 \times (BUN/7.7))} \times \exp^{h1}$$

$$Vd = 15.80 \times (BW/13.8)^{0.909} \times \exp^{h2}$$

Table 2 presents the parameter estimates and

Table 2. Parameter estimates and bootstrap results for the final population pharmacokinetic model.

Parameter	Final model ¹	Estimate based on 1000 bootstrap replicates ²	
	Estimate (SE)	Median	95%CI
q ₁ , CL (L/hr)	2.05 (0.103)	2.06	1.835-2.259
q ₂ , Vd (L)	15.80 (1.21)	16.00	13.181-18.434
q ₃ , BW on CL	1.110 (0.041)	1.107	1.028-1.189
q ₄ , BW on V	0.909 (0.0555)	0.911	0.796-1.022
q ₅ , SCr on CL	-0.592 (0.0624)	-0.584	-0.711 - -0.472
q ₆ , BUN on CL	-0.131 (0.0287)	-0.134	-0.189 - -0.072
w ² ₁ , IIVCL [%CV]	0.1330 (0.0183) [36.5]	0.1328 [36.4]	0.0982-0.1683 [31.3-41.0]
w ² ₂ , IIVVd [%CV]	0.1050 (0.0389) [32.4]	0.1027 [32.0]	0.0248-0.1848 [15.7-43.0]
s, RV [%CV]	0.0736 (0.0068) [27.1]	0.0725 [26.9]	0.0601-0.0870 [24.5-29.5]

BUN, blood urea nitrogen; BW, body weight; CI, confidence interval; CL, clearance; %CV, coefficient of variance equals to $\sqrt{\omega^2} \times 100\%$; IIV, inter-individual variability; RV, residual variability; SE, standard error; Vd, volume of distribution; q, w and s, values to be estimated by NONMEM.

¹Final model: $CL = q_1 \times (BW/13.8)^{q_3} \times (SCR/0.3)^{q_5} \times \exp^{(q_6 \times (BUN/7.7))} \times \exp^{h_1}$; $Vd = q_2 \times (BW/13.8)^{q_4} \times \exp^{h_2}$

²Bootstrap success rate = 99.8%

bootstrap confidence intervals. The typical values for the PK parameters normalized to median weight (13.8 kg), SCr (0.3 mg/dL), and BUN (7.7 mg/dL), were as follows: CL 1.8 L/hr; Vd 15.80 L, with a half-life of 6.08 hours. The close alignment of these values with median bootstrap replicates confirms the robustness and stability of the model estimates. The NONMEM code for the final model can be found in **Supplementary 2**.

The final model's standard GOF plots in **Figure 1** indicate no significant systematic bias. The observed concentrations compared to IPRED, and PPRED yielded acceptable results. There was no discernible pattern observed in the CWRES concerning PPRED or time after the last dose. Most CWRES values were evenly distributed around zero and fell within a standard deviation of ± 2 in normalized units.

Dose optimization

The final PK model identified dosing regimens to consistently achieve target AUC_{0-24}/MIC and AUC_{48-72}/MIC ratios of ≥ 400 mg·h/L. Assuming moderate correlation between BUN and SCr ($r^2 = 0.73$) (**Figure S2**), simulation tested doses from 20–100 mg/kg/day in 4 divided doses, with and without a loading dose. Overall, the elevated SCr was improving PTA but requiring dose reductions, while higher BW required higher doses to maintain the PTA. A loading dose of 25–35 mg/kg improved early AUC attainment (**Figure 2, Table S3–S6**).

For MIC 0.5 mg/L, maintenance doses of 60, 50,

30, and 20–30 mg/kg/day achieved 95–100% PTA across SCr strata (0.1–1.0 mg/dL) with $<10\%$ risk of $AUC_{24hr} > 800$ mg·h/L. At MIC 1 mg/L, a daily dose of 90 mg/kg/day was required to achieve 85–90% PTA in patients with SCr levels of 0.1–0.3 mg/dL, but this was associated with a nephrotoxicity risk of up to 30%. In comparison, the guideline-recommended dose of 60 mg/kg/day achieved only 50–60% PTA in the same group (**Table S3, Figure S3**). No regimen met efficacy targets at MICs ≥ 1.5 mg/L. $C_{min} > 15$ mg/L occurred in 50–90% of higher-dose regimens (**Table S3–S6**).

Discussion

This study sheds light on the PK parameters and dosing considerations of vancomycin in sepsis or septic shock children. Based on 580 samples collected through routine TDM, we employed a one-compartment model with first-order elimination to characterize vancomycin PK. Although vancomycin is broadly recognized to follow two-compartment kinetics, our dataset—comprised of 87% C_{min} —limited our ability to reliably estimate a two-compartment model. This sampling constraint is consistent with other retrospective studies²⁰ and likely contributed to the one-compartment model providing the best fit. The model estimated a mean CL of 0.13 L/kg/hr and a Vd of 1.14 L/kg, values that fall within the range reported in a recent systematic review of vancomycin PK in critically ill children (CL: 0.05–0.38 L/kg/hr, Vd: 0.1–1.16 L/kg)²⁰, helping to fill data gaps specific to children with sepsis or septic shock. Like many studies^{7, 21–23},

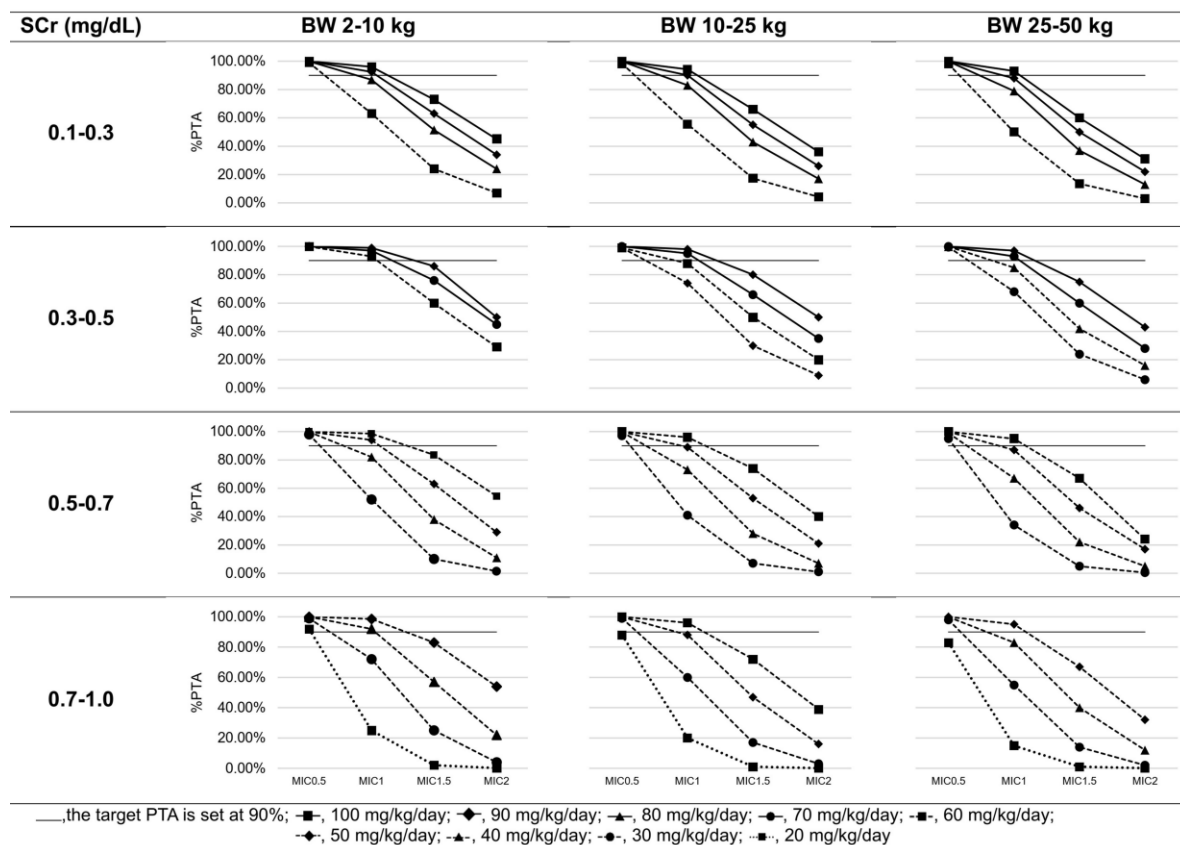


Figure 2. Displays the probability of target attainment (PTA) for various maintenance doses with loading doses of 25-35 mg/kg, across different minimum inhibitory concentrations (MIC) from 48-72 hours. This analysis includes simulated patient groups with serum creatinine (SCr) levels from 0.1 to 1.0 mg/dL across various body weight (BW) ranges.

adjusting the allometric weight exponent enhanced model accuracy. The exponent greater than 1 on CL and less than 1 on Vd implies that CL increases more rapidly, while Vd increases more slowly as body size increases.

Vancomycin is predominantly eliminated through glomerular filtration, with most studies using either eGFR or SCr as covariates.²⁰ However, eGFR estimates based on SCr can be influenced by non-renal factors like high-protein diets, muscle mass, or urea cycle enzyme activity, affecting GFR accuracy. Moreover, the Bedside Schwartz formula, often used for eGFR calculations, is not valid for children under one year. To enhance GFR accuracy, some researchers, including Chen et al, have incorporated BUN alongside SCr and height in their PopPK models.^{24,25} In our study, we directly included SCr and BUN in our model. Despite some collinearity from their moderate correlation between these two covariates, this approach improved model stability, as confirmed by scatterplots and bootstrap analysis. Notably, vancomycin CL decreased as SCr or BUN increased.

In individuals diagnosed with sepsis or septic shock, especially concurrent with malignancies or febrile neutropenia, an elevated CL is often observed and attributed to ARC, commonly defined by eGFR > 130 mL/min/1.73m², which increases drug elimination rates and risks subtherapeutic vancomycin levels.⁸⁻¹¹ However, our study did not identify significant covariates related to ARC or malignancies, nor did we find notable differences in sepsis or shock status, including the use of vasopressors.

Like several previous studies^{9,19,26,27}, we found that concurrent medications did not emerge as significant covariates, possibly due to variations in the type, dosage, and duration of concurrent medication use. Le et al.¹⁹ noted that the concurrent use of nephrotoxic drugs can increase the risk of nephrotoxicity, potentially leading vancomycin C_{min} ≥ 15 mg/L and AUC ≥ 800 mg·h/L. In specific circumstances, this may prompt consideration of alternative antibiotics.

The PK/PD target of this study was an AUC_{24hr}/MIC ≥ 400, which is the recommended

therapeutic threshold for *S. aureus* (particularly MRSA) infections. However, this target has not been established for other gram-positive organisms. For toxicity an $AUC_{24hr} \geq 800$ mg·h/L linked to a 33% risk of nephrotoxicity, while a $C_{min} \geq 15$ mg/L has been linked to more than a 2.5-fold increased risk of AKI.^{2,19} The discrepancy between C_{min} and AUC in our findings suggests that C_{min} is not a reliable indicator of AUC or nephrotoxicity in sepsis or septic shock children, potentially leading to inappropriate dose adjustments.

Based on our simulation results, we proposed an optimal vancomycin dosing regimen for children, which takes into consideration the patient's BW (2-50 kg) and SCr (0.1-1.0 mg/dL). To achieve the target PTA within the first 24 hours, we recommend a loading dose of 25-35 mg/kg. The current vancomycin TDM guidelines suggest dosing at 60 to 80 mg/kg/day for children aged 3 months to 12 years, and 60 to 70 mg/kg/day for those older than 12 years, including the consideration of a loading dose without reducing doses to achieve AUC/MIC targets for MIC ≤ 1 mg/L.² To broaden the evidence base, we also examined lower MIC scenarios, aiming to inform future clinical decisions in **Table 3**. Our simulations reveal that adhering to recommended doses could elevate nephrotoxicity risk, with $AUC_{24hr} \geq 800$

mg·h/L occurring in 30-60% of cases and $C_{min} \geq 15$ mg/L in 80-90% of cases.

When the MIC is 1 mg/L, higher vancomycin doses may be necessary to achieve target exposure, particularly in patients with preserved renal function. Although current guidelines recommend 60–70 mg/kg/day, emerging evidence—including studies by Chuphan et al.²⁸, He et al.⁸, and Gomez et al.²⁹—suggests that doses up to 90 mg/kg/day may be required in critically ill children or those with ARC, with escalating to 90-100 mg/kg/day in sepsis or burns.²⁹ However, the safety of dosing above 80 mg/kg/day remains uncertain, and caution should be exercised with doses approaching or exceeding 100 mg/kg/day due to the potential risk of nephrotoxicity. For children with mild to moderate renal impairment (SCr 0.5–1.0 mg/dL), reduced maintenance doses of 40–60 mg/kg/day are more appropriate to avoid excessive exposure.

While our simulations suggest that loading doses may help achieve target AUCs within the first 24 hours, clinical outcome data remains inconclusive. A meta-analysis by Mei et al.³⁰ showed that loading doses improved attainment of therapeutic C_{min} without increasing nephrotoxicity risk. However, no significant differences in clinical response were observed between groups. These findings highlight a

Table 3. Recommended maintenance dose of vancomycin to treat *Staphylococcus aureus* infections with minimum inhibitory concentration of 0.5 and 1 mg/L.

Serum creatinine (mg/dL)	Recommended daily maintenance doses (in 4 divided doses) ^A		
	Body weight 2-10 kg	Body weight 10-25 kg	Body weight 25-50 kg
Minimum inhibitory concentration of 0.5 mg/L			
0.1 – 0.3	60 mg/kg/day	60 mg/kg/day	60 mg/kg/day
0.3 – 0.5	50 mg/kg/day ^B	50 mg/kg/day ^B	50 mg/kg/day ^B
0.5 – 0.7	30 mg/kg/day ^B	30 mg/kg/day ^B	30 mg/kg/day ^B
0.7 – 1.0	20 mg/kg/day ^B	30 mg/kg/day ^B	30 mg/kg/day ^B
Minimum inhibitory concentration of 1 mg/L			
0.1 – 0.3	80 ^C -90 ^{D,E} mg/kg/day ^F	90 ^D mg/kg/day ^F	90 ^C -100 ^{D,E} mg/kg/day ^F
0.3 – 0.5	60 ^D mg/kg/day	60 ^C -70 ^{D,E} mg/kg/day	70 ^D mg/kg/day
0.5 – 0.7	50 ^D mg/kg/day	50 ^D mg/kg/day	50 ^C -60 ^{D,E} mg/kg/day
0.7 – 1.0	40 ^D mg/kg/day	40 ^C -50 ^{D,E} mg/kg/day	50 ^D mg/kg/day

^A Loading dose of 25-35 mg/kg is recommended to achieve the probability of target attainment (PTA) within the first 24 hours.

^B The current consensus guideline for therapeutic monitoring of vancomycin do not recommend decreasing the dose to achieve the AUC/MIC target when the MIC is < 1 mg/L.

^C %PTA 85-90%, see **Figure 2** for more information.

^D %PTA $\geq 90\%$, see **Figure 2** for more information.

^E Probability of $AUC_{24hr} \geq 800$ mg·h/L is greater than 30%, see **Figure S3** for more information.

^F We cannot recommend these doses as they exceed the limits established by the current consensus guideline for therapeutic monitoring of vancomycin. Please ensure to monitor serum concentrations to make appropriate dose adjustments.

PK advantage but underscore the need for larger, well-designed studies to clarify clinical benefits. Therefore, loading dose administration should be guided by clinical judgement, MRSA risk, local epidemiology, and individual patient factors such as hemodynamic status and concurrent nephrotoxic agents.

We cannot recommend vancomycin for *S. aureus* with a MIC greater than 1 mg/L due to the high risk of nephrotoxicity from increased dosing requirements. In such cases, alternative therapies should be explored. Additionally, since our simulations included patients with $\text{SCr} \leq 1.0 \text{ mg/dL}$, dosing guidance cannot be extended to those with more severe renal impairment, underscoring the need for close TDM in these populations.

Our study has several strengths, including a detailed analysis of CL dynamics and Vd in sepsis or septic shock children. The diverse dataset underpins a solid understanding of drug disposition in these patients, and the inclusion of empirical dosing data improves the real-world applicability of our findings. Importantly, the developed PopPK model—incorporating BW and renal function as covariates and providing MIC-specific dosing recommendations—offers a foundation for future development of model-informed precision dosing tools or mobile applications to support individualized vancomycin therapy in clinical practice.

However, it is important to recognize some limitations. First, we did not distinguish between ICU and general ward patients. Our mixed population aimed to enhance the generalizability of our findings across varied sepsis management scenarios. Second, the study's retrospective design and heavy reliance on $C_{\min}$ may introduce bias and limit model accuracy, particularly due to high η -shrinkage in one-compartment modeling. Although Bayesian forecasting is now preferred for AUC-guided TDM in children³¹, especially for individualized dosing, it was not applied in this study due to limited sampling. Instead, we employed a NONMEM-based PopPK approach, which was appropriate for the available dataset. Nonetheless, future model refinement may benefit from prospective data collection and inclusion of additional covariates, such as serum albumin, fluid intake, and urine output, to improve model robustness and individual-level prediction accuracy. Third, the broad age and weight range of our

participants enhance our findings' applicability but complicate precise dosing. Thus, caution is advised when applying these results to those at the extremes of the age and weight spectrum.

Lastly, the Society of Critical Care Medicine (SCCM) task force recently recommended the Phoenix Sepsis Score for identifying sepsis in children³², deviating from the IPSCC 2005 criteria used in our study. While aimed at highlighting children at higher mortality risk, these new definitions may not aid early recognition of sepsis or septic shock and tend to support a PICU-based consensus, even though sepsis occurs in general wards as well.^{33,34} Future research should explore the effectiveness of the new criteria.

Conclusion

Customized vancomycin dosing adjusted by BW and renal function may improve achievement of the currently recommended AUC targets for *S. aureus* at 24 and 48–72 hours in children with sepsis or septic shock. The proposed regimens, derived from PopPK modeling and MCS, are practical and potentially useful in clinical settings. However, caution is advised for $\text{MIC} > 1 \text{ mg/L}$ or $\text{SCr} > 1 \text{ mg/dL}$ due to limited supporting data.

Declarations

Authorship Statement

NB: Study design, applying for research funding, data collection, data analysis, manuscript writing and editing; SP: Contributed to the study design, supervised data collection, data analysis and interpretation; TW, PM: Contributed to the study design, supervised data collection, data analysis and interpretation; KL: Supervised data collection and interpretation. All authors contributed to the editing of the final manuscript. All authors attest to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

Ethic Approval and Informed Consent

This study received approval from the ethics committee of the Human Research Ethics Unit, Faculty of Medicine, Prince of Songkla University (REC.63-185-19-2). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant international guidelines on human experimentation. However, given the nature of this study, informed consent was not required by our institution.

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Conflict of interest

None declared.

References

- 1 Park DA, Lee SM, Peck KR, et al. Impact of methicillin-resistance on mortality in children and neonates with *Staphylococcus aureus* bacteremia: a meta-analysis. *Infect Chemother* 2013; 45: 202-210. 20130626. DOI: 10.3947/ic.2013.45.2.202.
- 2 Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2020; 77: 835-864. DOI: 10.1093/ajhp/zxaa036.
- 3 Oyaert M, Spriet I, Allegaert K, et al. Factors impacting unbound vancomycin concentrations in different patient populations. *Antimicrob Agents Chemother* 2015; 59: 7073-7079. 20150908. DOI: 10.1128/aac.01185-15.
- 4 Van Der Heggen T, Dhont E, Peperstraete H, et al. Augmented renal clearance: a common condition in critically ill children. *Pediatr Nephrol* 2019; 34: 1099-1106. 20190218. DOI: 10.1007/s00467-019-04205-x.
- 5 Sridharan K, Al Daylami A, Ajjawi R, et al. Clinical pharmacokinetics of vancomycin in critically ill children. *Eur J Drug Metab Pharmacokinet* 2019; 44: 807-816. DOI: 10.1007/s13318-019-00568-6.
- 6 Chen J, Huang X, Bu S, et al. The relationship between vancomycin AUC/MIC and trough concentration, age, dose, renal function in Chinese critically ill pediatric patients. *Pharmacol Res Perspect* 2021; 9: e00885. DOI: 10.1002/prp2.885.
- 7 Lanke S, Yu T, Rower JE, et al. AUC-guided vancomycin dosing in adolescent patients with suspected sepsis. *J Clin Pharmacol* 2017; 57: 77-84. 20160715. DOI: 10.1002/jcph.782.
- 8 He C-Y, Ye P-P, Liu B, et al. Population pharmacokinetics and dosing optimization of vancomycin in infants, children, and adolescents with augmented renal clearance. *Antimicrob Agents Chemother* 2021; 65: 10.1128/aac.00897-00821. DOI: doi:10.1128/aac.00897-21.
- 9 Abdel Hadi O, Al Omar S, Nazer LH, et al. Vancomycin pharmacokinetics and predicted dosage requirements in pediatric cancer patients. *J Oncol Pharm Pract* 2016; 22: 448-453. 20150615. DOI: 10.1177/1078155215591386.
- 10 Zhao W, Zhang D, Fakhoury M, et al. Population pharmacokinetics and dosing optimization of vancomycin in children with malignant hematological disease. *Antimicrob Agents Chemother* 2014; 58: 3191-3199. 20140324. DOI: 10.1128/aac.02564-13.
- 11 Lv CL, Lu JJ, Chen M, et al. Vancomycin population pharmacokinetics and dosing recommendations in haematologic malignancy with augmented renal clearance children. *J Clin Pharm Ther* 2020; 45: 1278-1287. 20200618. DOI: 10.1111/jcpt.13206.
- 12 Zane NR, Reedy MD, Gastonguay MR, et al. A population pharmacokinetic analysis to study the effect of therapeutic hypothermia on vancomycin disposition in children resuscitated from cardiac arrest. *Pediatr Crit Care Med* 2017; 18: e290-e297. DOI: 10.1097/pcc.0000000000001198.
- 13 Moffett BS, Morris J, Galati M, et al.

- Population pharmacokinetics of vancomycin in pediatric extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2018; 19: 973-980. DOI: 10.1097/pcc.0000000000001682.
- 14 Moffett BS, Morris J, Munoz F, et al. Population pharmacokinetic analysis of vancomycin in pediatric continuous renal replacement therapy. *Eur J Clin Pharmacol* 2019; 75: 1089-1097. 20190401. DOI: 10.1007/s00228-019-02664-7.
 - 15 Goldstein B, Giroir B and Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6: 2-8. DOI: 10.1097/01.Pcc.00000149131.72248.E6.
 - 16 Byon W, Smith MK, Chan P, et al. Establishing best practices and guidance in population modeling: an experience with an internal population pharmacokinetic analysis guidance. *CPT Pharmacometrics Syst Pharmacol* 2013; 2: e51. 20130703. DOI: 10.1038/psp.2013.26.
 - 17 Jaganath D, Jorakate P, Makprasert S, et al. Staphylococcus aureus bacteremia incidence and methicillin resistance in rural Thailand, 2006-2014. *Am J Trop Med Hyg* 2018; 99: 155-163. 20180510. DOI: 10.4269/ajtmh.17-0631.
 - 18 Pai MP, Neely M, Rodvold KA, et al. Innovative approaches to optimizing the delivery of vancomycin in individual patients. *Adv Drug Deliv Rev* 2014; 77: 50-57. 20140605. DOI: 10.1016/j.addr.2014.05.016.
 - 19 Le J, Ny P, Capparelli E, et al. Pharmacodynamic characteristics of nephrotoxicity associated with vancomycin use in children. *J Pediatric Infect Dis Soc* 2015; 4: e109-116. 20141103. DOI: 10.1093/jpids/piu110.
 - 20 Akunne OO, Mugabo P and Argent AC. Pharmacokinetics of vancomycin in critically ill children: a systematic review. *Eur J Drug Metab Pharmacokinet* 2022; 47: 31-48. 20211108. DOI: 10.1007/s13318-021-00730-z.
 - 21 Wang Y, Gao P, Zhang H, et al. How much vancomycin dose is enough for the MRSA infection in pediatric patients with various degrees of renal function? *Iran J Pharm Res* 2019; 18: 995-1009. DOI: 10.22037/ijpr.2019.1100654.
 - 22 Zhang H, Wang Y, Gao P, et al. Pharmacokinetic characteristics and clinical outcomes of vancomycin in young children with various degrees of renal function. *J Clin Pharmacol* 2016; 56: 740-748. 20151221. DOI: 10.1002/jcph.653.
 - 23 Zhang T, Cheng H, Pan Z, et al. Desired vancomycin trough concentration to achieve an AUC(0-24) /MIC ≥ 400 in Chinese children with complicated infectious diseases. *Basic Clin Pharmacol Toxicol* 2020; 126: 75-85. 20190828. DOI: 10.1111/bcpt.13303.
 - 24 Chen J, Huang X, Yu L, et al. Vancomycin population pharmacokinetics analysis in Chinese paediatric patients with varying degrees of renal function and ages: development of new practical dosing recommendations. *J Antimicrob Chemother* 2023; 78: 2037-2051. DOI: 10.1093/jac/dkad202.
 - 25 Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; 20: 629-637. 20090121. DOI: 10.1681/asn.2008030287.
 - 26 Avedissian SN, Bradley E, Zhang D, et al. Augmented renal clearance using population-based pharmacokinetic modeling in critically ill pediatric patients. *Pediatr Crit Care Med* 2017; 18: e388-e394. DOI: 10.1097/pcc.0000000000001228.
 - 27 Le J, Bradley JS, Murray W, et al. Improved vancomycin dosing in children using area under the curve exposure. *Pediatr Infect Dis J* 2013; 32: e155-163. DOI: 10.1097/INF.0b013e318286378e.
 - 28 Chuphan C, Sukarnjanaset W, Puthanakit T, et al. Population pharmacokinetics and pharmacodynamics of vancomycin in pediatric patients with various degrees of renal function. *J Pediatric Pharmacol Ther* 2022; 27: 419-427. 20220706. DOI: 10.5863/1551-6776-27.5.419.

- 29 Gomez DS, Campos EV, de Azevedo RP, et al. Individualised vancomycin doses for paediatric burn patients to achieve PK/PD targets. *Burns* 2013; 39: 445-450. 20120804. DOI: 10.1016/j.burns.2012.07.005.
- 30 Mei H, Wang J, Che H, et al. The clinical efficacy and safety of vancomycin loading dose: A systematic review and meta-analysis. *Medicine* 2019; 98.
- 31 Cafaro A, Stella M, Mesini A, et al. Dose optimization and target attainment of vancomycin in children. *Clin Biochem* 2024; 125: 110728. 20240205. DOI: 10.1016/j.clinbiochem.2024.110728.
- 32 Schlapbach LJ, Watson RS, Sorce LR, et al. International Consensus Criteria for Pediatric Sepsis and Septic Shock. *JAMA* 2024. DOI: 10.1001/jama.2024.0179.
- 33 Jabornisky R, Kuppermann N and González-Damrauskas S. Transitioning from SIRS to Phoenix with the updated pediatric sepsis criteria: the difficult task of simplifying the complex. *JAMA* 2024. DOI: 10.1001/jama.2023.27988.
- 34 Carlton EF, Perry-Eaddy MA and Prescott HC. Context and implications of the new pediatric sepsis criteria. *Jama* 2024 20240121. DOI: 10.1001/jama.2023.27979.