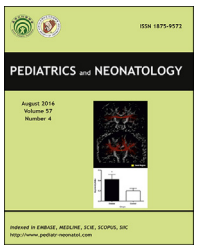
ARTICLE IN PRESS
+ MODEL
Pediatrics and Neonatology xxx (xxxx) xxx

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: http://www.pediatr-neonatol.com



Original Article

Reappraisal of therapeutic vancomycin trough concentrations with empirical dosing in neonatal infections

Tzung-Yi Lee [a,1], Yi-Li Hung [b,c,d,1], Chung-Min Shen [b,d], Chi-Lan Kao [a], Wu-Shiun Hsieh [b,e,f,*]

[a] *Department of Pharmacy, Cathay General Hospital, Taipei, Taiwan*
[b] *Department of Pediatrics, Cathay General Hospital, Taipei, Taiwan*
[c] *School of Medicine, National Tsing Hua University, Hsinchu, Taiwan*
[d] *School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan*
[e] *Department of Pediatrics, National Taiwan University Children's Hospital, Taipei, Taiwan*
[f] *Department of Pediatrics, National Taiwan University College of Medicine, Taipei, Taiwan*

Received Dec 25, 2021; received in revised form Apr 6, 2022; accepted May 17, 2022
Available online ■ ■ ■

Key Words
Dosing regimen;
Neonate;
Trough;
Vancomycin

Background: Vancomycin is commonly used for neonatal sepsis. However, consensus on an empirical neonatal vancomycin regimen remains uncertain. We aimed to reappraise the therapeutic optimum concerning vancomycin trough concentrations with empirical dosing and to evaluate the relationship between trough concentrations and predicted 24-h area under the curve (AUC_{24}).

Methods: This was a 3-year retrospective study. Neonates who were admitted to the neonatal intensive care unit with available vancomycin trough concentrations were enrolled. Trough levels were obtained before the fourth dose. Achievement of goal trough after implementing the vancomycin dosing regimen was based on the Practical Neonatology Medical Manual, published by the National Taiwan University College of Medicine.

Results: A total of 46 neonates were included for analysis. Coagulase-negative staphylococci were the most commonly identified pathogens of sepsis. Among these patients, 22 achieved goal trough levels of 10—20 mcg/mL. Trough levels of 5—10 or >20 mcg/mL occurred in 13 and 11 patients, respectively. A moderately positive correlation between trough and predicted AUC_{24} was found in all patients (Spearman's rho = 0.676, $p < 0.001$).

In patients with body weight 1200—2000 g and postnatal age >7 days, the serum creatinine of those with trough levels >20 mcg/mL was significantly higher than those with goal trough levels (0.61 vs. 0.45 mg/dL, $p = 0.01$). Among those with trough levels >20 mcg/mL, 5 patients received ibuprofen for patent ductus arteriosus closing prior to vancomycin treatment (45%, 5/

* Corresponding author. Department of Pediatrics, Cathay General Hospital, No. 280, Sec. 4, Ren Ai Road, Taipei, Taiwan.
E-mail address: hsiehws@ntu.edu.tw (W.-S. Hsieh).
[1] Equal contribution to this article.

https://doi.org/10.1016/j.pedneo.2022.05.018

11), compared to only 3 patients with trough levels <20 mcg/mL (9%, 3/35) ($p = 0.013$).
Conclusion: Only half of the neonates receiving empirical vancomycin regimen achieved goal trough levels of 10—20 mcg/mL. Higher serum creatinine or ibuprofen treatment may increase the risk of overly high trough levels. The vancomycin regimen needs further validation and modification to provide adequate dosing for optimal use in neonates.

1. Introduction

Vancomycin is commonly used with empirical dosing for late-onset sepsis (LOS) in neonatal intensive care units (NICUs). According to the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, 70% of LOS was caused by Gram-positive organisms, with coagulase-negative staphylococci (CONS) accounting for 68% of Gram-positive infections.[1] Other Gram-positive organisms include *Staphylococcus aureus*, *Enterococcus* spp., and Group B *Streptococcus*.[1] The worldwide prevalence of oxacillin-resistant *Staphylococcus* spp. is high, with the emergence of vancomycin-resistant staphylococcal strains.[2] In Taiwan, 97.4% of CONS isolates in a NICU were reported to be resistant to oxacillin but remained sensitive to vancomycin.[3] Therefore, vancomycin is usually used as first-line empirical treatment against the predominant pathogens causing LOS, such as CONS and methicillin-resistant *S. aureus* (MRSA). However, inadequate vancomycin dosing can increase the risk for the emergence of resistant organisms, ototoxicity, and renal failure.[4] Therefore, therapeutic drug monitoring was mandated for vancomycin and variations in trough concentrations were observed among treated neonates, with dose adjustments made after initial empirical dosing.

Vancomycin has been used for over 50 years, but questions remain regarding the optimal dose and therapeutic target for neonates. In fact, consensus on an empirical neonatal vancomycin regimen remains uncertain, and there are differences among suggested dosing guidelines.[5] The British National Formulary for Children (BNFc) recommends a 15 mg/kg/dose of vancomycin for neonates, with frequency based on postmenstrual age (PMA).[6] On the other hand, NeoFax® recommends vancomycin at 10 mg/kg/dose for sepsis and 15 mg/kg/dose for meningitis, utilizing a combination of PMA and postnatal age (PNA) to determine the dosing interval.[7] Both BNFc and NeoFax® show that a large proportion of patients (81 and 71.9%, respectively) had suboptimal trough concentrations of <10 mcg/mL.[8,9] A summary of empirical neonatal vancomycin regimens is presented in Table 1.[6,7,10,11]

It was recommended that vancomycin trough concentrations be maintained at >10 mcg/mL to avoid producing vancomycin-intermediately susceptible *S. aureus* (VISA).[12] Higher trough concentrations (15—20 mcg/mL) have been used for serious infections caused by MRSA in adults to attain a 24-h area under the curve (AUC_{24}) >400.[12] Based on updated AUC-guided vancomycin monitoring for MRSA infections, the recommendation is an AUC_{24} to minimum inhibitory concentration (MIC) ratio of 400—600 as the preferred pharmacokinetic (PK)/pharmacodynamic (PD) target to achieve efficacy while improving safety.[13] However, because supporting evidence in neonates is rare, adopting the same vancomycin PK/PD target for neonatal infections remains controversial. According to a study by Frymoyer et al.,[14] targeting a vancomycin trough concentration of ~10 mcg/mL in neonates is likely to achieve an AUC_{24} >400. Our practice uses goal trough levels of 10—20 mcg/mL as a surrogate for AUC_{24}. Otherwise, to estimate AUC_{24} by either linear PK equations or the Bayesian approach requires two vancomycin concentrations (peak and trough).[13] Neonatologists are reluctant to do extra blood draws in premature neonates because of possible iatrogenic anemia and the risk of infection.

The empirical neonatal vancomycin regimen in our hospital uses a 15 mg/kg/dose every 12 or 24 h for those with body weight <1200 g and every 8 or 12 h for those with body weight >1200 g, based on the Practical Neonatology Medical Manual, published by the National Taiwan University College of Medicine[11] (Table 1). We aimed to reappraise the therapeutic vancomycin trough concentrations by using empirical dosing and examine the relationship between vancomycin trough concentrations and predicted AUC_{24}.

2. Methods

2.1. Patient enrollment and setting

We enrolled neonates who were admitted to the NICU of Cathay General Hospital from January 2017 to December 2019 and received vancomycin therapy. Around 370—390 patients were admitted to the 10-bed NICU annually. All neonates received an empirical vancomycin regimen based on the Practical Neonatology Medical Manual, published by the National Taiwan University College of Medicine[11] (Table 1). Patients were excluded if a different empirical neonatal vancomycin regimen was used, trough concentration was determined prior to the third dose or ≥1 h before the next dose, or there was renal insufficiency (urine output <1 mL/kg/h). This study was approved by the Institutional Review Board of Cathay General Hospital (CGH-P110059).

2.2. Data collection

Medical records were reviewed retrospectively for the perinatal characteristics, vancomycin dosing regimen, trough levels, culture reports and diagnoses. Baseline

Table 1 Summary of empirical neonatal vancomycin regimens in reference books.

References	Postmenstrual age (weeks)	Postnatal age (days)	Weight (g)	Dose (mg/kg/dose)	Interval (h)
British National Formulary for Children 2014[6]	<29			15	24
	29–35				12
	>35				8
NeoFax® 2011[7]	≤29	0–14		10 (bacteremia)	18
		>14		15 (meningitis)	12
	30–36	0–14			12
		>14			8
	37–44	0–7			12
		>7			8
	≥45	ALL			6
Nelson's Textbook of Pediatrics 2020[10]		≤7	<1200	15	24
			1200–2000	7.5–11.3	12–18
			>2000	15	12
		>7	<1200	15	24
			1200–2000	5–7.5	8–12
			>2000	15	8
Practical Neonatology Medical Manual 2014[11,a]		≤7	<1200	15	24
			1200–2000		12
			>2000		12
		>7	<1200		12
			1200–2000		8
			>2000		8

[a] Regimen evaluated in this study.

serum creatinine before starting vancomycin was also recorded. The vancomycin trough concentrations of all neonates were analyzed by the particle-enhanced turbidimetric inhibition immunoassay method using a UniCel DxC 800 Synchron Clinical System (Beckman Coulter, Brea, CA, USA). A steady-state vancomycin trough concentration was measured within 1 h before the fourth dose. If the patient received more than one course of vancomycin treatment, only the trough concentration during the first course was included. We used VITEK 2 (bioMérieux, Marcy l'Etoile, France) for identification of bacterial isolates and antibiotic susceptibility testing. The volume of blood collection for culture is 1–3 mL according to the laboratory standard. Our faculty would conduct a follow-up blood culture soon after knowing the first culture result was positive. It was usually informed by the laboratory within 72 h after sampling.

2.3. Pharmacokinetic and clinical outcomes

The target vancomycin trough concentration was 10–20 mcg/mL. Our primary outcome was patients achieving trough concentrations between 10 and 20 mcg/mL by using the neonatal empirical dosing regimen. Trough concentrations <10 or >20 mcg/mL were considered inadequate. Because only trough concentration was monitored during clinical care at our institution, vancomycin clearance could not be calculated directly via linear PK equations. Furthermore, the wide range of distribution volume in neonates (0.49–0.736 L/kg)[5] makes extrapolation of peak level difficult. Thus, we estimated each patient's vancomycin clearance using the neonatal PK model by Capparelli: Cl_{vanco} (L/h) = Wt × (0.028/sCr + 0.000127 × AGE + 0.0123 × GA28) + 0.006 (where Cl_{vanco} is vancomycin clearance, Wt is weight in kg, sCr is serum creatinine (mg/dL), AGE is PNA (days) if sCr < 0.7 mg/dL and AGE = 0 if sCr ≥ 0.7 mg/dL, GA28 = 1 if GA >28 weeks and 0 if GA ≤28 weeks).[15] Predicted AUC_{24} was calculated as the daily dose divided by clearance. Secondary outcome measurements included the correlation between trough concentration and predicted AUC_{24} and the ability of trough level in predicting a negative blood culture within 72 h.

2.4. Statistical analysis

Numerical data were presented as median and interquartile range (IQR) due to skewed distribution by Shapiro–Wilk test. Range and percentage were also used in descriptive statistics. The relationship between trough concentration and predicted AUC_{24} was analyzed using Spearman's rank correlation. The receiver operator characteristic (ROC) curve was used to examine the ability of trough level in predicting a negative blood culture within 72 h. Kruskal–Wallis with post hoc Dunn test was performed to compare differences in demographic characteristics between patients with trough levels of 10–20 mcg/mL, <10 mcg/mL and >20 mcg/mL. Further sub-group comparisons based on dose categories were analyzed by using Mann–Whitney U test. A comparison of dichotomous data was done by Fisher's exact test. Data were analyzed using the SPSS statistical software package (version 22.0; SPSS,

Table 2 Demographic characteristics (n = 46).

Characteristics	Median (range)
Gestational age at birth (weeks)	32 (24–40)
Postnatal age at vancomycin start (days)	13.5 (2–26)
Postmenstrual age at vancomycin start (weeks)	34 (25–43)
Birth body weight (g)	1499.5 (611–3620)
Body weight at vancomycin start (g)	1512.5 (613–3650)
Baseline serum creatinine (mg/dL)	0.53 (0.2–1.06)
Vancomycin dose (mg/kg/day)	43.3 (14.3–47.6)
Vancomycin treatment duration (days)	7 (3–14)

Chicago, IL, USA). Statistical significance was defined as a p-value < 0.05.

3. Results

A total of 63 neonates with available vancomycin trough concentrations during NICU admission were enrolled. Of these, 14 neonates were excluded because they received a different empirical vancomycin regimen, 2 due to wrong timing of trough level examination, and 1 due to renal insufficiency. Finally, 46 neonates were available for analysis. Among them, 7 patients received more than one vancomycin treatment course, but only the trough level drawn during the first course was included for evaluation. Among the group, 27 (59%) were male. The median gestational age (GA) was 32 weeks (range 24–40 weeks), with a majority being premature (89%, 41/46). Vancomycin was started at a PNA of 2–26 days. Body weight at the start of vancomycin treatment was <1200 g for 12 patients (26.1%), 1200–2000 g for 20 patients (43.5%), and >2000 g for 14 patients (30.4%). Patient characteristics are listed in Table 2.

The most common indications for empirical vancomycin were bacteremia (50%, 23/46) and clinical sepsis (39%, 18/46); for the other 5 patients the indications were necrotizing enterocolitis, omphalitis, pneumonia, candidemia, and urinary tract infection. Among patients with positive blood cultures, CONS was the most commonly identified pathogen (61%, 14/23), which was resistant to oxacillin but sensitive to vancomycin in all cases. In addition, MRSA was found in 30% (7/23) of patients with bacteremia. There were 2 patients with positive blood cultures of *Klebsiella pneumoniae* (9%, 2/23). The vancomycin MIC of MRSA isolates was ≤1 mcg/mL in all cases.

The median vancomycin trough concentration was 14.93 mcg/mL (range 5.84–31.28 mcg/mL). Calculated median vancomycin clearance was 0.07 L/h/kg (range 0.03–0.15 L/h/kg). Predicted median AUC_{24} was 546 mg·h/L (range 192–979 mg·h/L).

A moderately positive correlation between vancomycin trough concentration and predicted AUC_{24} was found in all patients (Spearman's rho = 0.676, $p < 0.001$). At a trough level >10 mcg/mL, 91% (30/33) predicted AUC_{24} >400 was achieved. However, inter-individual variabilities existed, and predicted AUC_{24} >400 was also achieved in about half of the patients (54%, 7/13) with a trough level <10 mcg/mL.

The area under the ROC curve of vancomycin trough concentration was 63.5% (95% CI = 32.4–94.5%, p = 0.428). As a result, the diagnostic performance of vancomycin trough concentration in predicting a negative blood culture within 72 h for CONS or MRSA bacteremia did not reach statistical significance. The threshold trough concentration was 14.28 mcg/mL (sensitivity = 61.5%, specificity = 75%); this value had the highest positive likelihood ratio of 2.46 and lowest negative likelihood ratio of 0.51.

Of the 46 patients, a goal trough level of 10–20 mcg/mL was achieved in 22 (48%). Trough levels of 5–10 or >20 mcg/mL were found in 13 (28%) and 11 (24%) patients, respectively. A trough concentration <5 mcg/mL was not found in any patient. The median trough concentrations (IQR) of patients within different trough ranges were as follows: (1) trough 5–10 mcg/mL: 8.07 mcg/mL (7.12–9.16 mcg/mL); (2) trough 10–20 mcg/mL: 15.87 mcg/mL (11.57–17.72 mcg/mL); and (3) trough >20 mcg/mL: 22.72 mcg/mL (22.13–23.98 mcg/mL).

Differences in patient characteristics between those who achieved goal vancomycin trough level and those who did not are shown in Table 3. Only daily dose was found to be significantly lower in patients with trough concentrations <10 mcg/mL. Age, body weight, and sCr did not differ between patients with different trough ranges.

Table 3 Differences in patient characteristics.

Characteristics	Trough (mcg/mL), median (IQR)			p-value
	<10 (n = 13)	10–20 (n = 22)	>20 (n = 11)	
Daily dose (mg/kg/day)	29.4 (15.8–30.1)	43.4 (42–44.6)	44.1 (43.9–45.5)	<0.001[a]
Gestational age (weeks)	31 (26.5–36)	33 (30–35)	31 (30–34)	0.541
Postnatal age (days)	6 (4–18.5)	14 (10–21.3)	14 (12–15)	0.248
Postmenstrual age (weeks)	33 (28–37.5)	35 (33–36.3)	33 (32–36)	0.352
Birth body weight (g)	1102 (870–2497)	1623 (1215.8–2002.5)	1645 (1363–1740)	0.26
Body weight (g)	1150 (856–2690)	1626 (1305–2089.5)	1660 (1361–1960)	0.183
Serum creatinine (mg/dL)	0.49 (0.41–0.98)	0.49 (0.43–0.64)	0.6 (0.53–0.74)	0.33

[a] Trough <10 vs. 10–20 mcg/mL ($p = 0.005$); trough <10 vs. >20 mcg/mL ($p < 0.001$); trough 10–20 vs. >20 mcg/mL ($p = 0.588$) (Kruskal–Wallis with post hoc Dunn test).

Table 4 Vancomycin trough levels and sCr in neonates with different body weight and age.

Body weight	<1200 g		1200–2000 g		>2000g	
Age (days)	0–7	>7	0–7	>7	0–7	>7
Trough (mcg/mL)	Number of patients (median sCr, mg/dL)					
<10	4 (1)	4 (0.45*)	1 (0.68)	0	2 (0.51)	2 (0.31)
10–20	0	4 (0.6*)	0	9 (0.45*)	0	9 (0.47)
>20	0	0	0	10 (0.61*)	0	1 (0.28)

*$p < 0.05$, Mann–Whitney U test.

Based on the empirical neonatal vancomycin regimen, patients were divided into six dose categories according to body weight and PNA. Table 4 shows the number of patients with goal trough level achieved or not in each dose group. Vancomycin trough concentrations <10 mcg/mL were more commonly found in patients with body weight <1200 g (62%, 8/13). Ten of the 11 patients (91%) with a trough level >20 mcg/mL had a body weight of 1200–2000 g and PNA >7 days and received vancomycin at 15 mg/kg/dose q8h. Comparisons among patients with body weight <1200 g and PNA >7 days showed significantly lower sCr in those with a trough level <10 mcg/mL than those with a goal trough level (0.45 vs. 0.6 mg/dL, $p = 0.029$). In addition, for patients with body weight 1200–2000 g and PNA >7 days, sCr in those with a trough level >20 mcg/mL was significantly higher than those with a goal trough level (0.61 vs. 0.45 mg/dL, $p = 0.01$).

Among the 11 patients with vancomycin trough level >20 mcg/mL, 5 (45%, 5/11) received ibuprofen treatment to close patent ductus arteriosus (PDA) prior to vancomycin treatment, compared to only 3 who received ibuprofen treatment among those with a trough level <20 mcg/mL (9%, 3/35) ($p = 0.013$). The 5 patients with a trough level >20 mcg/mL treated with ibuprofen were all in the dose group with body weight 1200–2000 g and PNA >7 days, given vancomycin at 15 mg/kg/dose q8h.

4. Discussion

Previous studies targeting vancomycin trough concentration of 10–20 mcg/mL in neonates showed a low target achievement rate (25–34%) by empirical dosing regimens, and most patients had suboptimal trough concentrations <10 mcg/mL (59–72%).[9,16,17] The six dose categories in our regimen were based on the same weight and PNA ranges as those of Schleiss.[10] To target trough concentrations between 10 and 20 mcg/mL, we increased the weight-based daily dose (mg/kg/day) in three of the six dose categories, with all patients administered the 15 mg/kg/dose. Compared to a similar empirical neonatal vancomycin regimen used in a study by Dersch-Mills et al.,[17] our results show a higher percentage of patients with goal trough levels of 10–20 mcg/mL (48 vs. 34%), with a reduced suboptimal trough level of <10 mcg/mL (28 vs. 64.5%). However, our regimen had more patients with higher trough levels >20 mcg/mL (24 vs. 1.3%). While minimizing suboptimal treatment, our empirical dosing regimen may result in some patients having slightly elevated initial trough concentrations.

Our analysis could not reveal whether age or body weight had a determining impact on achieving vancomycin goal trough concentrations, since these two factors did not show significant differences among patients with goal trough levels of 10–20 mcg/mL and those with levels of <10 or >20 mcg/mL. We found that most patients with trough levels of <10 mcg/mL had body weight <1200 g, especially at PNA ≤7 days. More preterm neonates at lower PNA have higher total body water, which would result in lower plasma levels of hydrophilic drugs such as vancomycin by weight-based dosing.[18] Caution should also be taken because at lower PNA renal function is immature, which could decrease the clearance of drugs eliminated by kidney, such as vancomycin.[19] A decline in sCr with increasing PNA reflects an improved glomerular filtration rate and is consistent with the improvement in vancomycin elimination.[20,21] A high degree of variation in renal maturation of preterm neonates makes drug level monitoring and adjustment according to serum concentrations inevitable.

Among patients with body weight of 1200–2000 g and PNA >7 days, sCr was found to be higher in those with trough level >20 mcg/mL than those with 10–20 mcg/mL (0.61 mg/dL vs. 0.45 mg/dL, $p = 0.01$). Although sCr was used as an indicator of renal function, the median sCr of 0.61 mg/dL was still within the reference range for neonates.[22] Additionally, vancomycin clearance has been reported to be lower regardless of GA in patients with elevated sCr >0.7 mg/dL.[15] Thus, the causal relationship between vancomycin trough level and sCr remained unclear. Moreover, we found that neonates treated with ibuprofen for PDA before vancomycin administration had higher trough levels. We suspect that ibuprofen induced vasoconstriction of the renal afferent arteriole, resulting in decreased GFR. Vieux et al. found that ibuprofen was nephrotoxic in preterm infants and renal drug clearance may remain decreased for the first month of life.[23]

Although vancomycin monitoring guidelines recommend an AUC_{24}/MIC target of 400–600 for neonates with MRSA infection based on adult data,[13] the clinical correlation of AUC_{24}/MIC in neonates remains unclear. Population PK/PD modeling with Bayesian estimation was utilized in one study, and an AUC_{24} of 240–480 (assuming MIC = 1 mcg/mL) was proposed as an exposure target for neonates after balancing nephrotoxicity and efficacy for staphylococcal sepsis, but not specifically for MRSA infection.[24] A higher fraction of unbound vancomycin in neonates (median 0.9) may suggest a lower AUC_{24}/MIC target as compared to adults, with a median unbound fraction of 0.6.[25] There are no data on the optimal PK/PD target for CONS, which is the most common pathogen in neonatal late-onset sepsis.

Controversy remains regarding empirical vancomycin therapy for infants with CONS bacteremia, since no mortality difference was reported as compared to delayed therapy.[26] However, a survival benefit was reported for early empiric antibiotic treatment of infants with MRSA bacteremia.[27] Targeting an AUC_{24}/MIC >400 to empirically cover MRSA in the early course of therapy seems to be clinically relevant, because there was a 30% prevalence of MRSA bacteremia in our NICU. As a lower AUC_{24}/MIC target for CONS infections was proposed by Pham,[28] targeting an AUC_{24}/MIC >400 for MRSA would also serve for CONS infection.[29]

To estimate AUC_{24} by linear PK equations, both peak and trough concentrations are required. For Bayesian AUC estimation, it is also preferred to use both concentrations.[13] When considering the risks involved in frequent blood draws, it is difficult to abandon trough-only vancomycin monitoring in neonates. According to the literature on adults, a vancomycin trough level of 15–20 mcg/mL was recommended to attain AUC_{24}/MIC >400.[12] Nevertheless, in a small study of eight neonates with measurement of peak and trough concentrations, Bayesian estimation found that AUC_{24} >400 was achieved at a mean trough level of 7.8 ± 0.8 mcg/mL for all patients.[30] A study by Frymoyer et al. that enrolled 249 neonates evaluated the association between AUC_{24} and trough concentrations.[14] They found that a trough concentration of 7–11 mcg/mL was predictive of AUC_{24}/MIC >400 in >90% of neonates by Monte Carlo simulations.[14] A similar result of a trough concentration of 8–8.9 mcg/mL being predictive of AUC_{24}/MIC >400 was also found in an Asian neonatal population in Singapore.[31] Our ROC analysis showed the negative likelihood ratio was >0.5 for predicting a negative blood culture within 72 h, indicating that more than 50% of patients' blood cultures turned negative even with a trough concentration lower than the threshold level of 14.28 mcg/mL. Although inter-individual variations existed, for 91% of our patients, predicted AUC_{24} >400 was achieved at a trough level >10 mcg/mL. Therefore, we speculated that vancomycin trough concentrations >15 mcg/mL were not always necessary, especially if the MIC was ≤1 mcg/mL.

Our study has several limitations. First, using a negative blood culture within 72 h after vancomycin treatment instead of clinical cure as the outcome measurement would be confounded by false negative culture results, especially with the small blood volume drawn in neonates. Second, due to the retrospective chart review design, we could not measure both peak and trough vancomycin concentrations to obtain PK parameter data such as clearance and AUC_{24}. Thus, the patient's AUC_{24} was calculated as daily dose divided by clearance predicted from a previously published neonatal PK model.[15,16] Third, we did not evaluate vancomycin toxicities, and further studies with predefined nephrotoxicity and ototoxicity in neonates are needed to clarify clinical risks associated with the empirical neonatal vancomycin regimen. Finally, although the studied population spanned all six dose categories of our empirical dosing regimen, the sample size was small and not sufficiently powered to determine differences in patient characteristics in terms of goal trough level achievement within each dose category.

In conclusion, because of the complexity in neonatal pharmacology and the interrelated nature of covariates influencing vancomycin PK parameters, variations in published vancomycin dosing regimens exist, making therapeutic drug monitoring in neonates important to avoid bacterial resistance and drug toxicity. Each institution should validate its empirical regimen and modify it to meet therapeutic needs and minimize toxicity risks.

Declaration of competing interest

The authors declare that they have no conflict of interest.

References

1. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002;**110**:285–91.
2. Martins A, Cunha Mde L. Methicillin resistance in *Staphylococcus aureus* and coagulase-negative staphylococci: epidemiological and molecular aspects. *Microbiol Immunol* 2007;**51**:787–95.
3. Ho TS, Wang SM, Wu YH, Shen CF, Lin YJ, Lin CH, et al. Long-term characteristics of healthcare-associated infections in a neonatal intensive care unit. *J Microbiol Immunol Infect* 2010;**43**:407–15.
4. Mukhopadhyay S, Sengupta S, Puopolo KM. Challenges and opportunities for antibiotic stewardship among preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2019;**104**:F327–32.
5. Rodvold KA, Everett JA, Pryka RD, Kraus DM. Pharmacokinetics and administration regimens of vancomycin in neonates, infants and children. *Clin Pharmacokinet* 1997;**33**:32–51.
6. Paediatric Formulary Committee. *British national formulary for children 2014–2015*. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications; 2014. p. 289–90.
7. Young TE. *Neofax*®. 24th ed. Montvale, NJ: Thomson Reuters; 2011. p. 102–3.
8. Petrie K, O'Brien C, Bhushan S, Tonna A. Neonatal vancomycin trough level audit using British National Formulary for Children dosing. *Arch Dis Child Fetal Neonatal Ed* 2015;**100**:F278–9.
9. Ringenberg T, Robinson C, Meyers R, Degnan L, Shah P, Siu A, et al. Achievement of therapeutic vancomycin trough serum concentrations with empiric dosing in neonatal intensive care unit patients. *Pediatr Infect Dis J* 2015;**34**:742–7.
10. Schleiss MR. Principles of antibacterial therapy. In: Kliegman RM, St Geme JW, Blum NJ, editors. *Nelson's textbook of pediatrics*. 21st ed. Philadelphia: Saunders Elsevier; 2020. p. 1414–29.
11. Hsieh WS, Wu MH, Chen CY, editors. *Practical neonatology medical manual*. 2nd ed. Taipei: National Taiwan University College of Medicine; 2014. p. 434–5.
12. Rybak M, Lomaestro B, Rotschafer JC, Moellering Jr R, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009;**66**:82–98.
13. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, 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**:835–64.

14. Frymoyer A, Hersh AL, El-Komy MH, Gaskari S, Su F, Drover DR, et al. Association between vancomycin trough concentrations and area under the concentration-time curve in neonates. *Antimicrob Agents Chemother* 2014;**58**:6454–61.
15. Capparelli EV, Lane JR, Romanowski GL, McFeely E, Murray W, Sousa P, et al. The influences of renal function and maturation on vancomycin elimination in newborns and infants. *J Clin Pharmacol* 2001;**41**:927–34.
16. Madigan T, Teng CB, Koshaish J, Johnson KR, Graner KK, Banerjee R. Optimization of vancomycin dosing in very low-birth-weight preterm neonates. *Am J Perinatol* 2015;**32**:83–6.
17. Dersch-Mills D, Bengry T, Akierman A, Alshaikh B, Yusuf K. Assessment of initial vancomycin dosing in neonates. *Paediatr Child Health* 2014;**19**:291.
18. Chawla D, Agarwal R, Deorari AK, Paul VK. Fluid and electrolyte management in term and preterm neonates. *Indian J Pediatr* 2008;**75**:255–9.
19. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;**349**:1157–67.
20. Bueva A, Guignard JP. Renal function in preterm neonates. *Pediatr Res* 1994;**36**:572–7.
21. James A, Koren G, Milliken J, Soldin S, Prober C. Vancomycin pharmacokinetics and dose recommendations for preterm infants. *Antimicrob Agents Chemother* 1987;**31**:52–4.
22. Rudd PT, Hughes EA, Placzek MM, Hodes DT. References ranges for plasma creatinine during the first month of life. *Arch Dis Child* 1983;**58**:212–5.
23. Vieux R, Fresson J, Guillemin F, Hascoet JM. Perinatal drug exposure and renal function in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2011;**96**:F290–5.
24. Tang Z, Guan J, Li J, Yu Y, Qian M, Cao J, et al. Determination of vancomycin exposure target and individualised dosing recommendations for neonates: model-informed precision dosing. *Int J Antimicrob Agents* 2021;**57**:106300.
25. Smits A, Pauwels S, Oyaert M, Peersman N, Spriet I, Saegeman V, et al. Factors impacting unbound vancomycin concentrations in neonates and young infants. *Eur J Clin Microbiol Infect Dis* 2018;**37**:1503–10.
26. Ericson JE, Thaden J, Cross HR, Clark RH, Fowler Jr VG, Benjamin Jr DK, et al. No survival benefit with empirical vancomycin therapy for coagulase-negative staphylococcal bloodstream infections in infants. *Pediatr Infect Dis J* 2015;**34**:371–5.
27. Thaden JT, Ericson JE, Cross H, Bergin SP, Messina JA, Fowler Jr VG, et al. Survival benefit of empirical therapy for *Staphylococcus aureus* bloodstream infections in infants. *Pediatr Infect Dis J* 2015;**34**:1175–9.
28. Pham JT. Challenges of vancomycin dosing and therapeutic monitoring in neonates. *J Pediatr Pharmacol Ther* 2020;**25**:476–84.
29. Frymoyer A, Stockmann C, Hersh AL, Goswami S, Keizer RJ. Individualized empiric vancomycin dosing in neonates using a model-based approach. *J Pediatric Infect Dis Soc* 2019;**8**:97–104.
30. Croes S, Stolk LM. Vancomycin therapeutic guidelines: closer examination of neonatal pharmacokinetics. *Clin Infect Dis* 2011;**53**:966–7.
31. Tseng SH, Lim CP, Chen Q, Tang CC, Kong ST, Ho PC. Evaluating the relationship between vancomycin trough concentration and 24-hour area under the concentration-time curve in neonates. *Antimicrob Agents Chemother* 2018;**62**:e01647-17.