REVIEW ARTICLE

Population Pharmacokinetic Modelling of Vancomycin in Asian Neonates: A Narrative Review to Optimise Dosing Strategies.

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Abstract

Vancomycin exhibits highly variable pharmacokinetics (PK) in neonates, making standard dosing strategies often inadequate. This narrative review evaluates the current landscape of population pharmacokinetic (PopPK) modeling in Asian neonates to optimise dosing strategies. A comprehensive literature search was conducted across PubMed to locate English-language studies published between 2010 and 2025. Studies were selected if they utilised nonlinear mixed-effects modelling to describe vancomycin PK in Asian neonatal cohorts. Data regarding model structure, significant covariates, and validation methods were extracted from 11 identified studies, encompassing 1,359 neonates across six countries, and synthesised narratively. Findings indicate that body weight is the universal predictor for clearance (CL) and volume of distribution (Vd), while renal maturation markers (serum creatinine and postmenstrual age) significantly influence CL. Dynamic NICU factors, including daily fluid intake, diuretics, and vasoactive agents, were also found to critically impact drug disposition. While traditional efficacy targets use an $AUC_{24}/MIC \geq 400$, evidence suggests a neonatal-specific target of 240–480 may be safer for this population. Nephrotoxicity risk was notably increased at an AUC_{24} threshold $\geq$ 485 mg·h/L. Collectively, these models demonstrate that trough-only monitoring is an inaccurate surrogate for total exposure. The review advocates for the adoption of Bayesian-derived pharmacokinetics estimates for AUC monitoring and the development of localised PopPK models to ensure precision dosing and therapeutic safety in Asian neonatal subpopulations.

Keywords: *Dosing regimen, neonates, modelling/modeling, neonates, vancomycin.*

Introduction

Vancomycin remains the gold standard treatment for gram-positive infections, including coagulase-negative *Staphylococcus* and methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Due to its bactericidal activity, lower cost,[2] and superior safety profile during long-term therapy (>14 days) compared to newer agents like linezolid,[3] vancomycin is the first-line recommendation in the Infectious Diseases Society of America (IDSA) guidelines.[4]

Neonates are highly vulnerable to nosocomial infections due to their immunocompromised state and prolonged Neonatal Intensive Care Unit (NICU) stays.[5] In Malaysia (2015–2020), late-onset sepsis incidence reached 12% in extremely preterm and 5.3% in very preterm infants, with Gram-positive bacteria, primarily coagulase-negative *Staphylococcus* (18.3%) and *S. aureus* (9.9%), accounting for 39.3% of cases.[6] The 2024 National Antibiotic Resistance Surveillance (NSAR) reported a sharp rise in paediatric MRSA isolates, from 72 cases in 2023 to 200 cases in 2024.[7-8] As Vancomycin remains the only antibiotic in Malaysia with minimal reported resistance,[7] this surge necessitates urgent dosing optimisation to ensure efficacy and prevent emerging resistance.

Vancomycin's narrow therapeutic index makes its clearance (CL) and volume of distribution (V_d) highly sensitive to sepsis, renal function, and maturation.[4,9]These variations necessitate precise targets to balance efficacy and toxicity.[10-11] While intermittent infusion (IIV) is conventional, it often fails to reach targets,[12] for instance, standard regimens like Neofax leave around 76% of trough below 10 mg/L.[13] Although continuous infusion (CIV) could improve attainment, it remains impractical in neonates due to limited venous access and frequent interruptions.[14] Consequently, IIV remains the clinical standard of administration.

Neonatal pharmacotherapy is shifting toward Model-Informed Precision Dosing (MIPD) to account for diverse covariates like postmenstrual age (PMA), weight, and renal function.[15] While American Society of Health-System Pharmacists (ASHP)-IDSA guidelines now prioritise an AUC_{24}/MIC target of 400–600 by noting its superior correlation with reduced nephrotoxicity compared to traditional troughs, prospective data linking these targets to neonatal MRSA outcomes remains scarce.[4] Retrospective studies indicate no clinical benefit for troughs ≥15 mg/L or AUC_{24}/MIC≥400, nor increased mortality for troughs <10 mg/L.[4] Consequently, a consensus on an optimal standardised regimen has yet to be reached.

Population Pharmacokinetic (PopPK) modelling is recommended to optimise dosing. It employs the integration of advanced pharmacometrics and Bayesian forecasting allows for real time dose adjustments that account for the maturational shifts in renal function.[16] Crucially, up to 82% of CL variability can be addressed by identifying the correct covariates, hence reducing the need for invasive blood sampling.[17] However, the successful implementation of these trends in Asia requires localised data, as regional variances in neonatal physiology and clinical infrastructure often limit the direct application of Western-derived models.[18] For instance, Anderson et al.[17] found that size (49.98%), PMA (18.2%), and renal function (14.1%) accounted for the variance in CL among New Zealand preterm neonates. However, applying their dosing regimen to a Belgian cohort (preterm neonates) resulted in a low 33.7% attainment rate, with 66.3% of troughs falling below 10 mg/L.[13] This discrepancy suggests significant regional variance, even within the same ethnicity.

Significant postnatal physiological maturation,[19] ethnic diversity, and poor target attainment with IIV suggest re-evaluation of dosing strategies for Asian cohorts. It is prudent for Malaysia to develop its own neonatal vancomycin PopPK modelling, as Malaysian infants are often born smaller than their Caucasian counterparts, hence exhibit unique pharmacokinetics (PK) that may not be fully captured by universal models.[20] Currently,

there is a lack of synthesised evidence regarding how regional covariates, such as local neonatal growth patterns and specific clinical practices, affect dosing precision. This narrative review serves as a critical "Phase 1" analysis to identify the source population variabilities and clinical data gaps within the Asian neonatal literature. By synthesising these findings, the review establishes the essential evidence base required to pave the way for a subsequent Phase 2 research project, which is the development and validation of a high-precision PopPK model specifically for the Malaysian neonatal population. This phased approach ensures that future modelling is built upon a robust understanding of regional covariates, ultimately providing a localised framework to optimise therapeutic outcomes and combat the rising trend of MRSA in Malaysia.

Materials and methods

The literature selection process was conducted in the PubMed database in October 2025 using the keywords: vancomycin, neonates, infants, pharmacokinetic modelling/modeling, and dosing regimen. Articles were included if they were written in English and focused on vancomycin PK modelling specifically within Asian neonatal and infant populations. Articles were excluded if they were case reports, reviews, letters, surveys, or lacked full-text availability. Additionally, studies focusing on adult populations or including paediatric subjects >1 year old were excluded to maintain the neonatal focus of this review. No publication date restrictions were applied.

The scope of this narrative synthesis was specifically defined to evaluate the PopPK of vancomycin in Asian neonatal cohorts, focusing on studies that identified clinical covariates influencing drug disposition in neonates. The literature search retrieved a total of 646 articles, but only 11 articles were eligible. Six hundred thirty-five articles were excluded based on the inclusion and exclusion criteria for article selection. This review encompassed 11 primary studies published between 2004 and 2025, with a particular emphasis on diverse neonatal populations, including non-extremely preterm and critically ill infants.

The selected articles were reviewed in detail for data extraction. Regarding subject demographics, we extracted nationality, gestational status, sample size, and the total number of vancomycin samples. Furthermore, we documented the inclusion and exclusion criteria employed by the selected articles for their respective subject selection to ensure a thorough comparison of the study cohorts. Additionally, developmental and pharmacokinetic parameters, including PMA, postnatal age (PNA), post-conceptual age (PCA), gestational age (GA), CL and Vd were extracted. Furthermore, we documented the model development methodologies and the validation techniques used by each author to verify their models' predictive performance. Regarding covariate analysis, we identified significant factors influencing vancomycin CL and Vd as determined by the respective PopPK models. For dosing strategies, we extracted the efficacy targets and the final recommended regimens from each study. Furthermore, we recorded clinical target attainment rates, trough levels predictive of AUC_{24}/MIC targets, and the specific trough or AUC thresholds associated with nephrotoxicity. Finally, the model-derived AUC_{24}/MIC thresholds required for optimal clinical efficacy in neonates were recorded. All extracted data were systematically tabulated in Microsoft Excel.

The methodological quality and reporting integrity of the included studies were assessed using the ClinPK statement checklist**.**[21] Data synthesis was performed using a narrative synthesis approach. First, the characteristics and outcomes of the included studies were systematically tabulated to facilitate a side-by-side comparison of neonatal study populations, resultant mean CL and Vd, and dosing regimens. Second, a thematic analysis was conducted to identify recurring significant covariates and consensus on pharmacokinetic targets,

specifically AUC_{24}/MIC and trough level, across the different models generated respectively by the studies. Finally, the findings were integrated to provide an overview of current vancomycin dosing strategies and target attainment rates in Asian neonates, while highlighting areas of clinical agreement and the reasoning behind observed result discrepancies.

Results

A narrative synthesis was conducted on 11 independent studies spanning six Asian countries (Korea, China, Malaysia, Japan, Singapore, and Saudi Arabia).[20,22-31] The combined dataset represented a total of 1,359 neonates and 3,976 vancomycin serum concentration samples, yielding an average data density of 2.93 samples per patient. This synthesis captures a broad clinical spectrum, with gestational age ranging from extremely preterm (23.0 weeks) to full-term neonates.[20,22-31] Across the reviewed literature, typical CL values ranged from 0.0426 to 0.14 L/h, while Vd estimates varied between 0.296 and 1.19 L/kg.[20,22-31]These findings highlight the significant impact of developmental maturation on vancomycin pharmacokinetics within the neonatal population and provide a comprehensive overview of current modelling efforts in the region. Table 1 shows the demographic data, CL, and Vd estimates for each study.

The inclusion and exclusion criteria across the 11 identified studies reflected a focused effort to characterise vancomycin pharmacokinetics in stable yet vulnerable neonatal populations (Table 2). Most studies specifically targeted neonates with suspected or confirmed sepsis requiring intravenous therapy.[22-23,26-31] While the majority of the literature included both preterm and full-term neonates, a subset of the literature focused exclusively on very low birth weight (VLBW) or premature infants.[20,24,25] Common exclusion criteria included significant renal impairment (e.g., eGFR <30 mL/min/1.73 m^2), major congenital anomalies, and the use of extracorporeal membrane oxygenation (ECMO).[20,22-31] This consistency in excluding severe renal failure across the majority of the studies ensures that the reported CL values represent the typical developmental maturation of the neonatal kidney rather than pathological acute kidney injury.

Population PK modelling

The technical characteristics and methodological quality of the 11 included studies were summarised in Table 3. All studies utilised a one-compartment model with first-order elimination to describe vancomycin pharmacokinetics in neonates. NONMEM was the most frequently employed software for model development (n = 7),[20,22,23,26,28-30] followed by Monolix (n = 2),[24,31] Phoenix NLME (n = 2).[25,27]

Model robustness was extensively verified across studies using multiple validation techniques. Internal validation via the non-parametric bootstrap method was nearly universal, performed in 10 out of 11 studies to confirm parameter stability.[20, 22,23,25-31] visual predictive checks (VPC) and/or normalised prediction distribution errors (NPDE) were utilised in 81.8% (n = 9) of the papers to evaluate predictive performance.[22,24-31] Furthermore, four studies enhanced their findings through external validation using independent patient datasets.[27,29-31]

The methodological reporting quality, assessed via the 24-item ClinPK statement checklist, was consistently high across the included studies. The compliance scores ranged from 76.0% [20] to 95.5%, [31] with a median score of 85.7%. This demonstrates excellent reporting integrity, as nine out of the eleven studies exceeded the 80% benchmark commonly associated with high-quality clinical pharmacokinetic reporting. Most articles demonstrated particularly high compliance in the PK Modelling and statistical analysis domains, ensuring transparency in structural model selection, covariate screening, and the handling of inter-individual variability.

Key performance metrics reported across the models included coefficient of determination (R^2) ranging from 0.62[23] to 0.89[20] and CL inter-individual variability (IIV) ranging from 4.97% [27] to 37.9%. [28]

Thematic analysis of covariates for CL and Vd

The thematic analysis of the 11 studies identified four primary themes influencing vancomycin CL: body size, renal maturation, clinical/maturational status, and therapeutic interventions. [20,22-31] Body weight was the universal scaling factor for size, included in all 11 models (100%). Renal maturation was characterised by serum creatinine (SCR) (82%, n=9) and PMA (64%, n=7).

A distinct theme emerged regarding clinical and maturational status, where the intrinsic condition of the neonate at birth significantly impacted CL. Specifically, Lo et al. [20] identified small for gestational age (SGA) status as a significant covariate, while Kato et al. [25] incorporated very low birth weight (VLBW) status into their final model.

Finally, therapeutic and clinical interventions represented a critical theme for dose optimisation in neonates. This included the impact of co-administered medications, such as vasoactive agents (VAS) (associated with a 14% reduction in CL in Tang et al. [31]) and ceftriaxone, [30] as well as clinical management factors like daily fluid input, diuretic use,[27] and vancomycin infusion volume.[25] Together, these themes illustrate that a 'one-size-fits-all' age/weight model may be insufficient for neonates with complex clinical statuses or those receiving intensive pharmacological support.

As for Vd, a consistent finding was observed across all 11 studies. [20,22-31] Body weight is the sole significant predictor of Vd in the final pharmacokinetic models. Every reviewed study (100%) utilised weight-based scaling for Vd, typically using an isometric relationship (exponent fixed at 1.0). While some studies, such as Zhao et al. [27], explored the impact of clinical factors like albumin and daily fluid input, these variables did not reach statistical significance in the final Vd models. This suggests that while physiological fluctuations in fluid status occur in neonates, the total volume into which vancomycin distributes is primarily governed by the physical size of the neonate. Table 4 summarises the covariates identified.

Therapeutic target attainment and dosing impact

The narrative synthesis of clinical outcomes identifies a transition from traditional trough-based targets toward individualised, AUC-guided dosing strategies across the 11 Asian cohorts. [20,22-31] A primary finding of this synthesis is the identification of neonatal-specific efficacy thresholds; while the historical standard remains an $AUC_{24}/MIC \geq 400$, [4] Tang et al. [31] identified $AUC_{24}/MIC \geq 234$ as the optimal predictor for clinical effectiveness in neonatal staphylococcal sepsis, achieving a clinical effectiveness rate of 97%. In contrast, studies by Tseng et al. [26] and Lee et al. [22] utilised the traditional target of 400, though Lee et al. [22] observed a low clinical attainment rate in practice, with only 37.4% of analysed concentrations falling within the therapeutic trough range of 5–15 mg/L. [22]

Simulation data from the reviewed models indicate that the probability of target attainment (PTA) is highly sensitive to the minimum inhibitory concentration (MIC) of the pathogen. For pathogens with an MIC$\leq$ 0.5 mg/L, studies that performed PTA analysis (notably Kato et al. [25] and Chen et al. [29]) demonstrated that nearly all dosing regimens achieved >95% PTA for both the $AUC_{24}/MIC \geq$ 234 and $\geq$400 targets. However, for an MIC of 1 mg/L, achieving the $AUC_{24}/MIC \geq$ 400 target becomes significantly more challenging; models showed that attainment rates can drop to as low as 6–15% (for trough 5-10mg/L) unless aggressive dosing is employed.[29] Such intensified regimens frequently push serum exposures toward the toxic threshold, increasing the risk of nephrotoxicity without a guaranteed improvement in clinical efficacy. [32] Regarding safety, Tang et al.[31]

established an AUC_{24}≥485 as an independent risk factor for acute kidney injury (AKI).

A consistent theme across the recent literature was the quantified inadequacy of trough-only monitoring. Tseng et al. [26] demonstrated that significant inter-individual variability in neonates results in a single trough concentration corresponding to a range of AUC_{24} values spanning up to two-fold, rendering trough-only monitoring an unreliable surrogate for total exposure. This variability is further underscored by Tang et al.[31], who utilised their model to advocate for Bayesian-derived AUC monitoring over traditional trough targets, ultimately proposing a refined therapeutic window of AUC_{24} 240–480 to balance efficacy and safety in neonatal cohorts.[31] Detailed recommendations, therapeutic targets, and dosing regimens are presented in Table 5.

Discussion

The dominance of body weight in allometric scaling

Methodological approaches to weight-based scaling varied across the included studies. The majority of authors employed allometric scaling, typically with a fixed exponent of 0.75 for CL and 1.0 for Vd. [20,29,31] This approach reflects the non-linear physiological reality that renal maturation and drug clearance in neonates do not increase in direct proportion to body weight.

However, several studies deviated from this standard power-law model to better fit their specific populations. Kato et al. [25], focusing on a highly specific VLBW population, found that treating Vd as a population constant (1.19 L) provided superior model stability compared to weight-based scaling. [25] Furthermore, Li et al. [28] challenged the universal application of the 0.75 exponent, demonstrating that an estimated exponent derived from their local dataset was more representative of their patients than a fixed theoretical value. Moreover, allometric scaling of PK parameters to body weight using a fixed simple power function may inaccurately estimate CL in preterm neonates because it fails to capture the drastic, non-linear physiological changes associated with renal maturation. [33]

In conclusion, the methodological diversity observed, specifically the deviations from standard 0.75 allometric scaling, highlights that neonatal physiology cannot be generalised by a single universal formula. Consequently, developing localised models is a clinical necessity to ensure dosing precision and avoid systematic errors in specific populations such as Malaysian neonates.

Chronological maturation: the preference for PMA

A significant theme in the synthesis is the shift toward PMA as the preferred marker for maturation (64% of models). While older studies like Kimura et al. [23] utilised PCA, the majority of recent literature favours PMA. [20,22-26,28-29,31] This preference highlights the importance of accounting for both intrauterine development and postnatal growth. In cohorts focusing on preterm infants, such as those by Lo et al. [20] and Tseng et al. [26], PMA was a superior predictor of the rapid increase in glomerular filtration rate (GFR) that occurs as nephrogenesis completes postnatally, compared to PNA alone.[34]

Biochemical vs. functional renal markers (SCR and CLcr)

SCR remains the most frequently used biochemical covariate (82% of studies). This suggests that SCR is still considered the most practical bedside surrogate for renal function in Asian neonates. However, a significant challenge in neonatal dosing is the "creatinine lag," where SCR in the first days of life reflects maternal rather than neonatal renal function. [35] Gallini et al. [36] demonstrated that preterm neonates, especially those <32 weeks GA, experience a transient increase in SCR, peaking around day 4. This "creatinine blip" is attributed to the passive reabsorption of creatinine across the leaky, immature tubular basement membrane. [36] This physiological lag explains why SCR was

excluded or required correction in several reviewed models. For instance, Tang et al. [31] explored the use of standardised SCR initially but abandoned it for model simplicity. Lee et al. [22] and Alsultan et al. [24] incorporated CLcr into their modelling, while Lo et al. [20] and Zhao et al. [27] acknowledged that SCR alone was insufficient to accurately predict drug elimination in the early postnatal period and therefore incorporated other covariates into their modelling. Relying on SCR during this first week "instability phase" without accounting for PNA can lead to significant underestimation of the drug's true renal clearance. [34-36]

The impact of birth status: physiological discrepancies in SGA and VLBW neonates

A critical finding in this synthesis is that the "biological history" of the neonate at birth is a primary determinant of drug disposition, often creating discrepancies when standard maturational models are applied. Specifically, Lo et al. [20] identified that SGA infants exhibit a 20% reduction in vancomycin clearance compared to AGA peers. This discrepancy likely arises from the fact that intrauterine growth restriction can permanently alter renal development, leading to lower kidney volumes and a reduced total nephron count. [37] Similarly, the inclusion of VLBW status as a significant covariate by Kato et al. [25] underscores that size-based scaling alone may fail to capture the unique, immature physiology of the most vulnerable neonates. These findings reveal a critical gap in current practice: standard age-weight models may inherently overestimate clearance in SGA and VLBW subgroups, potentially leading to drug accumulation. Consequently, a "maturational correction" or a specific pathological covariate for birth status is necessary to ensure dosing safety and avoid vancomycin-induced toxicity in these high-risk populations.

Dynamic fluid balance and volume of distribution (Vd)

A significant discrepancy identified in this synthesis is the variability in Vd estimates, particularly the elevated volumes reported in VLBW cohorts, such as that by Kato et al. [25] (Vd = 1.19L for a median weight of 0.93kg). This represents one of the highest Vd values among the 11 reviewed studies and is intrinsically linked to the unique developmental physiology of immature neonates. Hydrophilic drugs like vancomycin distribute primarily into the extracellular fluid (ECF), which constitutes a much larger percentage of total body mass in neonates (approximately 55%) compared to 20% in adults. [38] Shaffer et al. [39] further demonstrated that the ECF is particularly expanded in preterm infants at birth (550 ±116mL/kg) and undergoes a rapid physiologic reduction during the first two weeks of life to approximately 350mL/kg.

While 10 out of the 11 studies utilised isometric weight scaling (fixing the power exponent to 1.0) to predict Vd, [20,22-24,26-31] Kato et al. [25] was the only study to estimate Vd as a population constant (1.19L) due to the unique physiological variability of their VLBW cohort. This emphasises that size-based scaling alone may under-predict distribution in critically ill VLBW infants who maintain an expanded ECF volume. [39] Furthermore, Zhao et al. [27] and Kato et al. [25] identified that vancomycin kinetics significantly correlate with daily fluid input (DFI) and volume of infusion, respectively. This suggests that aggressive fluid management in the NICU, common during septic shock, can dilute serum drug concentrations and acutely increase Vd. [40] These findings reveal a critical clinical discrepancy: in modern NICU environments where fluid balance is dynamic, traditional static weight-based models may fail to account for fluid-driven shifts in distribution. Consequently, clinicians should anticipate larger distribution volumes in VLBW neonates, potentially necessitating higher initial loading doses to avoid subtherapeutic peak concentrations.

Redefining efficacy: the unbound fraction and target divergence

A significant divergence identified in this synthesis is the proposal of a neonatal-specific efficacy target of $AUC_{24}/MIC \geq 234$. [31] While traditional adult-derived targets of 400 are maintained by some authors, [20,22,24-29] this lower threshold is supported by unique neonatal physiology. Smits et al. [41] demonstrated that neonates possess a significantly higher unbound (free) fraction of vancomycin at approximately 90%, compared to 70–80% in adults, due to developmental deficits in serum albumin and IgA levels. Because only the unbound drug is pharmacologically active, a lower total serum exposure in a neonate can provide a bactericidal effect equivalent to a higher total concentration in an adult. [31,40] This biological mechanism is clinically validated by Padari et al. [42], who found that higher targets of $AUC_{24} \geq MIC$ 300–400 did not improve effectiveness in neonatal staphylococcal sepsis compared to lower exposures.

The safe therapeutic window and toxicity ceiling

The adoption of a lower efficacy target ($AUC_{24}/MIC \geq 234$ vs. 400) provides a critical safety buffer in the narrow therapeutic window of the immature neonatal kidney. Tang et al. [31] identified an $AUC_{24} \geq 485$ as an independent risk factor for AKI. This threshold is considerably lower than the AUC_{24} 600–800 range, which is frequently identified in paediatric literature as a critical 'grey zone' where the risk of nephrotoxicity escalates. [4,43] Aiming for a target of 400 leaves a dangerously small margin of error before reaching the toxicity ceiling of $AUC_{24} \geq 485$. Furthermore, the poor correlation between troughs and AUCs, quantified as a two-fold range for a single trough value, [26,43,44], emphasises that historical trough standards are physiologically inaccurate surrogates for achieving these narrow, safe windows.

Clinical interventions and co-medications

The synthesis reveals critical discrepancies regarding the impact of concurrent pharmacotherapy on vancomycin disposition. Tang et al. [31] quantified a 14.1% reduction in vancomycin CL when VAS were co-administered, a finding likely attributed to haemodynamic instability and reduced renal perfusion in critically ill neonates. In contrast, Zhao et al. [27] and Kato et al. [25] investigated VAS during model building but did not find it to be a significant covariate in their final models. Given the higher methodological quality and clinical detail provided in the Tang et al. [31] analysis, their findings on VAS-mediated clearance reduction were prioritised as a key consideration for optimising dosing in hemodynamically unstable Asian neonates. Conversely, Li et al.[30] hypothesised that co-administered ceftriaxone could increase vancomycin clearance, potentially by competitively inhibiting protein binding and thus increasing the free fraction available for renal excretion. [30,45] Adding to this complexity, Zhao et al. [27] identified that the use of diuretics was associated with a significant reduction in vancomycin CL. This presents a clinical paradox: while diuretics are traditionally used to increase urine output, their association with reduced clearance may reflect underlying renal stress or the induction of acute interstitial nephritis, which can lead to drug accumulation. [27,46,47] These conflicting drug-drug interactions suggest that standard maturational models are insufficient for the "real-world" NICU environment, where the net effect of co-medications can significantly shift the therapeutic window.

Dosing diversity and clinical implementation

The synthesised evidence reveals a spectrum of dosing philosophies in Asian neonatal care, ranging from simplified fixed regimens to high-precision, multi-covariate models. Kato et al. [25] advocated for a practical 10 mg/kg three times a day (TDS) regimen for VLBW infants,

emphasising bedside ease. Conversely, Zhao et al. [27] and Tang et al. [31] demonstrated that co-medications are critical determinants of the initial dose; Zhao et al. [27] suggested a 20% dose reduction for diuretic use, while Tang et al. [31] quantified a 14.1% clearance reduction for neonates on VAS, necessitating a proportional dose reduction or interval extension. These findings highlight a critical discrepancy: traditional weight-age models likely overdose critically ill neonates requiring hemodynamic or diuretic support.

In summary, the different dosing regimens established were influenced by the significant covariates identified and the different therapeutics targets for the different populations. The transition from simplified regimens to complex models reflects a growing need for precision in neonatal care. While simplified TDS strategies offer clinical utility, multi-covariate matrices demonstrate that ignoring dynamic factors such as fluid input and diuretic use can lead to significant dosing errors. This diversity underscores that initial dosing tables are increasingly viewed as "starting points" rather than definitive guides.

Limitations

Several limitations in this narrative synthesis must be acknowledged. First, the primary data were predominantly derived from retrospective observational cohorts utilising sparse sampling (peak and trough levels), which may compromise the precision of pharmacokinetic parameter estimates compared to prospective, rich-sampling protocols. Second, there is a lack of multi-centre external validation across the diverse sub-populations and regional clinical practice standards within Asia. Furthermore, inter-study variability may be introduced by the diversity in bioanalytical methods used to measure vancomycin and creatinine across institutions.

Third, clinical outcome data were not uniformly reported. Several studies relied on Monte Carlo simulations to predict target attainment rather than correlating exposure with actual clinical success or microbiological cure. In studies that did evaluate clinical endpoints, the low incidence of vancomycin-induced AKI resulted in small sample sizes for toxicity analysis, leading to wide confidence intervals for risk thresholds. [31] Finally, the impact of dynamic clinical co-factors remains under-explored; most models focused on maturation (age and weight), but fewer integrated the influence of therapeutic interventions such as vasoactive support, diuretic use, or aggressive fluid resuscitation, which can drastically alter kinetics in critically ill neonates. [25,27,31]

Conclusion

This narrative review highlights the necessity of transitioning from traditional weight-age dosing matrices toward individualised, precision-based vancomycin therapy in Asian neonatal care. The synthesis of available population pharmacokinetic models confirms that while maturation remains the primary driver of drug disposition, standard predictors such as SCR often fail to reflect actual renal function during the early postnatal period due to developmental "creatinine lag." Furthermore, the expanded extracellular fluid volume characteristic of neonates and the significant influence of dynamic factors, including daily fluid intake and the use of vasoactive or diuretic agents, demonstrate that critically ill neonates are at high risk for dosing errors if clinical co-factors are ignored. Optimising the dosing strategy requires a fundamental shift in the definition of therapeutic success. Evidence from Asian cohorts suggests that a lower, neonatal-specific AUC_{24}/MIC target is clinically effective and provides a safer buffer against the identified nephrotoxicity ceiling. To bridge the gap between variable initial regimens and therapeutic safety, this review advocates for the adoption of Bayesian-derived AUC monitoring or estimates of pharmacokinetic parameters. By moving away from static trough-based targets, which fail to account for significant inter-individual exposure variability, clinicians

can more accurately navigate the narrow therapeutic window of the Asian neonate, ensuring maximal efficacy while minimising the risk of AKI.

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Authors' contribution
CSP contributed to manuscript preparation, data collection, and revisions. SM contributed to manuscript review, editing, and approval of the final version.

Conflict of interest statement
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Table 1: Summary of nationality, maturation level and population pharmacokinetics parameters (CL and Vd) by modeling

Authors	Nationality	Patients (n)	Samples (*k*)	GA (wks)*	PMA (wks)*	PNA (days)*	CL (L/h) [r]	Vd (L) [r]
Lee et al. (2021)	Korea	207	900	23.3–41.5	35.6 [24.0–48.4]	16.1 [0–114.8]	0.123 (26%)	0.296 (25%)
Zhao et al. (2025)	China	126	276	32 [29.4–37.9]	35.7 [32.9–40.0]	0 [0–2.8]	0.14 (3.15%)	1.04 (4.28%)
Lo et al. (2010)	Malaysia	116	835	23.0–31.0	23.6–33.4	1–32	0.0426	0.523
Kato et al. (2016)	Japan	10	26	26.8 ± 3.0	29.6 [26.1–34.4]	19.7 [11–28]	0.054 ± 0.005	1.19 ± 0.40
Kimura et al. (2004)	Japan	19	88	24.1–41.3	25.1–48.4	3–71	0.105 (22.9 CV%)	0.91 (20.8 CV%)
Tang et al. (2021)	China	182	411	22.3–41.3	22.3–44.4	1–87	0.09 (2.11%)	0.86 (3.02%)
Tseng et al. (2018)	Singapore	76	429	23.9–40.3	30.1 [25.1–57.5]	17.4 [4–223]	0.0519 (2.9%)	0.498 (2.7%)
Li et al. (2018)	China	80	165	34.7 ± 4.3	39.4 ± 3.6	32.3 ± 24.1	0.309 (5%)	2.63 (8%)
Alsultan et al. (2023)	Saudi Arab	236	311	28 [22–38]	29.8 [22–42]	10.7 [1–30]	0.09 (11%)	0.81 (6.6%)
Chen et al. (2018)	China	213	330	36.9 [25–42]	39.8 [28–47.9]	26 [6–59]	0.103	0.58 (4.6%)
Li et al. (2021)	China	94	205	37.2 ± 3.7	–	67.1 ± 80.9	10.3 (29.6%)	50.6 (7.5%)

*Values are expressed as median [range] or mean ±SD; [r] Values in parentheses represent Relative Standard Error (RSE%) unless otherwise specified as Coefficient of Variation (CV%)
Abbreviations: GA gestational age; **PMA** post menstural age; **PNA** post natal age; **CL** clearance; **Vd** volume of distribution; **n** total number of neonates; ***k*** total number of vancomycin serum concentrations collected and analysed; **wks** weeks

Table 2. Summary of Inclusion and Exclusion Criteria Across the 11 Reviewed Neonatal Vancomycin Pharmacokinetics Studies

Authors	Inclusion Criteria Highlights	Key Exclusion Highlights
Kimura et al. (2004)	Neonates requiring Arbekacin, Vancomycin, or Panipenem.	Patients with severe hepatic dysfunction.
Lo et al. (2010)	Premature infants (GA <32w, PMA <36w).	Neonates with missing covariate data.
Kato et al. (2016)	Very low birth weight (VLBW) infants (<1500g).	Renal failure, severe edema, or ECMO.
Tseng et al. (2018)	Neonates receiving IV vancomycin with ≥1 TDM level.	Patients with missing dosing/TDM records or covariates.
Chen et al. (2018)	Neonates and infants <2 months old.	Patients with missing dosing/sampling times.
Li et al. (2018)	Neonates with suspected Gram-positive infection.	Use of nephrotoxic drugs (e.g., Amphotericin B).
Tang et al. (2021)	Neonates requiring model-informed precision dosing.	Extracorporeal life support (ECLS/ECMO).
Lee et al. (2021)	NICU patients with suspected/proven sepsis.	Major surgery, renal replacement therapy.
Li et al. (2021)	Infants <1 year old with septicemia.	Incomplete therapeutic drug monitoring (TDM).
Alsultan et al. (2023)	VLBW infants in Saudi Arabia.	Major congenital anomalies affecting PK.
Zhao et al. (2025)	Non-extremely preterm (PMA ≥28w), NICU admission	Congenital renal dysplasia, GA <28w.

Abbreviations: VLBW very low birth weight; **ECMO** extracorporeal membrane oxygenation; **GA** gestational age; **PMA** post menstrual age; **PK** pharmacokinetics;

Table 3. Summary of Model Development, Performance Metrics, and Reporting Quality Scores (ClinPK) Across Included Studies

Authors	Model Software	Model Structure	Validation Method (Internal/External)	Model Performance Metrics	Stability	ClinPK Score (%)
Kimura T et al (2004)	NONMEM	One-compartment open model with first-order elimination	**Internal Validation**: 500 bootstrap replications **Predictive Performance**: Individual Bayesian estimates (POSTHOC) and linear regression of predicted vs. observed concentrations *(good predictive with bilateral symmetry)*	R^2: 0.62. **Residual Variability (ε)**: 3.22 mg/L. **Interindividual Variability (CV%)**: 22.9% for CL and 20.8% for Vd. **Regression Equation**: y = 0.7779x + 4.996.	Bootstrap mean estimates were similar to the original data set, indicating a stable model	76.2%
Kato H et al (2016)	Phoenix NLME	One-compartment model with first-order elimination	**Internal Validation**: 200 bootstrap resampling **Predictive Performance**: Basic GOF plots, individual weighted residuals (IWRES), NPDE, and VPC	**Correlation (*r*):** The correlation coefficient between individual predicted concentration (IPRED) and observed concentration (DV) was 0.98. **Bias:** MPE was 0.30 µg/mL. **Inter-individual Variability (CV%):** Estimated at 14.8% for CL and 29.4% for Vd.	Bootstrap mean values showed less than 10% difference from final estimates for most parameters (except intra individual Vd at 10.2%), indicating acceptable reliability and robustness.	85.7
Tseng SH et al (2018)	NONMEM	One-compartment model with first-order elimination	**Internal Validation**: 5000 boostrap replications. **Predictive Performance**: Prediction-corrected VPC and standard GOF plots	R^2: **0.74** *(Trough vs AUC24).* **BSV:** 13.0% for CL and 9.6% for Vd. **VPC Accuracy:** 7.69% of observed concentrations fell outside the 95% prediction interval	Median bootstrap parameter estimates concurred with original estimates, indicating a stable and robust final population model.	95.2
Chen YW et al (2018)	NONMEM	One-compartment model with first-order elimination	**Internal Validation**: 1000 bootstrap replications, NPDE **External Evaluation**: Performed on an independent dataset of 57 neonates and infants	**Internal Evaluation**: NPDE mean was 0.07 (theoretical mean is 0). **External Evaluation**: MPE was 12.3%. **BSV**: 26.8% for CL.	Bootstrap median estimates were highly similar to final population model values, and NPDE showed no trends across time or predicted concentrations.	85.7
Li ZL et al (2018)	NONMEM	One-compartment model with first-order elimination	**Internal Validation:** 2000 bootstrap replications, NPDE **Predictive Performance:** Diagnostic GOF plots	**Bias**: < 5% bias. **BSV**: 37.9% for CL.	Over 99% of bootstrap runs were successful, indicating a stable final model.	95.2
Lo YL et al (2010)	NONMEM	One-compartment model with first-order elimination	**Internal Validation:**1000 bootstrap replications **Predictive Performance:** Visual inspection of diagnostic scatter plots.	R^2 = 0.89 for individual-predicted concentrations. **Bias:** 0.30 mg/L. **BSV:** 20.5% for CL and 12.6% for Vd.	Bootstrap median parameter values were very close to the final model estimates and lay within the 95% intervals, indicating a stable and robust model	76
Tang Z et al (2021)	Monolix	One-compartment model with first-order elimination	**Internal Validation:** 2000 bootstrap replications, NPDE **External evaluation:** External data set (n=28)	**Bias**: <5% **External Evaluation**: MPE was 3.97%. **Variability**: IIV was 24% for CL and 11% for Vd.	Goodness-of-fit plots showed no obvious bias, and bootstrap results were close to final model estimates, indicating a precise and stable model.	95.5
Lee SM et al (2021)	NONMEM	One-compartment model with first-order elimination	**Internal Validation**: 1000 bootstrap replications. **Predictive Performance**: Graphical diagnostics (GOF plots) and prediction-corrected VPC	**Variability**: IIV was 12.3% for CL and 26.0% for Vd. **Predictive Check**: VPC confirmed good performance as observed data were adequately captured by 95% CI.	993 out of 1000 bootstrap runs were successful, and median values were close to final model estimates, indicating robustness.	81
Li ZL et al (2021)	NONMEM	One-compartment model with first-order elimination	**Internal Validation**: 1000 bootstrap replications, NPDE. **External Validation**: Applied final model to a validation group.	**Accuracy**: MPE 21.3%. **BSV:** 14.5% for CL.	Model demonstrated good stability across evaluation methods	80.9
Alsultan A et al (2023)	Monolix	One-compartment model with linear elimination	**Internal Validation**: Data split into training (70%) and validation (30%) sets. **Predictive Performance**: VPC and NPDE applied to the validation dataset	**Accuracy**: Mean NPDE was 0.043 with a standard deviation of 1.1, indicating limited bias. **Precision**: RSE for CL and Vd were 11% and 6.6% (below the <30% optimal threshold). **Variability**: IIV was 28% for CL and 24% for Vd.	The observed and predicted medians/percentiles in the VPC were similar, indicating this model captured most of the variability in data	90.5
Zhao K et al (2025)	Phoenix NLME	One-compartment model with first-order elimination	**Internal Validation**: 5000 bootstrap replications, NPDE **Predictive Performance**: VPC, diagnostic GOF plots	**External Validation**: MPE of 2.74%. **Variability**: IIV was 4.97% for CL.	All final model parameter values fell within the 95% CI of bootstrap-derived values, confirming model stability and estimate accuracy	90.5

Abbreviations: **R^2** coefficient of determination; **CV%** coefficient of variation; **CL** Vancomycin clearance; **Vd** Vancomycin volume of distribution; **GOF** goodness-of-fit; **NPDE** normalized prediction distribution errors; **VPC** visual predictive checks; *r* correlation; **MPE** Mean Prediction Error; **BSV** Between-Subject Variability; **IIV** Inter-individual variability; **CI** confidence interval; **RSE** residual standard error

Table 4. Summary of significant covariates influencing Vancomycin Clearance and Volume of distribution identified by PopPK models

Author (year)	Body Weight	PMA	PCA	SCR	CLcr	Other Significant Covariates
Kimura et al. (2004)	✓	-	✓	✓	-	-
Lo et al. (2010)	✓	✓	-	-	-	Status of SGA
Kato et al. (2016)	✓	-	-	✓	-	Vancomycin infusion volume, VLBW
Tseng et al. (2018)	✓	✓	-	✓	-	-
Chen et al. (2018)	✓	✓	-	✓	-	-
Li et al. (2018)	✓	✓	-	✓	-	-
Tang et al. (2021)	✓	✓	-	✓	-	Vasoactive agents (CL reduced 14%)
Lee et al. (2021)	✓	✓	-	-	✓	-
Li et al. (2021)	✓	-	-	✓	-	Ceftriaxone
Alsultan et al. (2023)	✓	✓	-	✓	-	-
Zhao et al. (2025)	✓	-	-	✓	-	Daily fluid input, Diuretics
Total (Frequency)	**11/11**	**7/11**	**1/11**	**9/11**	**1/11**	

Abbreviations: PMA Postmenstrual Age; **PCA** Post conceptual age; **SCR** Serum Creatinine; **CLcr** Creatinine clearance; ✓ Significant covariate in final CL model; **SGA** Small for gestational age; **VLBW** Very low birth weight; **CL** Vancomycin clearance

Table 5. Comparison of Vancomycin Dosing Strategies and Therapeutic Target Attainment in Asian Neonatal Cohorts.

Author (Year)	Target Outcomes	Recommendation	Remarks (PK/ Clinical findings)
Kimura T et al. (2004)	-	-	Vancomycin CL increase exponentially with PCA, and is smaller for PCA < 33-34 week than PCA > 33-34 week
Lo YL et al. (2010)	>80% of simulated subjects attained AUC_{24}/MIC≥400, with trough conc 5-20 mg/L, peak conc ≤50 mg/L	**Dosing regimen** (premature neonates): -TDD according to PMA and the status of either AGA or SGA **PMA (week)** / **TDD (mg/kg)**: **AGA** / **SGA** <26: 12.5 q24h / 10 q24h 26 - <28: 15 q24h / 12.5 q24h 28 - <30: 10 q12h / 15 q24h 30 - <32: 12.5 q12h / 10 q12h 32 - < 33: 15 q12h / 10 q12h 33 - <34: 15 q12h / 12.5 q12h 34 -<37: 20 q12h / 15 q12h	SGA criteria: Body weight was <10th percentile of the weight threshold for the respective GA *(S'pore fetal growth weight standard)*
	Trough conc: >20mg/L	>30% SGA neonates experienced high trough conc when on dosing for AGA neonates	
	Trough conc: <5 mg/L	Around 20% AGA neonates experienced subtherapeutic trough conc when on dosing for SGA neonates	
Kato H et al. (2016)	AUC_{24}/MIC≥400 & Trough 10-20 mg/L	Dosing regimen: 10mg/kg three times a day **Dose** / **% of attainment**: AUC_{24}/MIC≥ 400 / Trough 10-20 mg/L 10mg/kg TDS: 100 (MIC 0.5); 86.7 (MIC 1.0) / 70.5	Study with VLBW neonates
	Relationship between AUC_{24} and trough	AUC increased with trough. Trough > 9mg/L is needed for AUC_{24} ≥ 400	
Tseng SH et al. (2018)	Predictive of Trough conc on AUC_{24}	1. Trough conc correlate positively with AUC24 (r^2= 0.74). 2. An upper limit of AUC_{24} of 700 is used to minimise risk of nephrotoxicity. 3. Minimum trough required to achived AUC_{24}>400: 8-8.9 mg/L **Trough type** / **AUC_{24} target** / **Trough conc (mg/L)**: **8-8.9** / **10-14.9** / **15-20** Observed: % of troughs achieve AUC_{24}>400: 92 / 98 / 100 % of troughs AUC_{24}>700: - / 0 / ***17.6*** Median AUC_{24}: 464 / 542 / 610 Simulated: % of troughs achieve AUC_{24}>400: 97 / 100 / 100 % of troughs AUC_{24}>700: - / 0.1 / ***24.5***	Higher risk of toxicity is seen when trough conc is within 15-20 mg/L
Chen YW et al. (2018)	AUC_{24}/MIC≥400	Dosing regimen: **PMA (week)** / **Dosing (mg/kg)** 30-34: 14-15 q12h 36-40: 14-15 q8h ≥44: 18 q8h	
	Preditive of trough conc on AUC_{24}/MIC	Trough conc to achived AUC_{24}≥400: 5-15 mg/L Percentage of attainment AUC_{24}/MIC≥400: **MIC (mg/L)** / **Trough conc (mg/L)**: **<5** / **5-10** / **>10** / **>15** 0.5: 88% / 95% / 100% / - 1.0: 6% / 15% / 14% / 55% 2.0: 0% / 0% / 0% / 0%	
Li ZL et al. (2018)	AUC_{24}/MIC≥400	**Dosing regimen:** **Wt (kg)** / **PMA (weeks)** / **Scr (μmol/L)** / **Dosing (mg/kg)** 1.0-1.49 / 28-30 / 10: 15-20 q12h 60: 12.5-15 q18h 1.5-2.49 / 31-34 / 10: 12.5-17.5 q8h 60: 10-12.5 q12h 2.5-3.49 / 35-38 / 10: 17.5 -20 q8h 60: 15-17.5 q12h 3.5-4.49 / 39-42 / 10: 15-20 q6h 60: 10-12.5 q8h 4.5-5.5 / 43-45 / 10: 17.5-20 q6h 60: 10 q6h	No difference in CL between Caucasian and Chinese neonates.

Abbreviations: CL Vancomycin clearance; **PCA** Post conceptual age; **AUC** Area under the curve; **MIC** Minimum inhibitory concentration; **TDD** Total daily dose; **AGA** Appropriate weight for Gestational Age; **SGA** Small for Gestational Age**; PMA** Post menstrual age; **GA** Gestational Age; **Conc** Concentration; **VLBW** Very low birth weight; **Scr** Serum creatinine; **AKI** Acute kidney injury; **CLcr** Creatinine clearance; **q6h** 6hourly**; DFI** Daily fluid intake; **DA** Diuretics administration**; VAS** Vasoactive agents**; Wt** Weight

Table 5. Comparison of Vancomycin Dosing Strategies and Therapeutic Target Attainment in Asian Neonatal Cohorts.

Author (Year)	Target Outcomes	Recommendation	Remarks (PK/ Clinical findings)
Tang Z et al. (2021)	AUC_{24}/MIC	**Recommendation :** - AUC/MIC≥234 (97% treatment efficacy rate) - AUC_{24} 240-480 (MIC = 1 mg/L) **Dosing Regimen** (Reduced TDD in concomittant VAS): **PMA** / **Scr (µmol/L)** / **Dosing (mg/kg)**: No VAS / With VAS 25-27: 10: 17.5-20 q24h / 15-17.5 q24h 25-27: 90: 12.5-15 q24h / 12.5-15 q24h 28-31: 10: 15-17.5 q18h / 17.5 -20 q24h 28-31: 90: 10-12.5 q18h / 15-17.5 q24h 32-36: 10: 15-17.5 q12h / 12.5-15 q12h 32-36: 90: 10-12.5 q12h / 10 q12h 37-41: 10: 17.5–20 q12h / 15–17.5 q12h 37-41: 90: 12.5–15 q12h / 10–12.5 q12h 42-46: 10: 12.5–15 q8h / 17.5–20 q12h 42-46: 90: 10 q8h / 12.5-15 q12h	**AUC_{24} ≥ 485 mg.h/L** 95% CI: 328-554 mg.h/L Adjusted odds ratio: 11.31 (95% CI 1.95-65.54) **VAS** Adjusted odds ratio: 24.23 (95% CI 2.65-221.7)
	Vancomycin induced AKI	AUC_{24} ≥ 485 mg.h/L is independently predictive of AKI (19% AKI incidence)	
Lee SM et al. (2021)	AUC_{24}/MIC≥400	**Dosing regimen:** Dose and frequency based on PMA and CLCr. Required higher dose than recommended by Neofax **CLCr** / **Dose & Frequency** <15: 10-15mg/kg 24 hourly 15-30: 10-15mg/kg 8 /12/ 24 hourly 30 -60: 10-15mg/kg 8 /12 hourly 60-90: 10-20 mg/kg 8/12 hourly ≥ 90: 15 - 20mg/kg 8/12 hourly	
	Trough conc	Therapeutic range 5 -15 mg/L	
Li ZL et al. (2021)	Trough conc	In 3-9 months old infants, dose of 10mg/kg q6h will likely result in trough <5 mg/L. Higher dose is required. No appropriate dosing regimen is stated.	
Alsultan A et al. (2023)	1. >60% probability of AUC_{24} >400 ***and*** 2. <10% probability of AUC_{24}>800 or trough >20 mg/L	**Dosing regimen:** **PMA (week)** / **Scr (µmol/L)** / **Dosing (mg/kg)**: **AUC_{24} 400-600** / **AUC_{24} 400-800** ≤ 29: <53: 17.5 q12h / 17.5 q12h ≤ 29: 80-106: 17.5 q18h / 17.5 q18h >29: <53: 12.5 q8h / 20 q12h >29: 80-106: 20 q18h / 15 q12h	Study with VLBW neonates
Zhao K et al. (2025)	AUC_{24}/MIC≥400	**Dosing Regimen:** -Total daily dose (TDD) based on Scr, DFI and DA -TDD need to be reduced in the presence of diurectics, and increase with increment in DFI **Scr (µmol/L)** / **DFI** / **TDD (mg/kg/day)**: **DA** / **Non DA** 10: 100: 26 / 32 10: 700: 34 / 41 50: 100: 21 / 25 50: 700: 27 / 32 90: 100: 19 / 23 90: 700: 25 / 30	VAS, Albumin are not identified as significant covariate

Abbreviations: CL Vancomycin clearance; **PCA** Post conceptual age; **AUC** Area under the curve; **MIC** Minimum inhibitory concentration; **TDD** Total daily dose; **AGA** Appropriate weight for Gestational Age; **SGA** Small for Gestational Age**; PMA** Post menstrual age; **GA** Gestational Age; **Conc** Concentration; **VLBW** Very low birth weight; **Scr** Serum creatinine; **AKI** Acute kidney injury; **CLcr** Creatinine clearance; **q6h** 6hourly**; DFI** Daily fluid intake; **DA** Diuretics administration**; VAS** Vasoactive agents**; Wt** Weight

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