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FMUP FACULDADE DE MEDICINA
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Joaquim António Faria Monteiro

*Monitorização Terapêutica e Modelos Farmacocinéticos Populacionais de
Vancomicina em Subpopulações de Doentes Especiais /
Vancomycin Therapeutic Drug Monitoring and Population Pharmacokinetic
Models in Special Patient Subpopulations*

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Doutora Paula Maria Façanha Cruz Fresco**

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TÍTULO DISSERTAÇÃO

Vancomycin therapeutic drug monitoring and population pharmacokinetic models in special patient subpopulations

ORIENTADOR

Paula Maria Façanha Cruz Fresco

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DEDICATÓRIA

Este trabalho e toda a minha vida é dedicada aos meus amores maiores – a minha mamã, o meu papá e a minha maninha. Convosco aprendi o que significa o amor pelos outros, a generosidade e a atingir objetivos através do esforço. Em vós encontrei o lugar tranquilo onde sempre regressei para encontrar o rumo no meio da turbulência. Por vós persegui este objetivo por sempre acharem que seria um bom médico.

Dedico também à minha restante família e amigos, deste curso e do outro, do meu local de trabalho e da vida.

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A título póstumo também dedico este trabalho ao meu orientador de doutoramento que, além de ciência, ensinou-me a importância da humildade que o conhecimento acarreta – Prof Victor Jiménez Torres.

A todos- muito obrigado!

Prometo que irei ser um médico com muito de todos vós em mim.

Joaquim António Faria Monteiro

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ORIGINAL ARTICLE

Vancomycin therapeutic drug monitoring and population pharmacokinetic models in special patient subpopulations

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Abstract

Vancomycin is a fundamental antibiotic in the management of severe Gram-positive infections. Inappropriate vancomycin dosing is associated with therapeutic failure, bacterial resistance and toxicity. Therapeutic drug monitoring (TDM) is acknowledged as an important part of the vancomycin therapy management, at least in specific patient subpopulations, but implementation in clinical practice has been difficult because there are no consensus and agglutinator documents. The aims of the present work are to present an overview of the current knowledge on vancomycin TDM and population pharmacokinetic (PPK) models relevant to specific patient subpopulations. Based on three published international guidelines (American, Japanese and Chinese) on vancomycin TDM and a bibliographic review on available PPK models for vancomycin in distinct subpopulations, an analysis of evidence was carried out and the current knowledge on this topic was summarized. The results of this work can be useful to redirect research efforts to address the detected knowledge gaps. Currently, TDM of vancomycin presents a moderate level of evidence and practical recommendations with great robustness in neonates, pediatric and patients with renal impairment. However, it is important to investigate in other subpopulations known to present altered vancomycin pharmacokinetics (eg neurosurgical, oncological and cystic fibrosis patients), where evidence is still insufficient.

KEYWORDS

pharmacokinetics, special subpopulations, therapeutic drug monitoring, vancomycin

1 | INTRODUCTION

Vancomycin is the drug of choice for infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA),¹ the most prevalent

Abbreviations: ABW, actual body weight; AME, American; AUC, area under concentration versus time curve; AUTL, area under the trough level; CF, cystic fibrosis; CHN, Chinese; Ctough, trough concentration; CI, continuous infusion; CLcr, creatinine clearance; Clvan, vancomycin clearance; CNS, central nervous system; CSF, cerebrospinal fluid; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; GoR, grade of recommendation; ICU, intensive care unit; IVT, intraventricular; JPN, Japanese; LoE, level of evidence; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PPK, population pharmacokinetic; RCT, randomized controlled trial; SIRS, systemic inflammatory response syndrome; TDM, therapeutic drug monitoring.

multidrug resistant pathogen in the world. Therapeutic drug monitoring (TDM) is acknowledged as an important part of the management strategy when treating patients with this agent: safe and effective use of vancomycin requires compliance with recommendations concerning loading dose, TDM and dosage reduction in renal impairment and in other pathophysiological conditions. The emergence of vancomycin-resistant enterococci, and more recently, vancomycin-resistant *Staphylococcus aureus*, is directly related to vancomycin underdosing and is a problem of particular concern worldwide.¹ These facts turn urgent the need to develop strategies to improve both vancomycin prescribing and monitoring.

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The aims of the present work were as follows: to define the state of art of vancomycin TDM, based on the three most recent guidelines from USA, Japan, and China, to review TDM in specials populations and resume population pharmacokinetic (PPK) models of vancomycin.

2 | METHODOLOGY

The methodology followed was similar to that used by Ye and coworkers.¹ Three guidelines were selected as the basis of this work: the American from 2009 (AME),² the Japanese from 2013 (JPN)³ and the Chinese from 2016 (CHN)⁴ guidelines on vancomycin TDM. These guidelines were analyzed, compared, and recommendations were evaluated. Level of evidence (LoE) and grade of recommendation (GoR) used in this work are shown in Table 1. The LoE and GoR used are in agreement with the GRADE system,⁵ also used in the CHN guideline.⁴ For comparison purposes, the graduation scale used in AME² and JPN³ guidelines were transformed by two researchers, independently, and then discussed for consensus.

The “Population Pharmacokinetic Model review” addressed the items “Dose adjustment method” and “Special populations” since these were the items less detailed in the referred guidelines. This review was carried out using Ovid MEDLINE and EMBASE electronic databases. The search equations used were: “Vancomycin” AND “Pharmacokinetic Model” for articles written in English, in humans until July 2017. A total of 63 records were found and two investigators independently screened the identified titles and abstracts to select articles. Of these, 31 records were excluded, either because they were not carried out in humans, do not directly concerned vancomycin or were general reviews of antibiotic use. The 32 full texted articles were tested for eligibility and nine were discarded since the models were not defined or were developed without using nonlinear mixed effects modelling. Finally, 23 articles were included in the qualitative synthesis (Figure 1), from now on referred as the “PPK Model review”.

3 | THERAPEUTIC DRUG MONITORING

3.1 | Indication and relevance

In the guidelines investigated, only two guidelines refers situations where TDM is recommended. All clinical conditions where TDM is indicated present low quality of evidence. Therefore, these are considered as strong recommendations.

The literature review gathered evidence for the recommendation of TDM in additional special population groups [hematologic,

neurosurgery, extracorporeal membrane oxygenation (ECMO), neonates and pediatric cystic fibrosis (CF)]. Table 2 summarizes data relative to the analysis of the clinical relevance of TDM for specific patient conditions.

Authors could not find additional data on the clinical relevance of TDM, other than that described by the CHN guideline.⁴ However, a meta-analysis, including one randomized controlled trial (RCT) and five cohort studies, showed that TDM significantly increases the rate of clinical efficacy and decreases the rate of nephrotoxicity in patients treated with vancomycin.⁶ More recently, another RCT, comparing groups of patients treated with vancomycin (simple infections or infections with MRSA), with and without TDM also confirmed this conclusion.⁷ In fact, patients in the TDM group were discharged from the hospital more rapidly, reached clinical stability faster, had shorter courses of vancomycin and the time to initial target trough concentration was shorter. Moreover, in the MRSA infection subset, patients in the TDM group were also discharged from the hospital more rapidly, reached clinical stability faster, had shorter courses of vancomycin and attained initial target troughs in <5 days vs ≥ 5 days.⁷

Data on TDM implementation on hospitals is also scarce: in the last 10 years, only one paper concerning TDM implementation was identified. However, this paper describes that, in France, implementation of vancomycin TDM is quite high: vancomycin TDM was available in 97% (477/490) of hospitals.⁸ Unfortunately, a study carried out in Scandinavian countries showed that, in most cases, vancomycin TDM does not comply with recent recommendations/guidelines.⁹

Medical center implementation of the AME guideline,² with associated training, resulted in a significant short-term improvement in vancomycin dosing and TDM. The appropriateness of the prescribed dose increased from 51% of patients during the pre-period to 78% during the postperiod ($P < 0.0001$). Similarly, overall appropriateness of sampling of vancomycin troughs at steady state improved from 36% to 55% ($P < 0.03$). Specifically, the appropriate timing of troughs (within 30 minute of the next dose) increased from 37% (64/173) during the pre-period to 78% (149/191) during the postperiod ($P < 0.0001$).¹⁰

Another study claims that identification of improvement opportunities in TDM methodology and implementation over a 1-year period allowed a 37.5% reduction in inappropriately held vancomycin doses, although about 10% of doses remained as held inappropriately.¹¹ Moreover, this study highlights the difficulties in identifying barriers to change and modify healthcare worker behaviour.¹¹

3.2 | Dose adjustment methods

Methods for dose adjustment discussed in the guidelines are summarized in Table 3.

Although the guidelines for TDM of vancomycin do not recommend the use of nomograms, a novel vancomycin dosing nomogram has been recently developed and validated at two Canadian teaching hospitals by Thalakada and co-workers.¹² This nomogram was

Table 1. Level of evidence and grade of recommendation (using GRADE approach)⁵

Level of evidence (LoE)	Grade of recommendation (GoR)
A (High quality)	1 (Strong recommendation)
B (Moderate quality)	2 (Weak recommendation)
C (Low quality)	
D (Very low quality)	

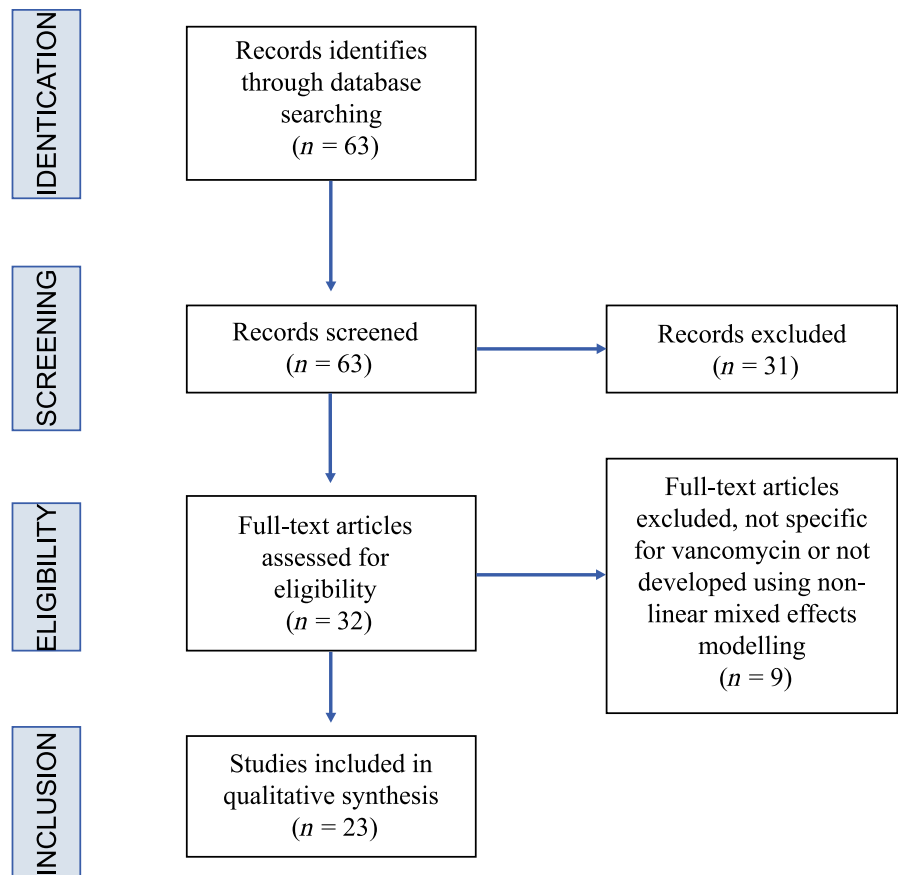


FIGURE 1 Population pharmacokinetic model review (PPK Model review) flow chart

Table 2. Guidelines review of TDM indication

Question	Answer (LoE/GoR)	Guideline (Reference)
Indication	1. TDM should be performed in patients who are likely to receive courses of more than three days. (B/1) 2. Intensive dosing, at high risk of nephrotoxicity, with serious infectious, unstable (deteriorating or improving) renal function, haemodialysis, obesity, low body weight and special conditions that cause fluctuating volumes of distribution. (C/1)	2013, JPN ³
	1. TDM should be performed in patients who receive concomitant nephrotoxic agents, ICU admissions, obese patients and those who have burns or impaired renal function. (C/1) 2. TDM should be performed in elderly patients and patients with concomitant hepatic diseases. (C/2)	2016, CHN. ⁴

CHN, Chinese; GoR, grade of recommendation; ICU, intensive care unit; JPN, Japanese; LoE, level of evidence; TDM, therapeutic drug monitoring.

Table 3. Guidelines review of dose adjustment methods

Question	Answer (LoE/GoR)	Guideline (Reference)
Dose adjustment methods	It should be noted that currently available nomograms were not developed to achieve targeted endpoints. Dose adjustments based in individual pharmacokinetic and verification of serum target achievement are recommended. (B/1)	2009, AME ²
	Vancomycin dosage should be administered and adjusted individually based on population pharmacokinetic methods (D/2)	2016, CHN. ⁴

AME, American; CHN, Chinese; GoR, grade of recommendation; LoE, level of evidence.

considered a useful tool that clinicians can use in selecting appropriate initial vancomycin regimens based on age and serum creatinine, to achieve high-target levels of 15-20 mg/L. The authors, however, stressed out that this tool should not replace clinical judgment for patients with unstable and/or reduced renal function.¹² Moreover, creatinine clearance-based nomograms for individualizing vancomycin

doses should be used with caution in patients who require substantially prolonged drug exposure such as those with infective endocarditis.¹³

The linear regression and Bayesian methods estimate, in general, more accurate dosage regimens. However, these methods require additional resources, such as information technology and healthcare

personnel with background training in pharmacokinetics. The Bayesian methods offer additional advantages such as calculation of doses based on a single-serum concentration and optimization of the patient's previous pharmacokinetic data to determine subsequent dosage regimens. Computerized programs, using the Bayesian estimation procedures, are able to achieve target concentrations in a greater percentage of patients, earlier in the course of therapy, than the empiric trough concentrations (C_{trough}) and population methods.^{14,15}

The "PPK Model review", in the adult population, found only six studies and, after analysis of the complete publications, three were excluded because they were not population models or were not developed using the nonlinear model of mixed effects methods. Table 4 describes the models found for the adult population in the mentioned review.

3.3 | Special populations

The need for clearer guidelines regarding vancomycin dosing and TDM for patient subpopulations has been recently reported.¹⁹

3.3.1 | Critically ill patients

The selected guidelines do not define special recommendations for this subpopulation. However, the literature review found 13 studies which are discussed below.

Significant challenges in vancomycin use in critically ill patients have been recently identified.¹⁹ There is wide variability in reported practices for antibiotic dosing and monitoring. Therefore, research to develop evidence-based guidelines to standardize practices in critically ill patients is urgently needed.²⁰

These patients may present very large volume distribution (V_d) as well as supranormal drug clearance.^{21,22} Augmented renal clearance has frequently been observed in critically ill patients which was strongly associated with vancomycin pharmacokinetics. As a consequence, two-thirds of these patients present subtherapeutic vancomycin concentrations.²³

Long duration of fasting and massive diarrhea have been associated with elevations in serum vancomycin concentrations, which suggest that TDM might be necessary during enteral vancomycin administration in critically ill patients.²⁴ Less than 40% of these patients attained therapeutic trough serum concentrations during the first 3 days of therapy.¹⁹ Patients with augmented renal clearance presented lower serum C_{troughs} despite receiving higher maintenance doses and several loading doses.¹⁹ Subjects requiring intensive care unit support are significantly more likely to have higher vancomycin 24-hour area under the concentration versus time curve (AUC₂₄) and AUC than those who do not need intensive care unit support. Although vancomycin serum C_{troughs} are predictive of vancomycin AUC, suboptimal exposure of vancomycin occurred in almost 20% of critically ill patients, despite C_{troughs} being within the target range. To ensure optimal AUC/MIC, especially in critically ill patients, estimation of the AUC should be mandatory.²⁵

Loading dose and target C_{trough} for this population, achieved based on recommendations published in the literature, were lower than expected.²⁶ Switching from intermittent to continuous infusion (CI) provided higher target attainment rates, a more robust drug exposure, a more rapid achievement of targeted drug levels with fewer subtherapeutic vancomycin levels observed,^{27,28} cheaper and logistically more convenient, less TDM and less nephrotoxicity.²¹ Furthermore, CI yielded stronger concentration-AUC correlations facilitating a single sample TDM strategy with AUC targets. A switch

Table 4. Population pharmacokinetic models developed for adults

N	Pharmacokinetic Model	Pharmacokinetic Parameters	Covariates	Reference
72	One-compartment	Cl = 4.90 L/h (if Cl _{cr} ≥ 80 mL/min); V _d =47.76 L	Cl _{cr} (if Cl _{cr} < 80 mL/min): Cl = 0.0654 × Cl _{cr}	[16]
106	Two-compartment	Cl = 3.95 L/h (if Cl _{cr} ≥ 85 mL/min); Healthy volunteers V ₁ (L) = 0.205 × WT V ₂ (L) = 43.4 Pneumonia V ₁ (L) = 0.720 × WT V ₂ (L) = 78.0 Bacteremia V ₁ (L) = 0.313 × WT Other infections V ₁ (L) = 0.523 × WT V ₂ (L)=43.4	Cl _{cr} (if Cl _{cr} < 85 mL/min): Cl = 0.0339 × Cl _{cr} + 0.243	[17]
398	Two-compartment	Cl = 2.99 L/h V ₁ = 0.675 L/kg V ₂ = 0.732 L/kg	Cl = 2.99 + 0.0154 × Cl _{cr} ABW (covariate of V ₁ and V ₂)	[18]

ABW, actual body weight; Cl, vancomycin clearance; Cl_{cr}, creatinine clearance; N, sample size; V₁, volume of the central compartment; V₂, volume of peripheral compartment; V_d, volume of distribution; WT, weight.

to CI may, therefore, improve clinical outcomes in vancomycin-treated critically ill patients.^{22,29}

Although optimal administration based on PPK analysis and/or a Bayesian method has improved prediction accuracy, serum concentrations of vancomycin in patients with sepsis often deviate significantly from predicted values. Systemic inflammatory response syndrome (SIRS) duration was identified as influencing vancomycin concentration. Modifying dosing according to SIRS duration will improve prediction accuracy of vancomycin concentration based on TDM.³⁰

Table 5 describes the two studies proposing PPK models for critically ill patients found in the “PPK Model review”.

3.3.2 | Pediatric patients

Only the JPN guideline³ presented evidence on the advantages of TDM on pediatric patients (Table 6).

Current recommended vancomycin dosing regimens in pediatric patients (40–60 mg/kg/day), result frequently in subtherapeutic concentrations.³³ Febrile neutropenia, a significant risk factor for augmented renal clearance in this subpopulation, indirectly influenced vancomycin clearance (Cl_{van}) due to increased glomerular filtration rate (GFR). Increasing the initial dose is, therefore, required for achieving optimal therapeutic concentrations in pediatric patients with febrile neutropenia.³⁴ The probability of achieving an AUC/MIC >400 using only one trough serum concentration and one minimum inhibitory concentration (MIC) in patients receiving 15 mg/kg every 6 hours is variable according to the method used to calculate AUC. In children, an AUC/MIC of 400 correlates with a C_{trough} of 11 mg/L using a trapezoidal method to calculate AUC.³⁵

For pediatric patients, monitoring of vancomycin C_{troughs} is a recommendation stated in the summary of product characteristics

and by several professional societies.³ During a study where vancomycin TDM was performed and 7935 vancomycin concentrations were obtained, the median C_{trough} increased from 10.9 to 13.7 mg/L,³⁶ which agrees with the recommendations published by the Infectious Disease Society of America.² These data suggest that vancomycin TDM is commonly performed in pediatric patients, and the majority of abnormal C_{troughs} are associated with appropriate modifications of the dosing regimen.³⁶ Nevertheless, vancomycin TDM practices are reported to be highly variable in children admitted to pediatric hospitals.³⁷ The frequency with which serum vancomycin concentrations were monitored in children increased after the publication of the adult guidelines. This fact made some authors claim that the development of pediatric consensus guidelines is needed to optimize patient care and resource utilization.³⁷

Pediatric PPK models for vancomycin with Bayesian estimation can be used to reliably predict vancomycin exposure in children: the use AUC instead of C_{troughs}, alone, can maximally optimize vancomycin administration in children.⁴¹ Compared with one sample, the two samples sampling strategy improved accuracy and precision in estimating and predicting future AUCs.⁴⁰

Overweight and obese pediatric patients may have elevated initial vancomycin C_{troughs} when empiric dosing is based on total body weight. This fact should make TDM mandatory in children.³⁸

In pediatric cancer patients, a V_d of 34.7 L was reported and clearance values that were correlated with body weight, tumor disease, and cyclosporine co-administration.³⁹ Based on simulation results, dose (mg/kg) should be individualized based on body weight and cyclosporine co-administration.³⁹

The “PPK Model review” in pediatric and neonatal patients found five and seven studies, respectively. From these, three were selected in pediatric and six in neonates. The excluded studies were

Table 5. Population pharmacokinetic models developed for critically ill patients

N	Pharmacokinetic model	Pharmacokinetic parameters	Covariates	Reference
206	One compartment	Cl = 4.6L/h Vd = 1.5L/kg	Cl = 4.6 × Cl _{cr} /100 ABW (covariate of Vd)	[31]
46	One compartment	Cl = 0.86 mL/min/kg Vd = 1.69 L/kg	Cl = 0.872 – 0.015 × age (years) – 0.007 × ApII + 0.234 × Ab + 0.346 Cl _{cr} L (mL/min/kg) ABW (covariate of Vd)	[32]

Ab, serum albumin (g/dL); ABW, actual body weight; ApII, APACHE II score; Cl, vancomycin clearance; Cl_{cr}, creatinine clearance; Cl_{cr}L, creatinine clearance by the Levey formula; N, Sample size; Vd, volume of distribution.

Table 6. Guidelines review of pediatric patients’ considerations

Question	Answer (LoE/GoR)	Guideline
Pediatric patients	<ol style="list-style-type: none"> 1. First trough concentration can be obtained before the fourth dose (on day 2 if administered every 6 h). (C/1) 2. Vancomycin 15 mg/kg every 6 h is recommended for infants and children, and doses should be adjusted according to the result of TDM. Although few data are available to guide the dosing regimen in adolescent patients of ≥12 years old, doses of 15 mg/kg may be given every 8 h. (C/1) 3. To date, there are limited data to support the efficacy and safety of targeting trough concentrations of 15–20 mg/L in children, and additional study is required. (Unresolved issue) 	2013, JPN ³

GoR, grade of recommendation; JPN, Japanese; LoE, level of evidence; TDM, therapeutic drug monitoring.

those that were not population models or were not developed using nonlinear modeling of mixed effects methods (Table 7).

(a) With cystic fibrosis

No reference concerning pediatric patients with CF was found in the three international guidelines evaluated.

The “PPK Model review” revealed only two studies concerning this population subgroup. One of these showed that vancomycin dosing of 60 mg/kg/day does not reliably achieve a vancomycin C_{trough} of 15–20 mg/L in pediatric patients with CF.⁵⁰ The second also reported that younger CF patients may require higher vancomycin doses.⁵¹

The PPK model found for this specific subpopulation is described in Table 7.

(b) Neonates

In neonates, vancomycin is the first choice for late-onset sepsis treatment. However, prescribing the right dose and dosing regimen remains a challenge in neonatal intensive care units.⁵² The high degree of pharmacokinetic variability in neonates makes TDM essential to ensure adequate therapeutic exposure⁵³ and prevent adverse renal outcomes.⁵⁴

When using TDM in neonates the basic rules apply. However, additional factors should also be taken into consideration. First, due to both pharmacokinetic variability and nonpharmacokinetic factors, the correlation between doses and concentration is poor, but can be overcome using more complex, validated dosing regimens. Second, the time to reach steady-state is increased, especially when no loading dose is used and, therefore, TDM sampling timing is of utmost importance in neonates. Third, the target concentration may be uncertain. Finally, because of differences in matrix composition (eg, protein, bilirubin), assay-related inaccuracies may differ in neonates.⁵⁵ With currently recommended vancomycin dosing, the therapeutic target of AUC/MIC > 400 is achieved only by 25% of neonates.⁵⁶ Most of C_{trough} in neonates achieved using two published dosing regimens did not reach the 10 mg/L.⁵⁷ These results illustrate the urgent need for prospective validation of neonatal vancomycin dosing regimens.⁵⁷

Several vancomycin dosing schedules have been proposed, mainly based on neonate's age (both postmenstrual and postnatal), body weight or serum creatinine level. Other covariates [eg, ECMO, indomethacin/ibuprofen, and growth restriction] of vancomycin pharmacokinetics have been reported in neonates. Because age or weight is

Table 7. Population pharmacokinetic models developed for pediatric and neonate patients

Patients	N	PK model	PK parameters	Covariates	Reference
Pediatric	15	Two-compartment	Cl V ₁ = 0.27 L/kg k ₁₂ = 1/h; k ₂₁ = 0.59/h	Cl = 0.018 × (ABW/70) + 0.460 × Cl _{cr} LBMcorrected (covariate of V ₁)	[41]
	6	Two-compartment	Cl = 0.11 L/h/kg V _{ss} = 0.63 L/kg t _{1/2} alfa = 0.8 h; t _{1/2} beta = 5.63 h	ABW (covariate of Cl and V _{ss})	[42]
	78	Two-compartment	Cl = 0.1 L/h/kg V ₁ = 0.27 L/kg V ₂ = 0.16 L/kg Cl _{distribution} = 0.16 L/h/kg	ABW	[43]
CF	67	One-compartment	Cl = 5.57 L/h/70 kg; V _d = 44.1 L/70 kg	ABW	[44]
Neonates	152	One-compartment	Cl = 0.068 L/h/kg V _d = 0.62 L/kg	ABW; Cl _{cr} ; PMA	[45]
	249	One-compartment	Cl = 0.276 L/h V _d = 1.75 L	Cl (L/h) = 0.345 (WT/2.9 kg) ^{0.75} × F _{mat} × (1/Cr _{mg/dl}) ^{0.267} F _{mat} = 1/(1 + [PMA _{wk} /TM ₅₀] ^{-Hill}) V _d (L) = 1.75 (WT/2.9 kg)	[46]
	70	One-compartment	Cl = 0.066 L/h/kg V _d = 0.572 L/kg	– PMA and co-administration of amoxicillin-clavulanic acid (covariate of Cl) – Co-administration of spironolactone (covariate of V _d)	[47]
	374	Two-compartment	Cl = 0.066 L/kg V _{dss} = 0.79 L/kg	– WT, Cr (covariate of Cl) – Postnatal age and prematurity (<28 weeks) (covariate of V _d)	[48]
	47	One-compartment	Cl = 0.276 L/h V _d = 1.75 L	Cl _{cr} and postnatal age (covariates of Cl)	[49]
	134	One-compartment	Cl = 0.18 L/h; V _d = 1.7 L	Cl = 0.18 × (WT/2.5) ^{0.75} × (0.42/Cr _s) ^{0.7} × (PMA/37) ^{1.4} V _d = 1.7 × (WT/2.5) ¹	[50]

ABW, actual body weight; Cl, vancomycin clearance; Cl_{cr}, creatinine clearance; Cr, creatinine; F_{mat}, maturation function; Hill, coefficient of Hill; LBM, lean body mass; N, sample size; PMA, postmenstrual age; TM₅₀, PMA when maturation reaches 50% adult clearance; V₁, volume of central compartment; V₂, volume of peripheral compartment; V_d, volume of distribution; V_{ss}, volume of steady state; WT, weight.

the most relevant covariates of renal maturation, these should be considered first in neonatal vancomycin dosing guidelines and further adjusted by renal dysfunction indicators (eg, ECMO and ibuprofen/indomethacin).⁵⁸

There is no consensus on vancomycin dosing in newborns and young infants. The empirical dosing method used was found inadequate in one-third of patients.⁵⁹ A simplified schedule of vancomycin seemed to lead to achieving target drug concentrations in most patients while avoiding renal toxicity.⁶⁰ CI in neonates is well tolerated, require less blood sampling and may result in improved attainment of target concentrations.⁶¹ A patient-tailored optimized dosing regimen should be routinely used to individualize vancomycin continuous administration.⁶² Several authors anticipate that complex validated dosing regimens, with subsequent TDM sampling and Bayesian forecasting, are the next step in individualizing therapy in neonates.⁵⁵

Modeling and simulation approaches have clear advantages in dosing optimization of antimicrobial agents in neonates.⁶³ Pharmacometric modeling and simulation approaches allow to characterize population average, pharmacokinetic parameters, intra and intersubject variability, and to identify and quantify key factors that influence antibiotics pharmacokinetic behavior during the neonatal period.⁶⁴ Simulations showed that the maintenance dose should be adjusted more precisely to each neonate based on weight and serum creatinine values.⁶⁵ A model-based vancomycin dosing calculator has been integrated in routine clinical care in several neonatal intensive care units. In this proof-of-concept study evidence for integrating model-based antimicrobial therapy in neonatal routine care is provided.⁶⁶ Monte Carlo simulations based on this PPK model suggest that vancomycin dosing guidelines based on

serum creatinine concentration have a greater likelihood of achieving Ctroughs of 5-15-mg/L compared with other dosing regimens.⁵⁰

Table 7 describes the studies proposing PPK models for neonates' patients found in the "PPK Model review".

3.3.3 | Elderly patients

The selected international guidelines also do not present specifications for this subpopulation. In the "PPK Model review" three studies were found concerning elderly patients.

The recommended target range of 15-20 mg/L for vancomycin Ctrough seems to be acceptable for controlling vancomycin exposure, although a value of approximately 11 mg/L was found as optimal and safer in elderly patients.⁶⁷ Efficacy of vancomycin was associated with area under the trough level (AUTL), a novel pharmacokinetic parameter.⁶⁸ Determining the target AUTL or Ctrough may enhance the efficacy of vancomycin therapy in elderly patients with MRSA pneumonia.⁶⁸ Given that nephrotoxicity may increase with a Ctrough >15 mg/L, this level should not be exceeded in this subpopulation.

3.3.4 | Obese patients

The guidelines point the use of actual body weight (ABW) for dose calculation but do not refer whether any adjustment is required for TDM in the obese patients' subpopulation. The "PPK Model review" allowed us to identify eight studies in this subpopulation.

Vancomycin dosing protocol led to the attainment of therapeutic Ctroughs in only 35.4% of obese patients.⁶⁹ Moreover, overweight

Table 8. Guidelines review of impaired renal function patients' considerations

Question	Answer (LoE/GoR)	Guideline
Patients with impaired renal function	<ol style="list-style-type: none"> Standard or reduced single doses are given every 24 h or at even longer intervals according to renal function. (C/1) To facilitate rapid attainment of target trough concentration, experts recommend an initial loading dose regardless of renal function. (C/1) As no nomogram predicts vancomycin concentrations precisely especially in patients with impaired renal function, dose should be adjusted individually based on measured vancomycin concentrations. (B/1) 	2013, JPN ³

GoR, grade of recommendation; JPN-Japanese; LoE, Level of evidence.

Table 9. Population pharmacokinetic models developed for patients with impaired renal function

Patients	N	Pharmacokinetic model	Pharmacokinetic parameters	Covariates	Reference
Impaired Renal Function	27	Two-compartment	Vd = 0.14 L/kg; K _{el} = 0.47/h; k ₁₂ = 1.5/h; K ₂₁ = 0.53/h	ABW (covariate Vd)	[75]
Hemodialysis	26	Two-compartment	Vd = 0.105L/kg; CLDV = 0.336 × CLDBUN, Residual interdialytic clearance = 2.25 mL/min (if Clcr < 2 mL/min)	Residual interdialytic clearance: If Clcr >2 mL/min = 2.25 mL/min + 0.59 × Clcr	[76]
Peritoneal dialysis	10	Two-compartment	Cl = 0.22 L/h; V1 = 41.20 L; Cl _a = 0.51 L/h	None	[77]

ABW, actual body weight; Cl, vancomycin clearance; Cl_a, clearance intercompartment (peritoneal and systemic); Clcr, creatinine clearance; CLDBUN, urea filter clearance; CLDV, vancomycin filter clearance; Cr, creatinine; N, sample size; V1, volume of central compartment; Vd, volume of distribution.

and obese pediatric patients may have elevated initial vancomycin C troughs when empiric dosing is based on ABW and, therefore, TDM should be mandatory for this specific subpopulation.³⁸

Vancomycin TDM showed that underdosing and overdosing occur more often and effective levels are less often achieved, in obese patients. TDM might be of special importance, in obese patients.⁷⁰ The majority of these patients present subtherapeutic concentrations, which increases the risk of treatment failure and bacterial resistance. Further studies are needed to determine the optimal dosing strategy in morbidly obese patients, ie with more than 100 kg and at least 140% of their ideal body weight.⁶⁹ Calculating individual pharmacokinetic parameters using equations may be a valid tool for dosing vancomycin in obese patients with renal insufficiency.⁷¹

TDM has been correlated with pharmacokinetic/pharmacodynamic optimization for vancomycin in the obese population with skin and soft tissue infections, and should be used in these cases.⁷² Using two serum vancomycin concentrations significantly improves subsequent target C trough attainment in the obese population.⁷³

3.3.5 | Patients with impaired renal function

The JPN guideline³ summarizes evidence and present specific recommendations for the subpopulation of patients with impaired renal function (Table 8).

The C troughs of 62.9% patients with high creatinine clearance (Clcr) were <10 mg/L.⁷⁴ Since augmented renal clearance was significantly associated with subtherapeutic vancomycin concentrations, it was necessary to devise adjusted dosage regimens for these patients, based on Clcr values.⁷⁴

The “PPK Model review” in patients with impaired renal function found seven studies: two general, three on hemodialysis, one on peritoneal dialysis and one on continuous hemofiltration patient). Four of those studies were excluded as they were not population models or they were developed without using nonlinear modeling of mixed effects methods. The remaining three studies proposing PPK for patients with impaired renal are described in Table 9.

(a) Hemodialysis patients

The JPN guideline³ summarizes evidence and presents recommendations for the subpopulation of patients undergoing hemodialysis (Table 10).

There is considerable variation in vancomycin pharmacokinetics in patients undergoing hemodialysis.⁷⁸ Attention must be paid to the reliability of several empiric dosing recommendations derived from small pharmacokinetic studies in heterogeneous populations. Follow-up TDM is suggested as essential to ensure that concentrations remain within the target range in these patients.⁷⁸

Pharmacokinetic variables of prolonged distribution phase,

Table 10. Guidelines review of patients receiving renal replacement therapy

Question	Answer (LoE/GoR)	Guideline
Patients receiving hemodialysis	<ol style="list-style-type: none"> 1. Initial dose of 15-25 mg/kg (as actual body weight) is recommended. As an initial dose of 15 mg/kg may not be adequate to achieve recommended trough concentrations, experts recommend that a loading dose of 20-25 mg/kg should be administered. (C/1) 2. As a greater amount of vancomycin is removed during hemodialysis, doses of 500 mg (7.5-10 mg/kg) after each dialysis treatment are given as maintenance doses. (C/1) 3. Weekly vancomycin dosing results in subtherapeutic serum levels and should be abandoned in a high-flux setting. (D/2) 4. Achievement of a steady-state concentration is delayed. Although there is no evidence concerning the timing of TDM, the committee recommend that TDM is performed within 1 week after the start of therapy. (C/1) 5. There is no consensus concerning the necessity of follow-up TDM in whom the dosage regimen was not altered. (Unresolved issue) 6. Blood samples for TDM should be drawn before dialysis treatment. Because of the rebound phenomenon, trough levels immediately after the completion of hemodialysis do not reflect the exact drug concentrations of patients. (C/1) 7. Although the maintenance of trough concentrations of <20 mg/L is desirable, there is no consensus concerning the concentrations causing adverse events. (Unresolved issue) 	2013, JPN ³
Patients receiving continuous renal replacement therapy	<ol style="list-style-type: none"> 1. An initial dose of 15-20 mg/kg (as actual body weight) is generally administered. Some experts recommend higher loading dose is required to achieve target trough concentrations. (C/1) 2. As a great amount of vancomycin is removed during continuous venovenous hemodiafiltration doses of 500 mg (7.5-10 mg/kg) are given every 24 h as maintenance doses. It is recommended to adjust the doses according to the result of TDM. (C/1) 3. In patients with residual renal function in whom the main purpose of this therapy is removal of several mediators that cause detrimental effects during sepsis, increased vancomycin dosing may be required according to the results of TDM. (C/1) 	2013, JPN ³
Patients receiving continuous ambulatory peritoneal dialysis	<ol style="list-style-type: none"> 1. Intraperitoneal vancomycin is well absorbed and therapeutic concentration in serum can be achieved over 1 week with single intraperitoneal administration (ie 30 mg/kg). (B/1) 2. To treat peritonitis related to this treatment, doses of 15-30 g/kg are given intraperitoneally every 5-7 days in anuric patients. For patients with residual renal function, the doses are increased by 25%. (B/1) 	2013, JPN ³

GoR, grade of recommendation; JPN, Japanese; LoE, level of evidence.

redistribution phase and rebound effect after completion of hemodialysis include: patient weight, residual renal function, and nonrenal clearance. Optimal vancomycin dosing recommendations are needed, but clinicians should always consider patient-specific variables, timing of administration and of sample collection and technical aspects of the dialysis procedure. Individualized vancomycin dosing regimens and TDM are necessary for patients receiving intermittent hemodialysis to ensure that optimal serum vancomycin levels are reached to adequately treat an infection.⁷⁹ Vancomycin removal during a typical 8-hour sustained low-efficiency dialysis (SLED) treatment approaches 36%.⁸⁰ SLED patients are, therefore, at risk for undertreatment of their infections. A re-dosing strategy should be considered (with at least 500 mg in most patients at SLED completion) if the estimated/measured predialysis level of vancomycin is 20–30 mg/L. As such, TDM is an essential part of any dosing scheme in dialysis patients, until further studies are carried out.⁸⁰

Table 9 describes the PPK models developed for hemodialysis patients found in the “PPK Model review”.

(b) Patients receiving continuous renal replacement therapy

The JPN guideline³ summarizes evidence and presents recommendations for the subpopulation of patients receiving continuous renal replacement therapy (Table 10).

Extracorporeal clearance of drugs increased with higher-intensity continuous renal replacement therapy. This increase was significant for vancomycin. In these patients, there is great variability in antibiotic pharmacokinetics, which complicates an empirical approach to dosing and suggests the need for TDM.⁸¹

CI produced more frequently therapeutic vancomycin levels and less frequently subtherapeutic levels compared to intermittent infusion. However, therapeutic levels were achieved infrequently by either dosing method. Given equivalent TDM costs and the lack of a clear clinical benefit, the role of CI remains to be defined, in spite of practical and theoretical advantages, particularly in burn patients.⁸²

(c) Patients receiving ambulatory peritoneal dialysis

The JPN guideline³ summarizes evidence and presents recommendations for this subpopulation (Table 10).

Clinical outcomes of gram-positive and culture-negative peritonitis were not associated with either the frequency or levels of serum vancomycin measurements in the first week of treatment when vancomycin is dosed according to International Society for Peritoneal Dialysis.⁸³

Table 9 describes the PPK models developed for this subpopulation.

3.3.6 | Burn patients

None of the evaluated international guidelines presents defined recommendations for this subpopulation. The literature review identified a study that shows that higher clearance and lower serum vancomycin concentrations in patients with severe burns may increase the risk of suboptimal bactericidal action and development of resistance, highlighting the need for dose individualization.⁸⁴

The “PPK Model review” found only one study in this subpopulation which is described in Table 11.

3.3.7 | Hematologic patients

None of the evaluated international guidelines presents defined recommendations for this subpopulation. The literature review showed that this is a not well explored issue. However, it is recognized that most patients with neutropenia have augmented Cl_{van}. A small group of patients that received vancomycin during two episodes, showed reversible augmented Cl_{van} in the nonneutropenic period. This indicates the importance of increasing the vancomycin daily dose in 30% in patients with neutropenia (15 mg/kg, 2x/d to 13 mg/kg, 3x/d).

Frequent TDM in patients with neutropenia can help prevent therapy failure due to low AUCs and toxicity due to high vancomycin C_{troughs}.⁸⁵ Recently, Suzuki and co-workers had proposed

Table 11. Population pharmacokinetic models developed for burn patients

N	Pharmacokinetic model	Pharmacokinetic parameters	Covariates	Reference
37	Two-compartment	Cl = 4.7L/h; V1 = 68.4 L; V2 = 73 L; Q = 4.54 L/h	CL = 4.7 × (Clcr/6.53); V1 = 68.4 × (WT/70) – 33.1 × BURN; V2 = 73 × (WT/70)	[84]

Cl, clearance; Clcr, creatinine clearance; N, sample size; Q, Intercompartmental clearance; V1, volume of central compartment; V2, volume of peripheral compartment; WT, weight.

Table 12. Population pharmacokinetic models developed for hematologic patients

N	Pharmacokinetic model	Pharmacokinetic parameters	Covariates	Reference
25	Two-compartment	Vc = 15 L/65 kg; Vd _{ss} = 38.9 L/65 kg; Cl _{distribution} = 9.32 L/h/65 kg	Clcr (covariate of Cl)	[88]
70 Children	One-compartment	Cl = 4.37 L/h; Vd = 119 L	Cl = 4.37 × (WT/20.2) ^{0.677} × (Clcr/191) ^{1.03} Vd = 119 × (WT/20.2) ^{0.838}	[89]

Cl, clearance; Clcr, creatinine clearance; N, sample size; Q, intercompartmental clearance; Vc, volume of central compartment; Vp, volume of peripheral compartment; WT, weight.

a target Ctrough of 11.5 mg/mL for febrile neutropenia in patients with hematological malignancies.⁸⁶ The high-dose, once-daily vancomycin nomogram attained trough levels greater than 10 mg/L in only 21% of patients with leukemia and a substantial number of adverse drug reactions were observed leading to the nonrecommendation of such regimen for outpatient therapy.⁸⁷

The “PPK Model review” found three studies in hematological patients. One was excluded because it was not a population model and the remaining two are described in Table 12.

(a) Transplanted patients

Current vancomycin dose regimens do not lead to recommended therapeutic serum concentrations in patients undergoing hematopoietic stem cell transplantation. Large variation in vancomycin pharmacokinetic parameters was observed among these patients, which further strengthens the need for TDM and individualization of vancomycin dosing in this subpopulation.⁹⁰

3.3.8 | Neurosurgery patients

Adult neurosurgical ICU patients showed a significantly elevated Cl_{van} (0.104 ± 0.036 L/h/kg).⁹² Augmented Cl_{van} should be considered when determining vancomycin doses in neurosurgical patients.⁹¹ Two dosing equations were derived to achieve optimal serum vancomycin concentrations for this subpopulation.⁹² Further research using TDM in the management of CNS infections, in this setting, in addition to work defining plasma and cerebrospinal fluid (CSF) concentrations associated with antibacterial efficacy and toxicity is mandatory.⁹³

The “PPK Model review” in neurosurgical patients found only one study that is described in Table 13.

(a) with spinal medulla lesions

Vancomycin dose selection in patients with spinal cord injury (SCI) is challenging due to difficulties in accurately estimating renal function in these patients.⁹⁵ A recent study suggests that the use of the

Chronic Kidney Disease Epidemiology Collaboration cystatin C equation may improve initial vancomycin dosing in the SCI population.⁹⁵

(b) with meningitis

Vancomycin penetrates the blood-brain barrier poorly. Therefore, determination of vancomycin in CSF is rarely performed. Limited data are available on intraventricular (IVT) vancomycin dosing for meningitis. CSF output and time from dose correlated with CSF concentrations and no relationship concerning CSF protein, white blood cell count or glucose was found.⁹⁶ Optimal regimens in this subpopulation are still unclear, and dosing of IVT vancomycin requires intricate consideration of patient specific factors and their impact on CNS pathophysiology. Higher quality clinical trials are necessary to characterize the disposition of vancomycin within the CNS, and to develop models for various pathophysiological conditions to facilitate understanding alterations of pharmacokinetic and pharmacodynamic parameters.⁹⁷

3.3.9 | Other populations

(a) Severe acute pancreatitis

Vancomycin Ctroughs were significantly reduced in this subpopulation and, therefore, patients with severe acute pancreatitis need higher doses to ensure clinical effects.⁹⁸

(b) Trauma patients

Vancomycin pharmacokinetics in this subpopulation is best described by a two-compartment open model; Cl_r was related to Cl_{van} (0.49 L/h) and decreases in the presence of furosemide (0.34 L/h). ABW influenced both the central (V1 = 0.74 L/kg) and peripheral Vd (V2 = 5.9 L/kg), but patients with age >65 years showed a larger V1 (1.07 L/kg).⁹⁹

(c) Extracorporeal membrane oxygenation (ECMO)

ECMO alters vancomycin pharmacokinetics in neonates. Data in adults is limited. Cl_{van} in patients receiving ECMO with a roller

Table 13. Population pharmacokinetic models developed for neurosurgery patients

N	Pharmacokinetic model	Pharmacokinetic parameters	Covariates	Reference
25	Three-compartment	V1 = 15.16 L; V2 = 46.10 L; V _{CSF} = 0.14 L; Q = 3.97 L/h; Q _{CSF} = 0.006 L/h; Cl = 7.98 L/h; Cl _{CSF} = 0.038 L/h	CSF albumin level	[94]

Cl CSF, cerebrospinal clearance; Cl, clearance; N, sample size; Q, intercompartmental distribution; Q_{CSF}, cerebrospinal distribution; V1, volume of central compartment; V2, volume of peripheric compartment; V_{CSF}, volume of cerebrospinal fluid.

Table 14. Population pharmacokinetic models developed for ECMO patients

N	Pharmacokinetic model	Pharmacokinetic parameters	Covariates	Reference
11	Two-compartment	Cl = 3.7 L/h; V1 = 31.8 L; V2 = 57.1 L	Cl = 3.7 × Cl _{CRRT} × Cl _{N_oCRRT}	[102]

Cl, clearance of vancomycin; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; N, sample size; V1, volume of central compartment; V2, volume of peripheric compartment.

pump was significantly lower than that in the matched cohort.¹⁰⁰ As a result of drug sequestration and increased Vd, the ECMO procedure might lead to a decrease in drug concentrations. Vancomycin concentration remained unchanged in the ex-vivo ECMO circuit primed with whole human blood.¹⁰¹

The literature review of PPK models found only one study, described in Table 14.

(d) Vascular surgery

The target concentration (10–25 mg/L) was achieved in 81% of all samples collected in one study of vascular surgery patients.¹⁰³ All patients achieved target concentrations at one or more-time points.

The regimen employed provided appropriate concentrations at the time of intervention. No potentially toxic concentrations or adverse reactions to vancomycin were reported in patients undergoing vascular surgery. Vancomycin given as CI delivers adequate serum concentrations.¹⁰³

4 | FUTURE PERSPECTIVES

Despite the availability of consensus guideline recommendations, practices for dosing and monitoring of vancomycin are not universally applied.¹⁰⁴

This review has gathered additional evidence that TDM has clinical relevance in several patient subpopulations (neonates, pediatric and with renal impairment) but there is still lack of research concerning other subpopulations (neurosurgical, oncological, cystic fibrosis).

An updated review of PPK models for specific subpopulations was carried out and models have been summarized for future reference/research and TDM refinements. Currently, most of these models have not been prospectively validated and TDM methodologies adaptations for specific populations are still not consensual. The use of dose adjustment methodologies based on PPK models and Bayesian estimation of parameters seems to gather the higher scientific consensus.

In the future, well designed prospective studies should be carried out to demonstrate the relevance of TDM, validate PPK models in clinical settings and find consensual refinement adaptations of TDM methodologies for specific patient subpopulations using vancomycin.

5 | COMPLIANCE WITH ETHICAL STANDARDS

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

CONFLICT OF INTEREST

The authors hereby confirm that they do not have any conflicts of interest to declare.

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