Université de Montréal

An Objective View into Vancomycin Therapeutic Monitoring Proposed Guideline Modifications and Controversy

A Population Pharmacokinetic and Bayesian-Based Modeling Perspective

Par

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Résumé

La vancomycine est l'un des antibiotiques les plus prescrits, principalement utilisé pour les infections suspectées et confirmées à Staphylococcus aureus résistant à la méthicilline (SARM). Les infections par des souches de SARM font peser une charge importante sur le système de santé, à laquelle s'ajoute l'incertitude qui demeure quant à la posologie optimale de la vancomycine. Les récentes lignes directrices révisées sur le suivi thérapeutique de la vancomycine, publiées en 2020, avalisent principalement l'estimation directe de l'aire sous la courbe de concentration en fonction du temps (AUC) par l'utilisation d'équations bayésiennes ou pharmacocinétiques (PK) de premier ordre pour le suivi thérapeutique.

Pour mieux informer la posologie de la vancomycine, nous avons d'abord mis à jour une revue précédente des analyses pharmacocinétiques de population (PopPK) de la vancomycine publiées chez les adultes et les enfants. Pour ce faire, nous avons déterminé les caractéristiques des modèles pharmacocinétiques rapportés et identifié les diverses sources potentielles de variabilité observées dans différentes sous-populations particulières. Motivés par la controverse existante autour des nouvelles directives de surveillance thérapeutique de la vancomycine et par l'absence d'une étude approfondie des méthodes recommandées, nous avons recueilli des données hospitalières et construit un cadre de modélisation qui nous a permis d'évaluer les recommandations des directives sur les méthodes de surveillance, tout en considérant une variété de scénarios et d'hypothèses cliniques réalistes.

Notre analyse a confirmé que la surveillance bayésienne est la méthode la plus rapide et la plus fiable, à condition qu'elle soit correctement mise en œuvre, la plus importante condition pour cela étant l'utilisation de modèles bayésiens a priori appropriés. De plus, nous avons montré que le suivi bayésien ne nécessite pas nécessairement des niveaux de concentration de types creux ou pic et peut en fait être réalisé en utilisant un niveau aléatoire. Aussi, nous avons démontré que l'utilisation correcte des équations pharmacocinétiques de premier ordre exigerait au moins deux mesures de concentration à l'état

d'équilibre. L'utilisation de la méthode creux-seulement de la vancomycine à l'état d'équilibre peut être tout aussi efficace dans certaines situations que nous avons explorées ici.

En considérant la larges étendue et la grande variabilité des populations traitées à la vancomycine en termes d'âge, de gravité de l'infection et de scénarios cliniques, cette thèse adopte un regard objectif pour évaluer quantitativement le gain potentiel de chaque méthode de surveillance de la vancomycine, en explorant leur adéquation en termes d'effort nécessaire, de disponibilité des ressources et de gain potentiel.

Compte tenu des lignes directrices sur la vancomycine récemment publiées et de la controverse qui persiste, nous pensons que cette thèse a permis de démêler la variété et la complexité de l'utilisation de la vancomycine et a apporté un éclairage supplémentaire plus objectifvement informé vers un suivi thérapeutique optimal de la vancomycine.

Mots-clés: Vancomycine, pharmacométrie, pharmacocinétique de population, effets mixtes non linéaires, suivi thérapeutique médicamenteux, simulation d'essais cliniques.

Abstract

Vancomycin is among the most prescribed antibiotics, mainly used for suspected and confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Infections by MRSA strains carry a substantial burden on the health care system, supplemented by the uncertainty that remains regarding vancomycin optimal dosing. The recent revised vancomycin therapeutic monitoring guidelines published in 2020, endorsed primarily the direct estimation of area under the concentration-time curve (AUC) through the use of Bayesian or first-order pharmacokinetic (PK) equations monitoring.

To better inform vancomycin dosing, we first updated a previous review of published vancomycin population pharmacokinetic (PopPK) analysis in both adults and children. This was accomplished by determining the characteristics of the reported pharmacokinetic models and identifying the potential various sources of variability observed in different special subpopulations. Motivated by the existing controversy around the new vancomycin therapeutic monitoring guidelines and the lack of a thorough investigation of the recommended methods, we collected hospital data and built a modeling framework that allowed us to assess the guideline recommendations of monitoring methods while considering a variety of realistic clinical scenarios and assumptions.

Our analysis affirmed that Bayesian monitoring is the fastest and most reliable method, conditional on its proper implementation, the most important being the use of proper Bayesian priors. Moreover, we showed that Bayesian monitoring does not necessarily require trough or peak concentration levels and can in fact be performed using a random level. Proper use of first-

order PK equations required at least two steady-state concentration measurements. Alternatively, simpler trough-only vancomycin monitoring near steady-state can be as effective in certain cases that we explored here.

By considering the wide ranges and the high variability in populations treated with vancomycin in terms of age, the severity of infection, and clinical scenarios, this thesis takes an objective look to quantitatively assess the potential gain of each vancomycin drug monitoring method, by investigating their suitability in terms of the effort needed, the availability of resources and the resulting gain.

Considering the recently released vancomycin guidelines and the ensuing controversies between well-established clinical teams, we believe that this dissertation helped untangle the variety and complexity of vancomycin use and brought additional insights towards a more objective and optimal vancomycin therapeutic monitoring.

Keywords: Vancomycin, pharmacometrics, population-pharmacokinetics, nonlinear mixed effects, therapeutic drug monitoring, clinical trail simulation

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Preface

This dissertation concerns the optimization of vancomycin therapeutic monitoring. It was prepared in article style and contains six chapters. In the first one, we provide key information relevant to understanding the clinical context of vancomycin use. In the second and third chapters, we revisited a highly referenced review, dating from 2011 in order to perform a thorough update of all vancomycin population pharmacokinetics models developed for adults and children separately. Both articles for the adult population and pediatrics were published in the journal of Clinical Pharmacokinetics. In the fourth and fifth chapters, we quantitatively evaluate vancomycin monitoring methods suggested by the revised vancomycin therapeutic monitoring guidelines, by considering various practical situations and available data and information. A general discussion provides an overall view of the subject considered in this thesis.

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List of Abbreviations

Abbreviations	Description
AIC	Akaike's Information Criterion
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
Allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration Time Curve
BMD	Broth Microdilution
BMI	Body Mass Index
BSV	Between Subject Variability
BW	Body Weight
CI	Confidence Interval
CKD	Chronic Kidney Disease
CL	Clearance
Cl_{cr}	Creatinine Clearance
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
CRRT	Continuous Renal Replacement Therapy
CWRES	Conditional Weighted Residuals
CV	Coefficient of Variation
ECMO	Extracorporeal Membrane Oxygenation
FOCEI	First Order Conditional Estimation with Interaction
GFR	Glomerular Filtration Rate

GIT	Gastrointestinal Tract
ICU	Intensive Care Unit
IIV	Inter-Individual Variability
IV	Intravenous
LLQ	Lower Limit of Quantification
MAP	Maximum A Posteriori
MDRD	Modification of Diet In Renal Disease
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-Resistant *Staphylococcus Aureus*
MSSA	Methicillin-Susceptible *Staphylococcus Aureus*
NONMEM	Non-Linear Mixed Effect Modelling Software
NCA	Noncompartmental Analysis
NPDE	Normalized Prediction Distribution Error
OFV	Objective Function
PD	Pharmacodynamics
PK	Pharmacokinetics
PMA	Postmenstrual Age
PNA	Postnatal Age
PcVPC	Prediction-Corrected Visual Predictive Checks
PopPK	Population Pharmacokinetics
Q	Intercompartmental Clearance
R^2	Coefficient of Determination
RR	Relative Risk
RRT	Renal Replacement Therapy
SAPII	Severity of Disease at The Time Of ICU Admission

SCM	Stepwise Covariate Modeling
SCR	Serum Creatinine
RMSE	Root Mean Squared Error
RV	Residual Variability
TDM	Therapeutic Drug Monitoring
VA	Veno-Arterial
V_c	Central Volume of Distribution
V_d	Volume of Distribution
V_p	Peripheral Volume of Distribution
VV	Veno-Venous

NONMEM Symbols

θ Theta: Fixed-effect parameters, such as clearance; θ is a vector of p parameters (θ_1, $\theta_{2,}$, … $\theta_{p)}$

$\varepsilon_{i,j}$ Epsilon: Intra-individual variability or the residual variability for an individual i at time *j*.

η Eta: Inter-individual or inter-occasion variability, $\eta_{i,}$ is a vector of individual subject estimates

ω^2 Omega: The variance of fixed-effect parameter θ_n, where n=1,2, ..p

σ^2 Sigma: The variance of residual error ε

Chapter 1

Introduction

1.1 Staphylococcus Aureus

Staphylococcus aureus (*S. aureus*) is a Gram-positive bacterium that can be part of the normal flora in healthy humans' skin and upper respiratory tract. *S. aureus* is a commensal organism that can turn opportunistic as it is the most common cause of skin and soft tissue infections (1, 2). These infections can range from mild localized to systemic life-threatening severe infections, such as in the case of severe endocarditis or sepsis. Signs and symptoms of *S. aureus* infections range from inconsequential skin discomforts, manifests as localized warmth, redness, swelling, and tenderness, to serious infections such as toxic shock syndrome that manifest with a sunburn-like rash, extreme fever, low blood pressure, reduced awareness, and multiple organ failure. *S. aureus* can also induce toxin-mediated poisoning. For example, eating contaminated food by *S. aureus* might cause abdominal pain, nausea, vomiting, or diarrhea due to the rapid action of staphylococcal toxins within 1–6 h (2-4).

Not long after the introduction of the then-new and effective antibacterial drug penicillin in the 1940s, *S. aureus* fast developed resistance mediated by the production of the enzyme β-lactamase. This enzyme rendered certain β-lactams antibacterial in the penicillin family, such as ampicillin and amoxicillin, ineffective (5, 6). Other classes and generations of antibacterial were then developed, such as β-lactamase-resistant drugs (e.g., cloxacillin and methicillin) and β-

lactamase inhibitors that can be used in combinations with other antibacterial drugs (e.g., clavulanic acid and sulbactam). However, during the 1960s, strains of *S. aureus* initially acquired a novel gene (mecA), which codes for a penicillin-binding protein, rendering penicillinase-resistant drugs ineffective, as well. The term methicillin-resistant *Staphylococcus aureus* (MRSA) was given for these strains (6, 7).

MRSA infections can be hospital-acquired, community-acquired, or community-onset (3, 8). The latter refers to MRSA originated in a hospital, circulated in the community, and had its onset in the community leading to hospital readmission. Infections by MRSA initially emerged in the healthcare setting, and strains associated with hospital-acquired infections are usually multi-resistant strains that are difficult to treat (8, 9). While the prevalence of community-acquired MRSA infections has been increasing in many countries over the last decade, MRSA strains prevalent with community-acquired MRSA infections were reported to retain susceptibility to many non-β-lactam antimicrobials (8, 9). However, this might not be the case with healthcare-associated MRSA infections. For these infections, pharmacotherapy includes glycopeptides such as vancomycin (since the 1950s) and teicoplanin, and other classes such as linezolid (since the 1970s) and daptomycin (since the 1980s), all of which their administration might be associated with side effects (10, 11).

In comparison to methicillin-susceptible *S. aureus* (MSSA), MRSA infections carry a significant burden on the healthcare system. Such complications, according to the World Health Organization survivance report, include a significant increase in the incidence of the progression to septic shock (relative-risk [RR] 1.52, 95% CI: 1.24 to 1.88, $P < 0.0001$), an increase in post-infection length of hospital stay by 4.6 days, and the intensive care unit (ICU) length of stay by an average of 4 days, increase in all-cause mortality (RR 1.61, 95% CI: 1.43 to 1.82, P <

0.00001), higher bacterium-attributable mortality (RR 1.64, 95% CI: 1.43 to 1.87, P < 0.00001), higher ICU mortality (RR 1.46, 95% CI: 1.23 to 1.74, P < 0.0001), and more than twofold risk increase in discharge to long-term care or secondary care facilities (12).

1.2 Vancomycin

Vancomycin is an antibiotic that is extensively used for MRSA infections and enterococci (group D *Streptococcus*) infections (13). The microbial coverage of this important glycopeptide antibiotic is broad and includes all gram-positive cocci, such as *S. aureus* and *Staphylococcus epidermidis,* diphtheroid, anaerobes, and clostridium species including *Clostridium difficile* (14-16). Vancomycin can be administered orally or intravenously for different indications. Oral vancomycin administration is used for the treatment of gastrointestinal tract (GIT) infections such as infections by C *difficile* (16). Vancomycin therapeutic drug monitoring (TDM) is not relevant to oral vancomycin administration due to poor vancomycin absorption through the GIT and its large molecular weight of roughly 1450 Dalton. On the other hand, vancomycin intravenous (IV) administration by either intermittent or continuous infusion, is used to treat systemic infections (17).

1.2.1 Mechanism of Action

Vancomycin exerts its bactericidal action through the inhibition of a structural polymer in the bacterial cell wall named peptidoglycan. Particularly, vancomycin binding to the C-terminal D-Ala-D-Ala prevents successive cross-linking (transpeptidation) of this precursor to the nascent

peptidoglycan chain (7), as demonstrated in Figure 1.1.

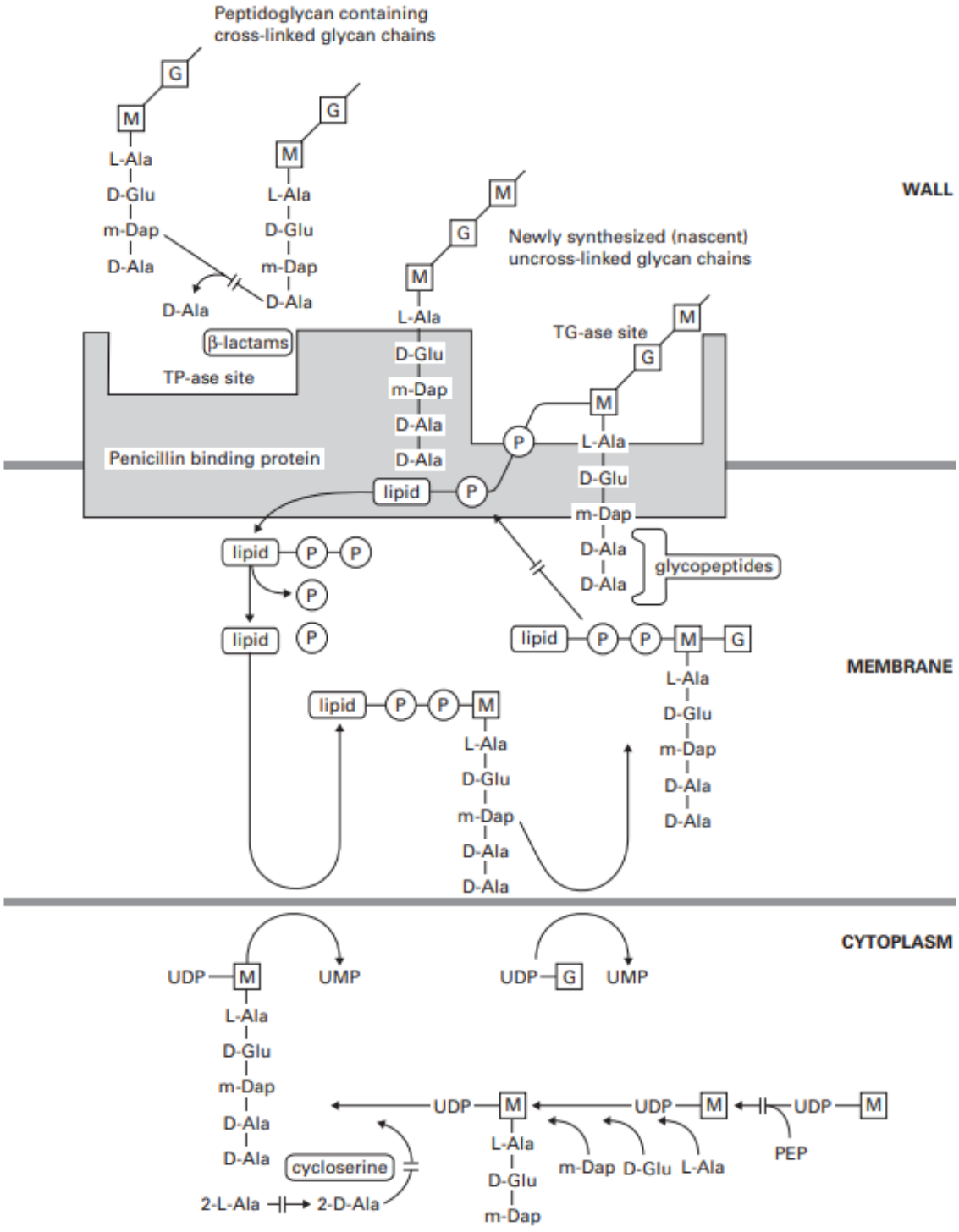

Figure 1. 1 Vancomycin molecular mechanism of interfering with the biosynthesis of peptidoglycan. The figure was adopted from (18) with permission.

Vancomycin intermittent IV administration is usually given based on the bodyweight over an infusion period of 1 to 2 h with a rate of 10 to 15 mg/min (≥1 h per 1 g) and at a solution concentration not exceeding 5 mg/mL, to prevent the development of infusion-related adverse reactions (17). An actual body weight-based loading dose of 20-35 mg/kg throughout 2-3 h followed by a maintenance dose can help minimize the risk of subtherapeutic concentrations and achieve the therapeutic range fast (19, 20). Achievement of therapeutic concentrations at the first days of therapy might be necessary for certain patient groups such as critically ill, dialysis, and renal replacement therapy patients. It should be noted that currently, no high-quality data from large randomized clinical trials support the administration of a loading dose despite its seeming importance (17).

Vancomycin is an excessively used antibiotic (21). A report indicated that 10% of hospitalized patients received vancomycin and its use was reported to be steadily increasing in the United States from 2006 to 2012, particularly in the intensive care unit (22), (23). Further, a single-day analysis of antibiotic use in 106 hospitals (n > 10,000 patients) demonstrated that vancomycin was the most prescribed antibiotic standing at 22.5% of all prescribed antibiotic courses (24). Consumption analysis of antibiotic use reported 157 days of vancomycin use per 1000 days of hospitalizations, a rate that is 125% higher than the combined rates of all other antibiotics included in the study, which were piperacillin-tazobactam, amikacin, and daptomycin (21, 22).

1.2.2 Vancomycin Monitoring Guidelines: A Historical Shift

The release of the original vancomycin consensus guidelines entitled “Therapeutic Monitoring of Vancomycin in Adult Patients: A Consensus Review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists” in 2009 introduced a shift in the practice of vancomycin therapeutic monitoring

(25). This 2009 consensus guideline concluded that vancomycin efficacy is best predicted by the ratio of the total area under the drug concentration-time curve over the minimum inhibitory concentration (AUC/MIC), indicating that efficacy is not only concentration-dependent but also time-dependent, i.e., exposure-dependent. This original guideline, therefore, recommended eliminating older practices of serum peak and trough routine monitoring (25).

However, at the time of the original guideline in 2009, the implementation of AUC/MIC faced a real practical challenge as AUC cannot be easily estimated in practice. Therefore, based on the assumed correlation between trough and AUC at the time the 2009 guidelines were published, trough samples were suggested as a surrogate for AUC. The recommended trough targets were based on the site of infection and the MIC of the pathogen. For complicated, serious, or deep-seated infections (such as meningitis, pneumonia, and endocarditis), a trough target of 15-20 mg/L if the MIC was ≤1 mg/L in patients with a normal renal function was recommended to ensure sufficient vancomycin concentrations and to minimize chances of the emerging resistance creep that was feared at the time of the original guidelines' release (25). The association between trough levels and safety and efficacy (i.e., increased incidence of nephrotoxicity) did not seem to be a major concern at that time, which might be due to the lack of strong evidence that was only available following the release of the original guidelines (25).

Many aspects of vancomycin administration were not addressed in the original guideline due to a lack of adequate data (19, 25). Dosing and monitoring recommendations were not made for morbidly obese, renal failure, and pediatric (other than neonates) patients. Other unaddressed aspects included specific recommendations for dialysis dosage adjustments, continuous infusion (CI) administration, and the safety profiles of > 3 g per day dosages (19, 25).

All of the aforementioned factors have led to the release of the revised guidelines in 2020 (19). These guidelines, while affirming the therapeutic target of AUC/MIC of 400 to 600, have abolished previously recommended trough-only monitoring, stating poor AUC-trough correlation and better monitoring approaches not available before. It is worth mentioning that this AUC/MIC of 400 to 600 is valid in the case MIC was determined using the broth microdilution [BMD] method. Direct AUC-guided monitoring approaches include the use of first-order PK equations and Bayesian-guided monitoring, as discussed in detail below. It also added many key points to vancomycin administration to special populations (19). These points will be discussed in detail below.

1.2.3 Minimum Inhibitory Concentration (MIC)

Determination of the MIC value is crucial to achieving the defined AUC/MIC target. However, the routine measurement of MIC values in many institutions is not common due to many factors, including that it is not practical, requires significant time and resources, varies per institution and method used, and is not very precise (19, 26). For example, variability in results within one level of dilution (i.e., ±1 $\log_2$ dilution error) is considered as acceptable variability according to the standards set by the Clinical Laboratory Standards Institute (CLSI). In other words, a MIC of 1 mg/L might not be confidently differentiated between one level of dilution of 0.5 mg/L and 2 mg/L (19). Additionally, using the disk diffusion method was reported to be insensitive for MRSA with reduced susceptibility to vancomycin as shown in Figure 1.2 (27). Another challenging variable is the system or method used to test MIC in many institutions. It is documented that different testing methodologies can produce varying MIC results despite the availability of advanced automation (26). For example, a study reported that using BMD, 92% of the strains had a MIC of 1 mg/L. However, when using MicroScan WalkAway (Beckman

Coulter, Brea, CA) and Etest (bioMérieux USA, Hazelwood, MO), a MIC of 1 mg/L was reported for only 70% of the strains. Further, only 41% of the strains had a MIC of 1 mg/L using Vitek 1 (bioMérieux) (28). Another study of the essential agreement (defined as the percent complete agreement + percent minor errors) using a reference commercial MRSA BMD test for 161 isolates reported that Vitek 2 and MicroScan WalkAway had 96.3% essential agreement, while it was 88.8% for BD Phoenix (BD, Franklin Lakes, NJ) and 76.4% for the Etest method at that specific site (29).

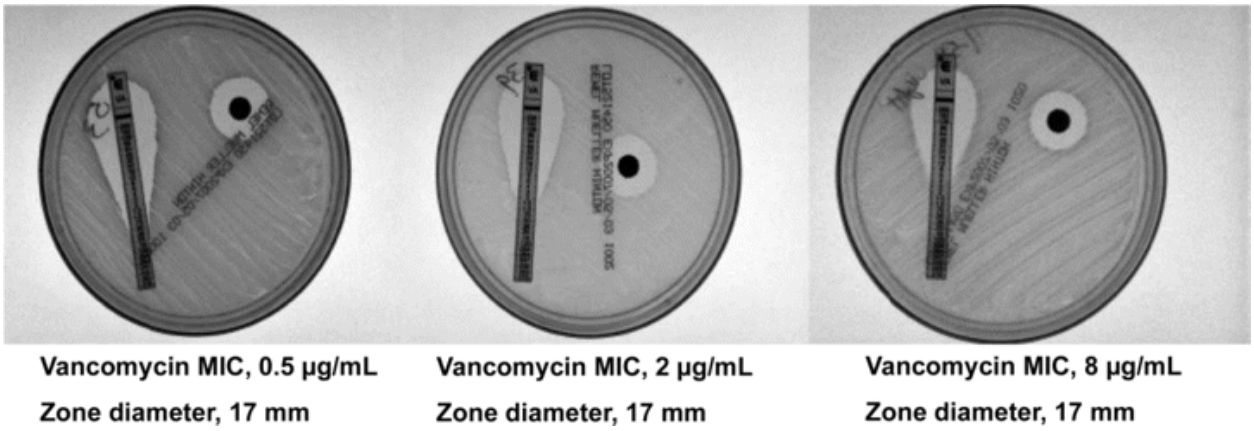

Figure 1. 2 Similar zone diameters but different vancomycin MICs using disk diffusion method for MRSA with reduced susceptibility for vancomycin. Adopted from (27) with authorization.

1.2.4 Pharmacokinetic/Pharmacodynamics (PK/PD) index

1.2.4.1 Efficacy

The exact AUC/MIC target was originally derived from in vitro/in vivo models which found that bactericidal activity (defined as one to two log reduction in bacterial inoculum) and the potential emergence of resistance in MRSA and vancomycin-intermediate *S. aureus* strains was associated with a cutoff AUC/MIC value 400 (30-32). This AUC/MIC of 400 was, further, supported by a large body of clinical data, although they were mostly observational single-center retrospective studies for patients with MRSA bloodstream infections (33-37). A limitation to many clinical data was that the methods used to estimate AUC and MIC. Many studies implemented a formula-

based approach to estimate vancomycin clearance (and consequently AUC) that was derived from the glomerular filtration rate. However, this approach is known to be imprecise (33-37). A single-center retrospective study of MRSA bacteremia patients, which estimated AUC using the Bayesian method and MIC using BMD, reported that outcomes were maximized when day 1 AUC/MIC_{BMD} ratio exceeded 521 and day 2 exceeded 650 (36). Similarly, the risk of vancomycin treatment failure for MRSA endocarditis patients was greatest among those with an AUC/MIC_{BMD} ratio of $\leq$ 600 (AUC was estimated using a Bayesian approach, as well) (38). Many other small retrospective studies that used Etest reported lower AUC/MIC thresholds (35, 39, 40). Additionally, a prospective multicenter observational study of MRSA bacteremia adult patients (n = 265) suggested that treatment failure was not significantly different between a prespecified day 2 of AUC/MIC_{Etest} ratio of $\geq$ 320 and AUC/MIC_{BMD} of $\geq$ 650, although best outcomes were observed with AUC/MIC_{BMD} of $\leq$ 515 i.e., absence of treatment failure and acute kidney injury (AKI) (41). Few studies evaluated the efficacy of AUC/MIC ratio of < 400, MIC values of 2 mg/L, and no studies evaluated outcomes in osteomyelitis and meningitis infections (17).

1.2.4.2 Toxicity: Acute Kidney Injury

Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) derived definition of acute kidney injury (AKI) is an increase in serum creatinine (SCR) of $\geq$ 0.3 mg/dL over 48 hours, although many studies usually defined AKI as 50% increase of serum creatinine (SCR) from baseline, $\geq$ 0.5 mg/dL increase in the SCR, or of 50% decrease in calculated creatinine clearance (CLcr) from baseline on 2 consecutive days without alternative explanations (42-44). Vancomycin-associated AKI usually develops 4 to 17 days after the initiation of therapy. AKI, even mild AKI, might have severe consequences, including a significant increase in morbidity, healthcare costs, and length of hospital stays, and a decrease in

long-term survival rates. Once AKI develops, it might lead to a permanent loss of full renal functions in many patients, especially in critically ill patients. Factors that might exacerbate the risk of nephrotoxicity might be the administration of concomitant nephrotoxins (e.g., piperacillin/tazobactam and flucloxacillin, loop diuretics, aminoglycosides, amphotericin B, and IV contrast dye), and other host-related factors such as being overweight, pre-existing renal dysfunction, and critical illness (17, 45, 46).

The prevalence of vancomycin-associated AKI varied across studies from 5% to 43%, with a relative risk of 2.45 (95% CI, 1.69-3.55) and an attributable risk of 59%. A prospective study showed that median trough concentrations and AUC in patients with AKI were 15.7 mg/L and 625, respectively, while patients without AKI had trough concentrations and AUC values of 8.7 mg/L or 423, respectively (45). Another study reported that mean AUCs were 600-800 in patients with AKI compared to 400-600 in those without AKI (P = 0.014) (47). Further, the risk of AKI substantially increases (2.5-fold) at AUC levels >1300 compared to lower AUC values (47-49). Another study reported a 3- to 4-fold increase in the risk of AKI incidence with AUC values of ≥ 677 on the first day, and AUC ≥ 683 or troughs of ≥18.2 mg/L on the second day of treatment (50). Based on available evidence, the AUC/MIC target that appears to be associated with best outcomes is between 400 and 600, which can minimize the likelihood of nephrotoxicity and maximize efficacy for suspected or confirmed serious invasive MRSA infections (17).

1.3 Pharmacokinetic Models

The primary goal of the application of clinical pharmacokinetics includes delivering an effective and safe individualized drug therapy, which can be allowed by understanding the relationship between drug concentrations and pharmacological responses. To achieve this, drug concentration can be monitored in clinics using assay procedures to determine whether a concentration is

therapeutic, subtherapeutic, or toxic, although no absolute boundaries in practice split these regions. Upon the administration of a given dose of the drug to a population, a variability in patients' responses can be expected due to variation in drug absorption, distribution, metabolism, elimination, disease state, and drug-drug interaction (51, 52).

Using a pharmacokinetic model allows to describe the system's behavior and summarize a large volume of data. Multiple PK modeling approaches can be deployed to describe the concentration-time profiles of a drug and to estimate its PK parameters. Traditional PK analysis, such as non-compartmental analysis (NCA) or nonlinear regression, might require many blood samples per individual. NCA does not require an assumption about drug distribution and might be very useful to obtain PK parameters such as the maximum concentration (Cmax) or half-time (53). While conducting well-structured and rich PK studies might be feasible with healthy volunteers, collecting such rich data might not be feasible especially for the most vulnerable of patients. For example, critically ill neonates are likely to require optimizing doses due to the potential of PK parameters alterations but might not be available for intensive PK studies. Compartmental PK assumes hypothetical body compartments characterized with a homogenous distribution. The number of compartments varies according to the rates of distribution. A central compartment usually represents highly infused organs or tissues that are in equilibrium with the systemic circulation such as the liver and kidney. The peripheral compartment might represent lower rate blood-infused organs such as fat tissues (52, 53).

Nonlinear mixed-effects models can make use of sparse data that is otherwise not beneficial to NCA or traditional PK analysis. In its essence, the nonlinear mixed-effects approach describes the PK profiles using mathematical and statistical models (54). It, therefore, can reduce the sample collection burden on a single subject and its associated cost by pooling sparse data from

many individuals without all of them necessarily contributing full-profile data (54, 55). With this enriched PK data from many subjects, models might gain strength as the population approach carries the ability to account for differences in PK between individuals (interindividual variability) and identify possible sources of variability, such as patients' specific characteristics or covariates that might correlate with PK parameters (56). A powerful tool in the realm of PopPK is the ability to generate a model-based simulation. These simulations allow us to understand the impact of certain simulation conditions and clinical scenarios on outcomes, which can, in turn, inform decision-making (55).

1.4 Bayesian Approach

Bayes' Theorem was named after Reverend Thomas Bayes and was first published by Richard Price after Bayes' death in 1761. It was independently rediscovered, used, and proved by Pierre-Simon Laplace in 1774 (57). Following the invention of the Markov Chain Monte Carlo method and the availability of powerful computational power for the public, the application of Bayesian analyses gained popularity as it allowed it Bayesian approach to do more than its counterpart frequentist approach (58). The Bayesian approach is crucial to current population modeling practices. In its essence, the Bayesian approach consists of two components, a prior and a likelihood of new observations under competing hypotheses, which are both combined to produce the posterior parameter distribution (Eq. 1) (57). In other words, the Bayesian approach can make use of available prior knowledge such as a previously developed PopPK model structure and its parameters estimates. This assumed PopPK model in addition to the present data that contains drug concentration, dosing history, and covariates have the advantage of enriching our understanding of a problem and its associated parameters (55). This might be extremely helpful in cases such as in the case of sparse data. Bayesian analysis has many popular

utilizations in pharmacometrics and clinical practice, such as the estimation of individual parameters and the identification of potential covariates, and dose optimization in therapeutic drug monitoring (55, 56). The Bayes theorem is stated as follows:

$$P(A|B) = \frac{P(B|A)\times P(A)}{P(B)} \quad \text{Eq. 1}$$

Where in our case here:

A represents the PK model parameters.
B represents observed measurements.
$P(A|B)$ is the posterior distribution (the conditional probability of A given B).
$P(B|A)$ is the likelihood (conditional probability of B given A).
$P(A)$ represents the prior probability distribution of A.
$P(B)$ represents the prior probability distribution of B.

1.5 Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) plays a crucial role in maintaining drug levels within the therapeutic target avoiding potential supratherapeutic and toxic range, and subtherapeutic and ineffective range. The use of TDM in clinical practice is more relevant for drugs with a narrow therapeutic range, especially when coupled with high inter-and intra-patient variability as well as an unpredictable dose-response relationship. Applications of TDM include dose individualizing, adherence to dosage, and drug-drug interactions (59). Ideally, proper clinical implementation of TDM might require a well-established relation between the PK and PD, such as AUC or concentrations with efficacy and toxicity. With the increasing amount of knowledge becoming available about the source of drug-response variability, one-size-fits all drug dosage does not seem to be a reasonable approach. Sources of drug-response variability can be classified as genetic and nongenetic as well as endogenous (e.g., physiological or pathological) or exogenous

(e.g. diet or other medicines). Variability in pharmacokinetics might arise from intrinsic differences in the rate and extent of drug absorption, distribution, and clearance (60). Factors contributing to drug absorption variability can include bile release and gastrointestinal motility, as well as the co-presence of conditions at drug administration, such as concomitant drugs or food (59). Variability in drug disposition might be sourced in drug metabolism, transporters, and organ function, such as renal function and single gene polymorphisms.

Individually tailored dosage regimens can potentially yield the most desired outcomes balancing between benefit and harm. Model-informed precision dosing (MIPD) refers to predicting drug dosage regimens using modeling and simulation (59, 61). Integration of modeling and simulation in informing precision dosing is not a new idea. It might be traced back to 50 years ago to the works of Sheiner (62) and Jelliffe (63). Terms used in the literature for this approach include individualized, personalized, and precision in tandem with terms such as therapy and treatment (60). Historically, its application did not reach the bedside due to difficulties in results interpretations. The waiting time after sample collection due to the need for data manipulation, interpretation, and clear communication by a specialized clinical pharmacologist might as well have limited its widespread. Individualized dose therapy can be achieved either a *priori* (i.e., using patients' characteristics such as weight and creatinine clearance) or a *posterior* (i.e., using drug administration information, dosage, plasma levels) (60).

With the progress achieved in modeling and simulation and its widespread in several milieu, including industrial, regulatory, and academic, its contribution in improving drug use has gained large recognition. In this thesis, backed by clinical data from McGill University Health Center (MUHC), we adopted a modeling and simulation approach that allowed an investigative look at the six decades-long controversial vancomycin dose optimization.

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Chapter 2

An Update on Population Pharmacokinetic Analyses of Vancomycin, Part I: in Adults

This review is an update to a 2012 vancomycin review entitled "Vancomycin: A Review of Population Pharmacokinetic Analyses" by Amelie Marsot et al. An update was deemed necessary due to the large number of population pharmacokinetics analyses that were published following Marsot's original review. We split our update into two parts, adult and pediatrics. This article concerning adults appeared in *Clinical Pharmacokinetics* "Aljutayli, Abdullah, Amélie Marsot, and Fahima Nekka. "An update on population pharmacokinetic analyses of vancomycin, part I: in adults." *Clinical pharmacokinetics* 59.6 (2020): 671-698"

2 Article I: An Update on Population Pharmacokinetic Analyses of Vancomycin, Part I: in Adults

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Abstract

Background: Despite the wide clinical use of vancomycin, controversy remains regarding its optimal dosage regimens. This can be attributed to the large between- and within-subject variability in the pharmacokinetics of vancomycin.

Aims: The review aimed at providing a synthesis of population pharmacokinetic (PopPK) models of vancomycin in adults, determining the most reported pharmacokinetic models, and identifying various sources of variability in different special subpopulations in order to better inform vancomycin dosing.

Methods: We conducted a systematic search through PubMed and EMBASE for PopPK studies of vancomycin published from January 2011 to May 2019. Inspection of the relevant lists of references was conducted, as well.

Results: A total of 30 studies were included. One- two-, three-compartments models were reported to best describe vancomycin PopPK in 13, 14, and 3 studies, respectively. Three compartment models were implemented in 3 studies to account for an additional cerebrospinal fluid (CSF) compartment. The most common predictors were creatinine clearance and bodyweight, in 20 and 13 studies, respectively. Estimated values of vancomycin clearance and total volume of distribution varied widely from 0.334 to 8.75 L/h (0.0054 to 0.1279 L/h/kg) and from 7.12 to 501.8 L (0.097-6.97 L/kg), respectively. Almost all studies implemented an exponential interindividual variability model, and the highest variability on CL was 99.2%.

Conclusion: This review highlights the wide ranges and the high variability of estimated PopPK parameters. This information can help guide dosing in different subpopulations. Yet, additional analyses with pooled subpopulations might be needed to confirm the necessity of modified dosage regimens.

2.1 Introduction

Vancomycin is a glycopeptide antibacterial that has been used, broadly, and for decades in eradicating serious gram-positive infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA) strains (1, 2). In fact, vancomycin can be regarded as the drug of choice in the management of many types of infections caused by the prevalent (MRSA) strains (2-4). However, despite its intensive use and the large number of studies related to its pharmacokinetics, adjusting and monitoring blood concentrations of vancomycin in the clinical practice remains controversial (2). This lack of consensus can be attributed, in part, to the large between- and within-subject variability in the population pharmacokinetic (PopPK) models of vancomycin. For example, a previous review by Marsot et al. reported a wide range of variability in the clearance (CL) and volume of distribution (V_d) of vancomycin of up to 45% and 48%, respectively (1). As a result, safety and efficacy profiles of vancomycin, including exposure-dependent nephrotoxicity and optimal therapeutic target, might be inherently affected by this variability. Due to these clinical challenges, vancomycin has been a focus of therapeutic drug monitoring (4).

When vancomycin is monitored, compelling evidence demonstrated improved outcomes in association with the pharmacokinetic/pharmacodynamic (PK/PD) index of the ratio of area-under-the-curve (AUC) over 24 hours to minimum inhibitory concentration (MIC) by broth microdilution (AUC/MIC_{BMD}) of ≥ 400 (2). On the other hand, the incidence of nephrotoxicity (i.e. acute kidney injury) was reported to be associated with elevated AUC/MIC values that surpass 700. While the odds of acute kidney injury (AKI) steadily increase with elevated AUC/MIC, the likelihood of AKI was reported to be 2.5 times more at an AUC/MIC of 1300 compared to lower values ($p = 0.02$) (5, 6). In addition, the mean incidence of AKI was

significantly more among patients who had AUC values within a range of 600-800, compared to patients who maintained lower AUC values within 400-600 (p = 0.014) (6). When monitoring a trough concentration, existing evidence suggests an increased risk of vancomycin-associated AKI with trough levels of 15-20 mg/L and as a function of trough concentrations (7). Further, recent studies have demonstrated reduced AKIs using AUC-guided monitoring in comparison to trough monitoring (8-11).

Since the previous review by Marsot et al. (1), a large number of PopPK studies have been published, with the aim of characterizing vancomycin PK in different subpopulations, determining possible PK alterations, and weighing the translation of their findings into informed dosing regimens. The goal of the current paper is to follow up on (1) to provide an update of vancomycin PopPK models, with the same vision of providing the reader with a systematic and comprehensive overview of all analyses made from January 2011 until May 2019. This includes a special emphasis on reporting the main features and differences in study populations, study designs, characteristics of the models, including significant covariates. However, this review is divided and presented into two separate parts based on age i.e. adults in this first part and pediatrics in the ensuing part, with the ultimate goal of contributing to the implementation of a well-informed therapeutic monitoring and dose optimization of vancomycin.

2.2 Methods

2.2.1 Search strategy

An electronic literature search of PubMed and EMBASE databases was systematically performed for relevant studies of vancomycin population pharmacokinetics, using time confinement from January 2011 to May 2019. Search terms employed for the PubMed inquiry were the following: vancomycin[TI] AND (population-pharmacokinetic* OR nonlinear-mixed-

effect* OR NONMEM OR PMETRICS) NOT (child*). Further, EMBASE was inquired for English and in-human studies using similar search terms. Moreover, a thorough inspection of all the pertinent lists of references was conducted to identify any additional relevant materials.

2.2.2 Inclusion Criteria

Studies were eligible for inclusion according to predefined criteria; (i) studied population: adult including geriatric patients; (ii) treatment: intravenous vancomycin administration; (iii) modeling approach: parametric nonlinear mixed-effects pharmacokinetic modeling; (iv) originality of data: original data and a non-recycled analysis; (v) language: published in English.

2.2.3 Exclusion Criteria

Excluded from this review were articles that (i) were in vitro or animal study, review, meta-analysis, or methodology articles; (ii) recruited children; (iii) used non-compartmental or non-parametric approaches; or (iv) missed the information required to classify according to these criteria.

2.2.4 Data Extraction

Relevant information was extracted from every article into data collection sheets. The extracted information included the first authors, year of publication, characteristics of the population in every study (e.g. number of patients (male/female), type of the special population, age, bodyweight, body mass index [BMI], creatinine clearance (CL_{CR}), and assessment of renal function), study clinical protocol (e.g. type of study i.e. retrospective or perspective, dosage regimen, administered doses, nature and frequency of sampling i.e. rich or sparse, number of samples), vancomycin quantification methods (assay, lower limit of quantification [LLQ], kit, and instrument), modeling approach (e.g. software used, model evaluation methods, methods of

covariate selection), formulae of PopPK structural and statistical models and the values of their parameters, and tested and retained covariates.

2.3 Results

2.3.1 Literature Screening and Characteristics of Investigated Populations

PubMed and EMBASE database search yielded a total of 82 and 160 studies, respectively. After applying the inclusion and exclusion criteria, twenty-nine publications were eligible for inclusion. One additional publication was identified based on our screening of references. Thus, in total, this update for adult patients includes thirty different population pharmacokinetic analyses conducted in fifteen countries, including 9 in China, 4 in the USA, 4 in South Korea, 2 in Belgium, and 2 in Spain, as well as one study in each of Australia, Chile, France, Germany, Japan, the Netherlands, Saudi Arabia, Serbia, Taiwan, and Thailand. The characteristics of the populations of all studies are summarized in Table 2.1. The total number of patients recruited in every study varied widely, and ranged from 9 patients (such as in Escobar et al.) to 1812 patients (such as in Goti et al.), while the median number of patients of all included studies was 72 per study (12, 13). Furthermore, ten studies had 30 patients or less (12, 14-23). In general, patients included in these studies subscribed to different special clinical subpopulations, such as critically ill, obese, and trauma patients. However, no specific diagnosis was mentioned in seven studies (22, 24-29). Four studies included a control cohort (16, 17, 30, 31).

2.3.2 Clinical Protocol and Study Designs

As the design nature of most of the studies was retrospective therapeutic drug monitoring, vancomycin was administered, mostly, according to the respective hospital standard of care dosage regimen. The study design of the remaining articles (n=11) was a prospective observational pharmacokinetic study (Table 2.2) (12, 14, 15, 17-22, 26, 32). Vancomycin route

of administration was either through an intermittent or continuous intravenous (IV) infusion. While almost all studies reported intermittent IV administration, continuous infusion in four articles was used (20, 25, 33, 34). The only exception was by Li et al. who reported an additional intraventricular administration of 10 mg combined with the IV administration of 990 mg to yield a total vancomycin dose of 1000 mg (19). Further, all vancomycin samples were blood samples except for in three studies, in which additional CSF samples were withdrawn, as well (19-21). The number of samples per patient varied widely, even within the same study. For example, Goti et al. reported a range of 1 to 36 samples per patient (13). Overall, eight studies implemented a rich sampling scheme of more than six samples per patient (Table 2.2) (12, 15, 17-22). Sampling at a steady-state condition was reported in eleven studies (14, 17, 19, 20, 24, 26, 31-33, 35, 36). In contrast, three studies reported obtaining vancomycin samples before achieving steady-state conditions (15, 16, 18). The rest of the studies (n=16) did not report the steady-state status. To quantify these samples, most of the studies used a variety of immunoassay, while five quantified vancomycin levels using liquid chromatographic methods (Table 2.3) (12, 19-21, 28).

2.3.3 Population Pharmacokinetic Analysis

As shown in Table 2.4, the vast majority of the included studies used NONMEM to analyze their data and implement the PopPK models. Phoenix NLME and Monolix software packages were used in four and two studies, respectively (Table 2.4) (18-21, 23, 35). The bootstrap procedure, which is an internal evaluation method, was used in 22 studies. In addition, external evaluations were used in 10 studies. However, all studies performed other forms of model evaluations, goodness-of-fit plots, and model diagnostics plots. Vancomycin PK was best described by a two-compartment model in fourteen analyses (12, 13, 15, 16, 18, 22, 23, 27, 31, 35, 37-40). Nevertheless, many studies opted for a one-compartment model (n=13), owing to its simplicity

and clinical practicality (14), the sparsity of data (24, 28, 29, 32-34), and the condensation of the samples around trough levels while at steady-state conditions (24, 28, 30, 32). Three-compartment models were found more suitable to describe the additional CSF compartment in three papers (19-21).

2.3.4 Estimated Clearance

In general, these PopPK analyses estimated the typical CL of vancomycin widely, ranging from 0.334 to 8.75 L/h (0.0054 to 0.1279 L/h/kg) and having a median of 3.22 L/h (interquartile range, 2.32-4.9), which is equivalent to 0.0458 L/h/kg (interquartile range, 0.03-0.077) (Tables 2.5, 2.6, and 2.7). It should be noticed that these statistics excluded all vancomycin CL values from the CSF compartments (19-21). High estimated CL values (above the third interquartile of 4.9 L/h) were observed in the following cases: patients with or during postoperative neurosurgery, post-craniotomy meningitis, early and late phase of neurosurgical treatment, obese, open-heart surgery, patients with CL_{CR} < 80 mL/min, and in a Chinese population with CL estimated by cystatin C (14, 18-21, 26, 29, 30, 32). Estimated CL in the lower spectrum (below the first interquartile of 2.32 L/h) were observed in the following ten cases: in South Korean patients with continuous renal replacement therapy (CRRT) or hemodialysis, non-hemodialysis CL in Austrian patients during high-flux hemodialysis, Serbian patients with normal or impaired renal function, men and women with post-sternotomy mediastinitis, Thai patients, trauma patients when taking furosemide, and ICU patients with mechanical ventilation (23, 27, 31, 34, 38-40).

2.3.5 Estimated Volume of Distribution

A drastic variation in the estimated volumes of distribution was observed. For one-compartment models, the lowest estimated value was 7.12 L (0.088 L/kg), which was for patients with normal kidney function (31). On the contrary, the highest estimated V was 154 L (2.53 L/kg), which was

for geriatric patients (36). In the case of two-compartment models, estimates of both the central (V_1) and peripheral (V_2) volume compartments varied widely. However, when considering the total volume of distribution (i.e. $V_{total} = V_1+V_2$), the lowest was 29.2 L (0.417 L/kg), which was estimated for patients with high-volume hemofiltration (12). The two highest estimated V_{total} were 501.8 L (6.97 L/kg) and 478 L (6.64 L/kg) for geriatric and non-geriatric adult trauma patients, respectively (40). In addition, the overall median for all estimated V_{total}, including one-, two-, and three-compartment models, was 80.7 (range: 7.12-501.8; interquartile range: 47.8 - 97.15) L, which is equivalent to 1.16 (range: 0.088-6.97; interquartile range: 0.72-1.465) L/kg (Tables 2.5, 2.6, and 2.7).

2.3.6 Modeling of the Random Effects

With the exception of a proportional random between-subject variability (BSV) model in Purwonugroho et al. (27), almost all studies used an exponential model (Tables 2.5, 2.6, and 2.7). However, we were not able to infer the type of random BSV model in one study (24). The highest BSV values were observed in a BSV estimation on V_2 with a coefficient of variation (CV) of 101% (16), followed by an estimation of BSV on CL with a CV of 99.2% (39). Residual error models were expressed with the combined additive proportional, proportional, additive, and exponential models in 11, 9, 4, and 3 studies, respectively. Further, a power error model was used in one study (21). The type of residual error models used in the remaining two studies was not inferable (12, 41).

2.3.7 Inclusion of Covariates

Covariates tested and included in the models varied depending on the special subpopulation (Table 2.8). Methods of covariates selection include biological plausibility and stepwise covariate modeling (SCM). A consistent significant covariate is CL_{CR}, which was incorporated

into twenty PopPK models (13-15, 17-19, 22, 25, 27-30, 32-36, 39, 40). One possible explanation for CL_{CR} to have not emerged as a significant covariate in some of the remaining ten studies was the presence of renal deficiency. Bodyweight appeared frequently to describe V_d. Two studies reported a significant effect of concomitant drugs, including aminoglycosides and furosemide (30, 40). Other rarely reported significant covariates on CL include albumin, aspartate aminotransferase, fibrinogen (18, 31). In addition, rarely reported significant covariates on V_d include fat-free mass and age (37).

2.4 Discussion

Vancomycin is a vital antibiotic in the management of MRSA infections (1, 2). Evidenced by the large publications number, dose optimization of vancomycin has been an ongoing research interest given its wide between- and within-subject variability, emerging resistance, evolving therapeutic targets, and potential nephrotoxicity (4). In fact, more than seventy population pharmacokinetic analyses have been published since 2011 that aimed at describing vancomycin pharmacokinetics in adults and children. Thus, an update to our previous review was deemed necessary (1).

The present update includes thirty different population pharmacokinetics analyses conducted in fifteen countries. No systematic trends were observed in the PK estimates (i.e. CL and V_d) between different countries. The estimated CL and V_{total} varied widely between studies, ranging from 0.334 to 8.75 L/h (0.03-0.078 L/h/kg) and from 7.12 to 501.8 L (0.097- 6.97 L/kg), respectively. However, one limitation to this statistic is the lack of uniformity in the reported V_d units (i.e., seven articles reported a weight-adjusted volume of distribution, while others reported an absolute V_d), as well as weight adjustments method, as six studies reported the median weight while the rest reported the mean weight. Furthermore, interpretation of such ranges should be

viewed cautiously considering the overall PopPK settings, including differences in the sample sizes, study designs, intensities of sampling, methods of covariates modeling, and parametrization. Thus, these structural and statistical model differences might render generalizations between models inaccurate.

Most of the studies aimed primarily at describing vancomycin pharmacokinetics in special subpopulations, including critically ill, obese, neutropenic, geriatric, trauma, and renal impaired patients, as well as the patients who underwent surgery, and mechanical support (e.g. hemodialysis, hemofiltration, renal replacement therapy, and extracorporeal membrane oxygenation [ECMO]) (12-21, 23, 30-35, 37, 38, 40, 42). Therefore, we will partition our discussion section accordingly although clinical groups might not be mutually exclusive. The primary objectives of the remaining studies were to describe vancomycin PopPK in Chinese or Thai populations, as well as to investigate the effect of age, MRSA, or serum cystatin C and other renal function descriptors on the PK of vancomycin. In addition, almost all studies conducted Monte Carlo simulations based on their developed PopPK models to optimize vancomycin dosage regimens in the respective subpopulation. However, a clinical discussion about vancomycin optimal dosage regimens in special subpopulations is beyond the scope of this review, considering the current shift in the therapeutic target from using trough levels as a surrogate marker to directly estimating AUC/MIC to guide vancomycin dosing (2, 4).

This review includes all adults (i.e., young and elderly) as a single patient group. However, differences in vancomycin PK parameters between young and older patients (geriatrics) might be clinically anticipated. A study on Chinese geriatric patients (age ≥ 65) with pneumonia estimated vancomycin CL to be 2.45 L/h (36). Although values of vancomycin CL in geriatrics might seem

lower compared to younger patients, this is likely due to the natural decline of renal function (28).

The predominant renal route of excretion for vancomycin instigated many researchers to study the influence of different descriptors of renal function on the predictability of PopPK models (14, 19, 25-27, 31). While serum creatinine has been widely used as a marker for renal function, it has few pitfalls, including limited accuracy in elderlies, patients with low muscle mass, and in a case of myopathy. Cystatin C might serve as an alternative biomarker, owing to its stable production rate between different genders, patients with different muscle masses, and during different health conditions (e.g. acute inflammatory responses) (24, 26). This led some to believe that cystatin C is a better predictor of vancomycin clearance compared to CL_{CR} (24, 26). Chung et al. concluded the existence of a better correlation between vancomycin CL and cystatin C compared to serum creatinine (24). In addition, Liu et al. reported that the estimation of the glomerular filtration rate (GFR) using cystatin C outperformed the estimation using serum creatinine in predicting vancomycin therapeutic targets (26). Other renal function descriptors, such as Modification of Diet in Renal Disease (MDRD) and its variations, were evaluated by Ji et al., who concluded no significant differences between these various descriptors compared to using Cockcroft–Gault equation (25).

Many of the studies included in this review were designed as retrospective therapeutic drug monitoring studies (13, 16, 23-25, 27-31, 33-36, 38-40, 42). In addition, according to the clinical practice during the period these studies were being conducted, many aimed at achieving a predefined trough level around steady-state. A large enough sample size was a limitation for many studies (12, 14-23). Thus, parameter estimates and the power to detect significant covariates might have been slightly compromised. While the influence of more than 60 different

covariates was evaluated, the most identified significant covariate was CL_{CR}. However, 10 of the studies (33%) did not report it as a significant covariate, but, rather, modeled using other renal function descriptors, such as GFR, serum creatinine (SCR), continuous renal replacement therapy (CRRT) status, hemodialysis, or none of the renal function descriptors (Tables 2.5, 2.6, and 2.7). Other covariates, such as bodyweight and age, were frequently included in the models. Stepwise covariates selection was the most commonly reported method.

2.4.1 Critically Ill, Trauma, and Cardiac Surgery Patients

Existing evidence substantiates the belief that critical illnesses, such as cardiogenic shock and organ transplantation, as well as clinical intervention and mechanical support during critical illness, can alter the pharmacokinetics of a drug (43-46). As a result of such alterations, many studies were conducted to warrant optimal therapeutic vancomycin levels (12, 15-17, 23, 34). Moreover, V_d might be a concern in critically ill septic patients. Roberts et al. estimate of V_d in critically ill septic patients was relatively high (i.e. 1.5 L/kg) (33). However, Medellín-Garibay et al. estimated V_d to be 1.03 L/kg in a critically ill population, many of whom (44%) were septic, and of which 50% suffered septic shock (34). Moreover, unique significant covariates in this subpopulation include mechanical ventilation, which was reported to decrease CL by 20% compared to the control group of the respective study (34).

Medellin-Garibay et al. studied the influence of trauma on the PK parameters of vancomycin. The reported V_2 value in this study was noticeably high (5.9 L/kg), while the reported intercompartmental clearance (Q) was noticeably low (0.81 L/h) (40). Multiple complications during invasive open-heart surgery can lead to an altered PK parameter of vancomycin. Alqahtani et al. studied patients who underwent open-heart surgery and reported a slightly elevated CL value of 6.13 L/h and a low V_2 of 3.88 L (18). On the other hand, Mangin et al.

aimed at describing vancomycin PK in post-mediastinitis critically ill patients (23). The estimated PK parameters were relatively low, with values of 1.91 L/h, 1.25 L/h, and 21.9 L for CL in men, CL in women, V_1, respectively. Noteworthy, CL was reported to increase proportionally with bodyweight, but inverse proportionally with serum creatinine, as well as the severity of disease at the time of ICU admission (SAPII). In addition, CL_{CR} was not included in the model, probably since a proportion of the population suffered renal impairment. Interestingly, Q was influenced by diabetes mellites, which was attributed to the effect of microangiopathy defecting the permeability of tissues (23).

2.4.2 Patients on Extracorporeal Membrane Oxygenation

Numerous studies aimed at understating and quantifying the impact of ECMO on the PK parameters of vancomycin (16, 46). The use of ECMO provides support for life-threatening cardiac, cardiorespiratory, and respiratory failures (47). However, many details might vary between ECMO procedures. Overall, the procedure involves external blood oxygenation using an external circuit. However, there are three types of cannulation modes used to drain a patient's blood, including a veno-venous (VV), veno-arterial (VA) or a hybrid (VVA) mode. Prevalence of infections, risk of nephrotoxicity, sequestration effect, and alterations to the renal and cardiovascular systems substantiated the clinical interest in ECMO subpopulation (15-17, 44-50).

In this review, three studies aimed at describing the pharmacokinetics of vancomycin in adults during ECMO (15-17). It is to be noticed that the additional non-compartmental analyses conducted in Wu et al. and Donadello et al. did not meet the inclusion criteria and, thus, were excluded from this review (16, 17). Wu et al. reported a significant decrease in vancomycin CL compared to a matched cohort when a specific pump is used (i.e. roller pump) (17). However, a similar effect (i.e. decrease in CL) did not appear when using a centrifugal pump, which might

be attributed to the fact that those patients were less critically ill in comparison to the ECMO patients with a roller pump (17). Excluding the roller pump case, all three studies concluded no to minimal clinical significance regarding any differences in vancomycin PK parameters between ECMO and non-ECMO adult patients. This conclusion seems consistent regardless of study design (i.e. matched control cohort), sampling frequency (i.e. rich versus sparse), and the significant covariates affecting PK parameters. Nevertheless, PK parameter estimates varied widely between these studies (15-17). The wide variation in the estimated parameters might be attributed to the very small sample size recruited in every study, significant differences between study populations (e.g. inclusion of patients with end-organ dysfunction and renal replacement therapy), and other potential confounding factors, including priming fluids and the specifications of ECMO apparatus (48-50). Further, a relatively high BSV was estimated on CL (CV=77%) by Moore et al. (15), and on V_2 (CV=101%) by Donadello et al.(16) Therefore, although a larger body of evidence favors no significant effect, the exact role of ECMO on the PK of vancomycin might remain undefined (47).

2.4.3 Morbidly Obese Patients

The standard practice of dosing vancomycin based on total body weight might pose additional risks of nephrotoxicity for obese patients (51, 52). Evidence shows that a bodyweight heavier than 101 kg might be associated with increased incidences of nephrotoxicity, which might be attributed to higher drug exposure or large daily doses of more than 4000 mg/day (51, 52). Our report included one study that aimed at describing vancomycin PK in morbidly obese patients (BMI $\geq$ 40 kg/m^2) (14). This study estimated a V_d of 0.51 L/kg (14). Despite evaluating many covariates, V was best correlated with total bodyweight (14). Finally, it is worth mentioning that

Bury et al. reported that allometric scaling to fat-free mass in non-obese patients was associated with a significant improvement in model fit (37).

2.4.4 Patients with Hematological and Oncological Disorders

Previous evidence suggests increased CL in hematological diseases (53). While vancomycin is crucial in the management of febrile neutropenia, Bury et al. reported a significant association between neutropenia and an increase in vancomycin clearance by 27.7% (37). Noteworthy, the population in Bury et al. included patients with solid tumors and hematological malignancies (37). Moreover, during a hematopoietic stem cell transplant (allo-HSCT), Okada et al. suggested that the dilution effect of the breakdown of hematopoietic stem cells during allo-HSCT pre-treatments might lead to an overestimation of creatinine clearance, which in turn can influence the estimation of vancomycin clearance (35). Additionally, Okada et al. reported a relatively normal total volume of distribution value of 95.3 (39.2 and 56.1 for V_1 and V_2, respectively) (35).

2.4.5 Neurosurgical Patients

Numerous studies reported decreased vancomycin serum levels and the need for higher doses of vancomycin in neurosurgical populations compared to other patients (54-56). This can be attributed to the physiological changes associated with neurosurgery which can be manifested in a form of augmented renal clearance (42, 56). Kim et al. reported significantly higher values of CL in neurosurgical patients compared to the control group of the corresponding study of 0.10 ± 0.13 versus 0.07 ± 0.025 L/h/kg for the neurosurgical and control group, respectively (30). However, the limitation of Kim et al. is that the design of the study was not control-matched, with the surgical group being significantly younger and having lower serum creatinine levels (30).

Additional three studies confirmed the trend of elevated CL, reporting 7.8, 8.7, and 11.87 L/h (19-21). These elevated values were attributed to hyperosmotic diuretics administered to decrease the intracranial pressure and the hypervolemia status of these patients (19-21). In addition, estimations of the V_1 were consistently low in these studies (i.e. 15.16, 27.84, and 11.87 L) (19-21). Another investigated neurosurgical condition was post-craniotomy meningitis, which is a life-threatening condition that might require admission to the intensive care unit (32). Lin et al. estimation of CL in patients with post-craniotomy meningitis was 7.56 L/h, which confirms the trend of elevated CL in neurosurgical patients (32).

2.4.6 Kidney Disease, Renal Replacement Therapy, and Hemodialysis

2.4.6.1 Chronic Kidney disease

The objective of Zaric et al. study was to identify the determinants of vancomycin clearance in patients with mild or moderate chronic kidney disease (CKD), as well as patients with normal kidney function (31). The authors reported that the daily dose of vancomycin and serum levels of aspartate aminotransferase (AST) influence vancomycin clearance in CKD patients. Serum AST levels were shown to correlate with reductions in glomerular filtration rate in CKD patients (31, 57, 58). The correlation between higher doses and higher clearance values was explained by the possible role of vancomycin tubular toxicity in reducing renal reabsorption, leading to higher CL values. In contrast, fibrinogen, an inflammation biomarker, emerged as a determinant of vancomycin CL in the control group (i.e. patients with normal kidney function). A noticeable observation from this article is that significant vancomycin levels were as high as 200 mg/L and 100 mg/L for normal and CKD patients, respectively. Additionally, the study was limited to one measurement of vancomycin concentration per patient (31).

2.4.6.2 Hemodialysis, Hemofiltration, and Renal Replacement Therapy

The estimated vancomycin CL and V_1 in patients receiving hemodialysis were reported to differ significantly compared to non-hemodialytic patients (13, 39). For example, in the former group, Goti et al. reported reduced CL and V_1 estimates by 35% (from 4.5 to 3.15 L/h) and 50% (from 58.4 to 29.2 L), respectively (13). Furthermore, Bae et al. reported CL to be drastically different in patients receiving hemodialysis (CL = 0.334 L/h) compared to patients not receiving hemodialysis or renal replacement therapy (CL = 2.82 L/h) (39). Moreover, CL was associated with an elevated BSV, as high as 99.2% (39). During high-flux hemodialysis, Hui et al. used two CL parameters to express non-hemodialysis and hemodialysis vancomycin CL, reporting CL estimates of 0.443 and 3.86 L/h, respectively (38). Levels of BSV on V_d were relatively high for the hemodialysis subpopulation. For example, Hui et al. reported BSVs on V_1 and V_2 of 84.5% and 94.8%, respectively (38). Moreover, Goti et al. estimated the value of BSV on V_1 to be 81.6% (13).

Renal replacement therapy (RRT) appeared to be associated with a drastic reduction in the estimated CL values (0.716 for patients receiving RRT compared to 2.82 L/h for patients not receiving RRT) (39). However, Udy et al. estimated the median of CL in septic critically ill patients receiving RRT to be 2.9 L/h (41). A similar CL value (i.e. 2.9 L/h) was reported by Escobar et al. although the study population was critically ill patients with refractory septic shock receiving continuous venous hemofiltration (12).

2.5 Conclusion

This review included thirty population pharmacokinetic analyses on vancomycin. Most of the studies aimed, initially, at developing a PopPK model in a special subpopulation in order to determine the PK profile and the corresponding PK parameters that are key for the optimization

of vancomycin dosage regimens. In addition, evaluation of the influence of more than 60 covariates on the PK parameters revealed consistent significant covariates, including CL_{CR} and bodyweight. Studies included in this review reported very wide ranges of estimated CL and V_{total}. Reported between-subject variability was as high as 99.2% on CL, and as high as 101% on V_2. While this review was meant to lay out a comprehensive synthesis of reported PopPK observations in various patients' subpopulations, additional research with pooled data from different subpopulations might be warranted to draw a solid conclusion about the need for and the way of adjusting vancomycin dosage regimens in a specific subpopulation.

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Table 2. 1 Summary of patients' demographics for all PopPK studies included in this review

Study	Publication year	Country	Population						Assessment of renal function
			Patients group	N (male/female)	Age (y)[a]	Bodyweight (kg)[a]	BMI (kg/m^2)[a]	CL_{CR} ($mL/min/1.73\ m^2$)[a]	
Adane et al. (1)	2015	USA	Extremely obese	29 (19/10)	43.0 (38.5-53.0)[b]	147.6 (142.8-178.3)[b]	49.5 (44.3-54.8)[b]	124.8 (106-133.9)[b]	Normal
Alqahtani et al. (2)	2018	Saudi Arabia	Open-heart surgery	28 (17/11)	51.7 ± 15.9 [18-78]	79.6 ± 17 [52-111.8]	29.8 ± 5.6 [20.2-41.9]	83.5 ± 29.3 [33.4-125]	NR
Bae et al. (3)	2019	South Korea	General	220 (139/81)	63 [21-98]	61.6 [30.0-126.7]	NR	77.0 (4.57–279)	Patients underwent CRRT (n=9) and HD (n=20)
Bury et al. (4)	2019	Netherlands	Neutropenia	116 (67/49)	61.4 ± 13.4	NR	25.5 (5.9)[b]	150 (140)[b]	NR
Chung et al.(5)	2013	South Korea	General	678 (400/278)	56 [18-96]	62.3 [27-140]	NR	NR	Normal
Deng et al. (6)	2013	China	Chinese adults	72 (53/19)	54.07 ± 18.38 [18-99]	61.12 ± 10.70 [37-85]	NR	82.09 ± 36.19 [10.56-175.1]	NR
Donadello et al. (7)	2014	Belgium	ECMO	11 (4/7)	43 [19-59]	70 [46-86]	26 [18-29]	64 [39-99]	Patients received CRRT (n=7)
			Control	11 (5/6)	55 [24-64]	70 [47-95]	24 [18-29]	61 [46-109]	
Escobar et al. (8)	2014	Chile	High-volume hemofiltration	9 (5/4)	57 ± 14	70 ± 18	27 ± 9	NR	Patients underwent hemofiltration, with six anuric and three oliguric patients before the beginning of the HVHF sessions
Goti et al. (9)	2018	USA	Hemodialysis	1812 (969/843)	57 [17-101][c]	79 [33-255][c]	NR	62 [4–150][c]	Included many patients with end-stage renal disease
Hui et al. (10)	2019	Australia	Hemodialysis	48 (38/10)[d]	61.5 [23-86][c]	78 [40-226][c]	NR	NR	Patients underwent hemodialysis; likely end-stage renal disease
Ji et al. (11)	2018	China	Chinese	160 (106/54)	78 [42-95][c]	65 [38-90][c]	22.31 [12.85-36.89][c]	58.02 (5.45–224.0)[c]	NR
Kim et al. (12)	2016	South Korea	Neurosurgical	64 (30/34)	50.6 ± 15.0	63.2 ± 11.6	NR	113.6 ± 48.3	Included renally impaired patients
			Control	68 (37/31)	61.6 ± 15.7	61.0 ± 12.7	NR	79.0 ± 44.0	
Li et al. (13)	2015	China	Postoperative neurosurgical	16 (9/7)	46.8 ± 14.0 [25-67]	69.8 ± 9.9 [51-84]	NR	116.2 ± 31.5 [71-182]	Normal
Li et al. (14)	2016	China	Postoperative neurosurgical	20 (10/10)	45.25 ± 15.96 [19-70]	68.90 ± 12.07 [46-87]	NR	NR	Normal
Li et al. (15)	2017	China	Postoperative neurosurgical	25 (18/7)	50.2 ± 17.0 (21-81)	69.4 ± 11.9 (46-93)	NR	142.8 ± 51.7 [73.1-246.4]	Normal
Lim et al. (16)	2014	South Korea	Infected with MRSA	20 (15/5)	59.3 ± 12.9	63.1 ± 15.7	NR	96.6 ± 31.1	Normal
Lin et al. (17)	2016	China	Post-craniotomy meningitis	100 (66/34)	51.6 ± 16.9 [18-86]	59.1 ± 10.0 [38-85]	NR	104.7 ± 43.9 [9.5-216.9]	NR
Liu et al. (18)	2019	China	General	200 (128/72)	47.4 ± 15.42	61.3 ± 12.06	NR	123.75 ± 59.96	NR
Mangin et al. (19)	2014	France	Post-Sternotomy Mediastinitis	30 (26/4)	63 [35-81][c]	82 [62-104][c]	28 [22-36][c]	NR	NR
Medellín-Garibay et al. (20)	2015	Spain	Trauma	118 (53/65)	74.3 ± 14	72 ± 15	27.5 ± 5	90.5 ± 52	NR
Medellín-Garibay et al. (21)	2017	Spain	Critically ill	54 (38/16)	65.0 ± 12.3	75.0 ± 20.1	28.5 ± 7.0	106.3 ± 64.5 [27.2-271.6]	Included patients (n=15) with CL_{CR}< 60 ($ml/min/1.73\ m^2$)
Moore et al. (22)	2016	USA	ECMO	14 (11/3)	47 ± 16 [19-72]	95 ± 27	NR	84 ± 37	Included renally impaired patients (n=7)

Study	Publication year	Country	Population						Assessment of renal function
			Patients group	N (male/female)	Age (y)[a]	Bodyweight (kg)[a]	BMI (kg/m^2)[a]	CL_{CR} ($mL/min/1.73\ m^2$)[a]	
Okada et al. (23)	2018	Japan	Allogeneic hematopoietic stem-cell transplantation	75 (49/26)	49 [17-69]	59.4 [39.4-104.5]	NR	113 [47-253]	Included patients (n=6) with moderate renal impairment
Purwonugroho et al. (24)	2012	Thailand	Thai	212 (112/100)	66.62 ± 18.38	57.64 ± 11.62	NR	35.07 ± 29.83	Included renally impaired patients
Roberts et al. (25)	2011	Belgium	Critically ill (septic)	206 (127/79)	58.1 ± 14.8	74.8 ± 15.8	25.9 ± 5.4	90.7 ± 60.4	NR
Udy et al. (26)	2013	Belgium	Critically ill (septic patients undergoing CRRT)	81 (53/28)	61.0 ± 15.6	83.4 ± 22.1	NR	NR	Patients underwent CRRT
Usman et al. (27)	2018	Germany	General	144 (93/51)	62 [16-88][c]	79.5 [40-177][c]	NR	89.8 (11.3–313.6)[b]	NR
Wu et al. (28)	2016	Taiwan	ECMO	11 (6/5)	47.18 ± 16.85	66.57 ± 17.53	NR	74.1 ± 25.42	Included patients (n=3) with CL_{CR}< 60 ($ml/min/1.73\ m^2$)
			Control	11 (6/5)	49.00 ± 17.16	64.07 ± 12.34		84.41 ± 34.47	Included patients (n=4) with CL_{CR}< 60 ($ml/min/1.73\ m^2$)
Zaric et al. (29)	2018	Serbia	Impaired kidney function	78 (46/32)	67.00 ± 10.74 [33-86]	78.52 ± 16.64 [60-180]	NR	54.38 ± 17.70 [30-87]	Patients with mild to moderate chronic kidney failure
			Normal kidney function	32 (21/11)	59.15 ± 14.46 [27-86]	81.37 ± 10.11 [60-103]	NR	112.90 ± 10.94 [90-120]	Normal
Zhou et al. (30)	2019	China	Geriatric	70 (49/21)	78.3 ± 6.96	60.7 ± 10.2	NR	56.3 ± 22.1	NR

CL_{CR}: creatinine clearance, BMI: body mass index, NR: not reported, ECMO: extracorporeal membrane oxygenation, CRRT: continuous renal replacement therapy, HD: hemodialysis, HVHF: high-volume hemofiltration, MRSA: methicillin-resistant Staphylococcus aureus

[a]Values are expressed as mean ± standard deviation [range] (interquartile range)

[b]Values are expressed as median (interquartile range)

[c]Values are expressed as median [range]

Table 2. 2 Summary of the clinical protocols for studies included in this review

Study	Study type	Vancomycin administration		Samples			
		Dosage regimen	Administered doses (mg)[a]	samples per patient	Total samples	Sampling at steady state	Sampling frequency
Adane et al. (1)	Prospective pharmacokinetic study	Typically: 15 mg/kg	4000 [3625–4375][b] mg/day	3.2[c]	93	Yes	Peak, trough, and random
Alqahtani et al. (2)	Prospective pharmacokinetic study (rich sampling design)	1000 mg two hours before skin incision, then q12h for two days	Twelve patients received additional doses, as their surgeries lasted for more than 4 h	6	168	No	Six blood samples: before skin incision, at the beginning of the cardio-pulmonary bypass (CPB), 1h after the beginning of the CPB, before skin closure, and 24 h and 48 h after the first dose
Bae et al. (3)	Retrospective (TDM)	NR	NR	4.64[c]	1020	NR	NR
Bury et al. (4)	NR	NR	NR	6.4[c]	742	NR	Peak and trough
Chung et al. (5)	Retrospective	NR	1922 [250-4500] mg/day	2.0[c]	1373	Yes	Peak and trough
Deng et al. (6)	Retrospective (TDM)	500 or 1000 mg over 1 h	NR	2.32[c]	167	NR	Peak and trough
Donadello et al. (7)	Retrospective	LD: 35 mg/kg over 4 h; MD: the respective hospital standard of care	ECMO, LD: 2500 [1610 to 2975][b]; MD: 1125 [750 to 3000][b] mg/day	ECMO: 3	ECMO: 33[c]	sampled within first 24 h	4, 12, and 24 h
			Control, LD: 2450 [1645 to 3500][b]; MD: 1,200 [750 to 2500][b] mg/day	Control: 3	Control: 33 [c]		
Escobar et al. (8)	Prospective pharmacokinetic study (rich sampling design)	1 g q24h	NR	8	68	NR	0, 0.5, 1, 2, 4, 6, 9 and 12 h
Goti et al. (9)	Retrospective (TDM)	NR	NR	One sample per patient in 1215 patients out of the total 1812 patients	2765	NR	NR
Hui et al. (10)	Retrospective (TDM)	hospital 1: 1000–1500 mg, as long as vancomycin concentrations of less than 20 mg/L were achieved; hospital 2: (i) off HFHD: weight-based LD and MD of 25 and 20mg/kg, respectively, (ii) on HFHD: weight-based LD and MD of 30 and 25mg/kg, respectively, as long as vancomycin concentrations of less than 25mg/L were achieved.	LD: 1500 [1000–4500][b] mg ; MD: 1500 [500–4500][b] mg	3 [1-22][b]	180	NR	NR
Ji et al. (11)	Retrospective	1000 mg q12h	NR	2 [1-17][a]	NR	NR	Trough
Kim et al. (12)	Retrospective (TDM)	The respective hospital standard of care	The initial dose for the neurosurgical group: 1981 ± 219 mg/day	Neurosurgical: 3 [1-12][a]	Neurosurgical: 181	NR	NR
			The initial dose for the control group: 1810 ± 387 mg/day	Control: 2 [1-21][a]	Control: 178		
Li et al. (13)	Prospective pharmacokinetic study (rich sampling design)	1000 mg IV over 1 h, then 9000 mg continuous IV infusion over the following three days at a rate of 125 mg/h	NR	17.75[c]	284	Yes	0, 1, 1.08, 1.25, 1.5, 2, 3, 5, 7, 9, 13, 17, 21, 25, 33, 41, 49, 57, 65, and 73 h
Li et al. (14)	Prospective pharmacokinetic study	Low dose group: total of 6.5 g (0.5 g over 1 h, then 6 g continuous infusion over 3	NR	19.5[c]	389	NR	0, 1, 1.08, 1.25, 1.5, 2, 3, 5, 7, 9, 13, 17, 21, 25, 33, 41, 49, 57, 65,

Study	Study type	Vancomycin administration		Samples			
		Dosage regimen	Administered doses (mg)[a]	samples per patient	Total samples	Sampling at steady state	Sampling frequency
	(rich sampling design)	days (0.083 g/h)); high dose group: total dose of 10 g (1 g over 1 h, then 9.0 g continuous infusion over 3 days (0.125 g/h))					and 73 h
Li et al. (15)	Prospective pharmacokinetic study (rich sampling design)	1000 mg (10 mg intraventricular and 990 mg IV) q12h	NR	10.48[c]	262	Yes	72.25, 72.5, 73, 75, 77, 80 h
Lim et al. (16)	Prospective pharmacokinetic study (rich sampling design)	1000 mg over 2 h q12h	NR	5.6[c]	112	NR	0, 0.75, 1–3, 3–5, 5–8, 8–12, 72 and 144 h
Lin et al. (17)	Prospective pharmacokinetic study (trough samples)	The respective hospital standard of care	1910.6 ± 314.2 [1000-3000]	1.71[c]	179	Yes	Trough
Liu et al. (18)	Prospective pharmacokinetic study	Doses of 250, 500, 750, 1000, 1250 or 1500 mg over 1 h	916.60 ± 226.56	5[c]	514	Yes	Trough and random levels at 1, 2, 5, or 7 h
Mangin et al. (19)	Retrospective (TDM)	The respective hospital standard of care	NR	14 [1-34][b]	359	NR	Trough and at the end of hemodialysis sessions
Medellín-Garibay et al. (20)	Retrospective (TDM)	The respective hospital standard of care	Initial dose: 25.3 ± 7.8 mg/kg/day	[1-16][a]	392	NR	Peak and trough
Medellín-Garibay et al. (21)	Retrospective (TDM)	The respective hospital standard of care	80% of the patients received LD: 12 ± 5 mg/kg, and MD: 60 mg/h [14 to 180 mg/h]	8 [1-36][a]	874	NR	NR
Moore et al. (22)	Prospective pharmacokinetic study (rich sampling design)	The respective hospital standard of care	NR	4.6[c]	65	Sampled after first intermittent infusion	Routine TDM trough levels, and at 30, 60, 120, 240, and 360 min
Okada et al. (23)	Retrospective	NR	2400 [1000-4500][b] mg/day	2.8[c]	217	Yes	Peak, trough, and as necessary
Purwonugroho et al. (24)	Retrospective (TDM)	The respective hospital standard of care	NR	1.84	319	NR	Peak, trough, and random
Roberts et al. (25)	Retrospective (TDM)	The respective hospital standard of care	NR	NR	NR	Yes (pseudo-steady-state)	Daily
Udy et al. (26)	Retrospective (TDM)	The respective hospital standard of care	LD: 1640 ± 550 mg/kg; MD for day 1: Infusion dose 23.7±8.1 (mg/kg/24 h)	[2 -3][a]	199	NR	Daily at 8 a.m. and at 24, 48 and 72 h
Usman et al. (27)	Retrospective (TDM)	The respective hospital standard of care	1000 [500-1500][b]	1.8 [1-7][a]	256	NR	Trough
Wu et al. (28)	Prospective pharmacokinetic study (rich sampling design)	LD: 15-25 mg/kg; MD: According to K = CL/V_d, where V_d = 0.7 L/kg, and CL = 0.695*CL_{cr}, to achieve trough levels within 10-20 mg/L	NR	ECMO: 10[c] Control: 10[c]	ECMO: 110[c] Control: 100[c]	Yes	0.5, 1, 2, 3, 5, 7, 11, 23, 35, 47 h
Zaric et al. (29)	Retrospective (TDM)	The respective hospital standard of care	Impaired renal function: 1650 ± 540 [500-3000] mg/day Normal renal function: 1930 ± 430 [1000-3000] mg/day	Impaired kidney function: 1[c] Normal kidney function: 1[c]	Impaired kidney function: 78 Normal kidney function: 32	Yes	NR

Study	Study type	Vancomycin administration		Samples			
		Dosage regimen	Administered doses (mg)[a]	samples per patient	Total samples	Sampling at steady state	Sampling frequency
Zhou et al. (30)	Retrospective (TDM)	Dose 1: 500 mg every 6, 8, 12, 24 or 48 h; dose 2: 1000 mg every 8 or 12 h	1550 ± 770 mg/day	1.79 [1-5][a]	125	Yes	Peak and trough

LD: loading dose, MD: maintenance dose, TDM: therapeutic drug monitoring, IV: intravenous, CL: clearance, V_d: volume of distribution, HFHD: high-volume hemofiltration, NR: not reported
[a]Values are expressed as mean ± standard deviation [range]
[b]Values are expressed as median [range]
[c]Estimated values

Table 2. 3 Vancomycin quantification methods used by the studies included in the review

Study	Quantification method			
	Assay	LLQ (mg/L)	Kit	Instrument
Adane et al. (1)	Particle-enhanced turbidimetric inhibition immunoassay	0.8	VANC Flex Reagent Cartridge (Siemens Healthcare Diagnostics Ltd., Newark, DE)	Dimension clinical chemistry system analyzer (Siemens Healthcare Diagnostics Ltd.)
Alqahtani et al. (2)	Chemiluminescent microparticle immunoassay	0.5	ARCHITECT *i*Vancomycin Assay Kit	Architect I4000SR immunoassay analyzer
Bae et al. (3)	NR	NR	NR	NR
Bury et al. (4)	Spectrophotometric homogeneous enzyme immunoassay	NR†	Emit 2000 Vancomycin Assay	Viva-E system
Chung et al. (5)	Fluorescence polarization immunoassay	NR	NR	Cobas Integra 800 Analyzer (Roche)
Deng et al. (6)	Fluorescence polarization immunoassay	2	NR	TDx FLx assay system (Abbott Laboratories)
Donadello et al. (7)	Particle-enhanced turbidimetric inhibition immunoassay	0.8	Dimension® XPand® (Siemens Healthcare Diagnostics)	NR
Escobar et al. (8)	LC-MS/MS	0.63	NR	Acquity TMUPLC System (Waters Corp., Milford, MA)
Goti et al. (9)	ELISA method	NR	NR	NR
Hui et al. (10)	Chemiluminescent immunoassay	2	ARCHITECT *i*Vancomycin Assay Kit	Architect iVancomycin (Abbott Laboratories, and Advia Centaur, Siemens Healthcare)
Ji et al. (11)	Fluorescence polarization immunoassay	2	Vancomycin protein assay kit (Abbott Laboratories, USA)	TDx-FLx assay system (Abbott Laboratories)
Kim et al. (12)	Chemiluminescent microparticle immunoassay	NR	ARCHITECT *i*Vancomycin Assay Kit	NR
Li et al. (13)	HPLC with UV detection	NR	NR	NR
Li et al. (14)	HPLC with UV detection.	NR	NR	NR
Li et al. (15)	HPLC with UV detection.	NR	NR	NR
Lim et al. (16)	Fluorescence polarization	1.39	NR	COBAS INTEGRA fluorescence polarization system
Lin et al. (17)	Enzyme multiplied immunoassay	2	SYVA Viva-E/V-Twin (Siemens Laboratoires)	NR
Liu et al. (18)	Enzyme multiplied immunoassay technique (EMIT)	2	Vancomycin Assay Test Kit	Siemens Viva-E Drug Testing System
Mangin et al. (19)	Particle-enhanced homogenous turbidimetric immunoassay	2	QMS Vancomycin (Thermo Scientific, Middletown, VA, USA)	NR
Medellín-Garibay et al. (20)	Immunoassay	1.7	NR	Roche/Hitachi Cobas c assay system
Medellín-Garibay	Immunoassay	1.7	NR	Roche/Hitachi Cobas c assay system

Study	Quantification method			
	Assay	LLQ (mg/L)	Kit	Instrument
et al. (21)				
Moore et al. (22)	Glucose-6-phosphate dehydrogenasebased enzyme immunoassay	1.7	NR	Roche Cobas C501 (Roche Diagnostics, Indianapolis, IN)
Okada et al. (23)	Glucose-6-phosphate dehydrogenasebased enzyme immunoassay	2	Emit 2000 Vancomycin Assay	NR
Purwonugroho et al. (24)	Fluorescence polarization immunoassay	2	NR	Axsym system (Abbot Laboratories, Abbot Park, Ill, USA)
Roberts et al. (25)	Fluorescence polarization immunoassay	0.6 (mg/mL)	TDx (Abbott Laboratories)	NR
Udy et al. (26)	Particle-enhanced turbidimetric inhibition immunoassay	0.8	Dimension Xpand (Siemens Healthcare Diagnostics)	NR
Usman et al. (27)	HPLC	0.25	NR	NR
Wu et al. (28)	Fluorescence polarization immunoassay	2	AxSYM system (Abbott Laboratories)	NR
Zaric et al. (29)	Immunoassay	NR	NR	Cobas® e601 Analyzer (Roche Diagnostics, Mannheim, Germany)
Zhou et al. (30)	Chemiluminescent microparticle immunoassay	3	NR	ARCHITECT i1000 system (Abbott Laboratories)

LLQ: lower limit of quantification, HPLC: high-performance liquid chromatography, LC-MS/MS: liquid chromatography-tandem mass spectrometry, NR: not reported
† refer to the article

Table 2. 4 Population pharmacokinetic modeling methods and techniques used by the studies included in the review

Study	Compartments	Modeling		
		Software	Validation	Covariate modeling
Adane et al. (1)	One-compartment	NONMEM 7.3	Internal	SCM
Alqahtani et al. (2)	Two-compartment	Monolix 4.4	Internal	SCM (forward inclusion and backward elimination)
Bae et al. (3)	Two-compartment	NONMEM 7.4	Internal: bootstrap (n=1000)	Visual screening, generalized additive model, SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.01$))
Bury et al. (4)	Two-compartment	NONMEM 7.3	Internal	SCM
Chung et al. (5)	One-compartment	NONMEM 7.1	Internal: bootstrap (n=1000)	Generalized additive model and SCM (forward inclusion and backward elimination)
Deng et al. (6)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=2000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$))
Donadello et al. (7)	Two-compartment	NONMEM 7.2	Internal: bootstrap (n=1000); external validation (n=5)	SCM and biological plausibility
Escobar et al. (8)	Two-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	NR
Goti et al. (9)	Two-compartment	NONMEM 7.3	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Hui et al. (10)	Two-compartment	NONMEM 7.3	Internal: bootstrap (n=1000) and NPDE	SCM
Ji et al. (11)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000) and NPDE; external validation (n=58)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Kim et al. (12)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=2000); external validation: (i) neurosurgical (n=24), and (ii) control (n=26)	SCM
Li et al. (13)	Three-compartment	Phoenix NLME 1.2	Internal (n=2000)	SCM (forward inclusion ($P < 0.01$) and backward elimination ($P < 0.001$))

Study	Compartments	Modeling		
		Software	Validation	Covariate modeling
Li et al. (14)	Three-compartment	Phoenix NLME 1.2	Internal: bootstrap (n=1000); external validation (n=16)	SCM (forward inclusion ($P < 0.01$) and backward elimination ($P < 0.001$))
Li et al. (15)	Three-compartment	Phoenix NLME 7.0	Internal: bootstrap (n=1000)	SCM (forward inclusion and backward elimination)
Lim et al. (16)	Two-compartment	NONMEM 7.1.2	Internal	NR
Lin et al. (17)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=2000), and NPDE; external (n=20)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.01$))
Liu et al. (18)	One-compartment	NONMEM 7.3	Internal: bootstrap (n=1000); external validation (n=74)	SCM (forward inclusion ($P < 0.05$) and stepwise elimination ($P < 0.001$))
Mangin et al. (19)	Two-compartment	Monolix 4.14s	NR	NR
Medellín-Garibay et al. (20)	Two-compartment	NONMEM 7.2	Internal: bootstrap (n=200); external validation (n=40)	Generalized additive model and SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Medellín-Garibay et al. (21)	One-compartment	NONMEM 7.3	Internal: bootstrap (n=1000); external validation (n=18)	Generalized additive model and SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Moore et al. (22)	Two-compartment	NONMEM 7.3	Internal: bootstrap (n=1000)	Full covariate model approach
Okada et al. (23)	Two-compartment	Phoenix NLME 7.0	Internal: bootstrap (n=1000); external validation (20 patients)	SCM (forward inclusion ($P \leq 0.05$) and backward elimination ($p \leq 0.01$))
Purwonugroho et al. (24)	Two-compartment	NONMEM VII	External (n=34)	SCM (forward inclusion and backward elimination)
Roberts et al. (25)	One-compartment	NONMEM 6.1	Internal: bootstrap (n=1000)	SCM and biological plausibility
Udy et al. (26)	One-compartment	NONMEM 6.1	Internal	NR
Usman et al. (27)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.01$))
Wu et al. (28)	One-compartment	NONMEM VI	Internal: bootstrap (n=200)	SCM (forward inclusion and backward elimination)
Zaric et al. (29)	Two-compartment	NONMEM 7.3	Internal: bootstrap (n=200)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.01$))
Zhou et al. (30)	One-compartment	NONMEM 7.3	Internal: bootstrap (n=1000) and NPDE	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.01$))

SCM: Stepwise covariate modeling, NPDE: normalized prediction distribution error, NR: not reported

Table 2. 5 Characteristics of the population pharmacokinetic models developed by the studies included in this review (one-compartment)

Study	CL (L/h)			V_d (L)			BSV		RV		
	Formula	Parameter	Value	Formula	Parameter	Value	CL	V_d	Exponential	Proportional	Additive
Adane et al. (1)	θ_2*(CL_{CR_TBW}/125)	θ_2	6.54	V_d (L/kg) = θ_1* TBW	θ_1	0.51	26.70%	23.90%		18.9%	
Chung et al. (2)	CL_{POP} * (1+θ_{CL_AGE}*[AGE-57]) * (1 + θ_{CL_TBW} * [TBW-60.8]) * (1 + θ_{CL_SCr} * [SCr-0.8]) * (CYSTATIN C/0.91)$^{\theta CL\_CYSTATIN}$ if female, apply 1 + θ_{CL_SEX}	CL_{POP}	4.9	V_{POP} * (1 + θ_{v_AGE}*[AGE-57]) * (1 + θ_{V_TBW} * [TBW-60.8]) if female, apply 1 + $\theta_{\_Vsex}$	V_{POP}	46.2	24.70%	25.10%		6.39%	1.40 mg/L
		θ_{CL_AGE}	-0.00420		θ_{V_age}	0.00580					
		θ_{CL_TBW}	0.00997		θ_{V_TBW}	0.00661					
		θ_{CL_SCr}	-0.322		θ_{V_sex}	-0.119					
		$\theta_{CL\_CYSTATIN}$	-0.780								
		θ_{CL_SEX}	-0.150								
Deng et al. (3)	If CL_{CR} < 80 (mL/min): CL= θ_1 *CL_{CR}	θ_1	0.0654		V_d	47.76	45.35%	39.25%		30.71%	1.21 mg/L
	If CL_{CR} ≥ 80 (mL/min): CL= θ_2	θ_2	4.9								
Ji et al. (4)	CL*(1+θ_{CLCR}*[CL_{CR}-80])*(75/AGE)$^{\theta AGE}$	CL	2.829	V_d = θ_{Vd}	θ_{Vd}	52.14	32.42%	28.87%		26.79%	2.64 ng/mL
		θ_{CLCR}	0.00842								
		θ_{AGE}	0.8143								
Kim et al. (5)	Early phase: θ_1 × (eCL_{CR}/95.8) × θ_3^{TOXI} × θ_4^{LC} + θ_5^{NEUR} Late phase: θ_2 × (eCL_{CR}/95.8) × θ_3^{TOXI} × θ_4^{LC} + θ_5^{NEUR} Early phase in neurosurgical patients only, CL= 7.29 × (eCL_{CR}/113.6)$^{0.563}$ × 0.881^{TOXI} Late phase in neurosurgical patients only, CL= 6.80 × (eCL_{CR}/113.6)$^{0.563}$ × 0.881^{TOXI}	θ_1	4.39	Early phase: θ_6 Late phase: θ_7 Early phase in neurosurgical patients only Late phase in neurosurgical patients only	θ_6	83.7	ω^2 = 0.125			8.59%	1.92 mg/L
		θ_2	3.69		θ_7	107					
		θ_3	0.811		V_d	81.1					
		θ_4	0.511			116					
		θ_5	2.42								
Lin et al. (6)	θ_{TV} * (CL_{CR}/104.71)$^{\theta CLCR}$	θ_{TV}	7.56		V_d	101	31%		ε = 20.2%		
		θ_{CLCr}	0.89								
Liu et al. (7)	θ_{CL} * (GFR/105.5)$^{\theta GFR}$ * (AGE/48.5)$^{\theta AGE}$ * (WT/60)$^{\theta WT}$	θ_{CL}	5.07	V_d = θ_V	θ_V	46.3	20.80%	18.10%		15.90%	1.28 mg/L
		θ_{GFR}	0.524								
		θ_{AGE}	-0.309								
		θ_{WT}	0.491								
Medellín-Garibay et al. (8)	Without mechanical ventilation: CL = θ_1 * (CL_{CR}/100)$^{\theta 3}$ With mechanical ventilation: CL = θ_1 * (CL_{CR}/100)$^{\theta 3}$ * θ_4	θ_1	2.86	V_d (L/kg) = θ_2 * WT	θ_2	1.03	28.40%	49.10%			4.3 mg/L
		θ_3	0.75								
		θ_4	0.8								
Roberts et al. (9)	θ_2 * CL_{CR}/100	θ_2	4.58	TVV (L/kg) = (θ_1 * WT)	θ_1	1.53	38.90%	37.40%		19.9%	2.4 mg/L
Udy et al. (10)	NR	CL (median)	2.9		V_d	0.8 (L/kg)	34.70%	49.80%		†	
Usman et al. (11)	θ_{CL*} (1+θ_{CL_CLCR}*[CL_{CR}-CL_{CR_median}])	θ_{CL}	2.32	θ_{Vd}	θ_{Vd}	19.2	20.40%			38.50%	
		θ_{CL_CLCR}	0.0018								
		CL_{CR_median}	89.8								
Wu et al. (12)	CL (mL/min/kg) = θ_1 * CL_{CR}	θ_1	0.0145	V_d (L/kg) = θ_2 * (AGE(years)/47.9)$^{\theta 3}$	θ_2	0.83	38.30%	21.20%	16.30%		
					θ_3	0.44					
Zhou et al. (13)	θ_1 * (CL_{CR}/56.28)$^{\theta 3\_CLCR}$	θ_1	2.45	V_d = θ_2	θ_2	154	ω_{CL} = 0.174	ω_V = 0.339		σ_1 = 0.0657	σ_2 = 0 FIX
		θ_{3_CLCR}	0.542								

CL: clearance , V_d: volume of distribution , BSV: between-subject variability , RV: residual variability , CLCR_TBW: Creatinine clearance based on total body weight , TBW: total body weight, SCr: Serum creatine, CLCR:

Creatinine clearance (mL/min/1.73m²) , TOXI : co-administration of a nephrotoxic drug, eCL_{CR}: estimated creatinine clearance , NEUR : neurosurgical patient, GFR: glomerular filtration rate, NR: not reported, WT: bodyweight

†: refer to the respective article for more details

Table 2. 6 Characteristics of the population pharmacokinetic models developed by the studies included in this review (two-compartment)

Study	CL (L/h)			V_1 (L)			V_2 (L)			BSV			RV		
	Formula	Parameter	Value	Formula	Parameter	Value	Formula	Parameter	Value	CL	V_1	V_2	Exponential	Proportional	Additive
Alqahtani et al. (14)	CL * $(CL_{CR}/83.5)^{0.514}$ * $(albumin/35.5)^{0.854}$	CL	6.13	θ_{V1} * $(WT/79.6)^{0.466}$	θ_{V1}	40		V_2	3.88	22.10%	6.34%	61.20%		15.20%	0.055 mg/L
Bae et al. (15)	CL for patients who did not receive CRRT or HD treatment: θ_1 * $(CL_{CR}/72)^{\theta 2}$ CL_{CRRT}: CL for patients who received CRRT CL_{HD}: CL for patients who received HD treatment	θ_1 θ_2 CL_{CRRT} CL_{HD}	2.82 0.836 0.716 0.334		V_1	31.8	θ_3* (WT/60)	θ_3	75.4	99.20%		49.20%		σ = 0.253	
Bury et al. (16)	θ_1 + (1+θ_2*(CL_{CR}-104)) *$\theta_3^{NEUTROPENIA}$	θ_1 θ_2 θ_3	3.22 0.00834 1.277	θ_5*(FFM/57.2)	θ_5	45.8	θ_6*(FFM/57.2)	θ_6	51.7	31%	35.20%	97.80%		16.70%	2.07 mg/L
Donadello et al. (17)	CL * CL_{CRRT} * CL_{NOCRRT}	CL CL_{CRRT} CL_{noCCRT}	3.7 0.6 1		V_1	31.8	-	V_2	57.1	16.40%	57.10%	101%	8.50%		
Escobar et al. (18)	TVCL = θ_1/100	TVCL	2.7		V_1	11.9	-	V_2	17.3	NR	NR	NR	†	†	†
Goti et al. (19)	θ_1 *$(CL_{CR}/120)^{\theta 2}$ * θ_3 ^{DIAL}	θ_1 θ_2 θ_3 ^{DIAL}	4.5 0.8 0.7	θ_4 *(WT/70) * θ_5 ^{DIAL}	θ_4 θ_5 ^{DIAL}	58.4 0.5	-	V_2	38.4	39.80%	81.60%	57.10%		22.70%	3.4 mg/L
Hui et al. (20)	NR	CL_{HD} CL_{NHD}	3.86 0.443	NR	V_1	45.3	NR	V_2	45.6	ω_{CLNHD} (CV%) = 69.5%	84.50%	94.80%		43.50%	
Lim et al. (21)	θ_1 *CL_{CR}/100	θ_1	3.96	$V_1 = \theta_2$	θ_2	33.1	V2 = θ_3	θ_3	48.300	40.10%	35.70%			ε = 0.231	
Mangin et al. (22)	θ_{CL} * θ_{FEMALE} * $(BW/70)^{0.75}$ * $(SAPSII/50)^{\theta SAPSII}$ * $(SCr/100)^{\theta SCr}$	θ_{CL} θ_{FEMALE} θ_{SAPSII} θ_{SCr}	1.91 0.66 -0.50 -0.90	θ_{Vc} * $(WT/70)^1$	θ_{Vc}	21.9	θ_{Vp} * $(WT/70)^1$	θ_{Vp}	68	ω_{CL} = 0.29		ω_{V2} = 0.153			7.32 mg/L
Medellín-Garibay et al. (23)	θ_1 * CL_{CR}	θ_1	0.49	V_1 (L/kg) = θ_2 * TBW (Age > 65 years)	θ_2	1.07	V2 = θ_4 * TBW	θ_4	5.9 (L/kg)	37%	40%			19.2%	4.1 mg/L
	θ_5 * CL_{CR} (If furosemide)	θ_5	0.34	V_1 (L/kg) = θ_6 * TBW (Age ≤ 65 years)	θ_6	0.74									
Moore et al. (24)	θ_2 *(1+(θ_5*CL_{CR}-83))	CL	2.83	θ1 * (1+θ_6*(WT-94.5))	V_1	24.2	θ_4* (1+θ_7*(WT-94.5))	V_2	32.3	77%	34%			σ^2 = 0.0067	
Okada et al. (25)	θ_2*$(CL_{CR}/113)^{\theta 6}$	θ_2 θ_6	4.25 0.78	θ_1* $(WT/59.4)^{\theta 5}$	θ_1 θ_5	39.2 0.78	V2 = θ_3	θ_3	56.1	25.20%	14.20%	66.90%		17.20%	
Purwonugroho et al. (26)	θ_1 *CL_{CR}	θ_1	0.044	V_1 (L/kg) = θ_2* Age	θ_2	0.542	V2 (L/kg) = θ_4	θ_4	44.200	35.78%	20.93%	57.27%			4.51 mg/L
Zaric et al. (27)	Normal renal function: θ_1+θ_3*FIB	θ_1 θ_3	0.0727 0.205	V = θ_6	θ_6	7.47	NR	NR	NR	ω^2 = 0.059					σ^2 = 0.05
	Impaired renal function: θ_2 +θ_4*DD+θ_5*AST	θ_2 θ_4	0.284 0.000596	V = θ_7	θ_7	29.9				ω^2 =0.135					σ^2 = 0.045

					θ_5	0.00194													

CL: clearance, V_1: central volume of distribution, V_2: peripheral volume of distribution, BSV: between-subject variability, RV: residual variability, WT: Bodyweight, CL_{CR}: creatinine clearance (mL/min/1.73m²), HD: hemodialysis, NHD: non-hemodialysis, CRRT: continuous renal replacement therapy, NEUTROPENIA: 1 or 0 for the presence or absence of neutropenia, respectively, FFM: fat-free mass, CL_{CRRT}: CL relative to population parameter estimate for CL for patients not receiving continuous renal replacement therapy, CL_{NOCRRT}: CL relative to population parameter estimate for CL for patients not receiving continuous renal replacement therapy, NR: not reported , DIAL: hemodialysis status, SAPSII: the simplified acute physiology score, SCR: serum creatinine, TBW: total bodyweight, FIB: Fibrinogen (g/L), DD: Daily dose (mg/day), AST: AST (IU/L)
† Refer to the respective article for more details

Table 2. 7 Characteristics of the population pharmacokinetic models developed by the studies included in this review (three-compartment)

Study	**CL (L/h)**			**V_1 (L)**			**V_2 (L)**			**V_3 (L)**			**BSV**					**RV**
	Formula	**CL**	**CL_{CSF}**	**Formula**	**Parameter**	**Value**	**Formula**	**Parameter**	**Value**	**Formula**	**Parameter**	**Value**	**CL**	**CL_{CSF}**	**V1**	**V2**	**V3**	**Proportional**
Li et al. (28)	NR	7.98	0.04		V_1	15.16	NR	V_2	46.1	NR	V_{CSF}	0.14						σ_1=45.4% σ_2=58.24%
Li et al. (29)	NR	8.75	0.02	27.87 + 0.96 * (WT - 69)	V_1	27.84	NR	V_2	19.8	NR	V_{CSF}	0.12	28.63%	0.71%	21.58%	25.72%	91.18%	$\sigma_{1:CL}$= 0.82‡, $\sigma_{2:CLCSF}$ = 0.55‡
Li et al. (30)	CL = 11.87 * [1 + 0.0043 * (CL_{CR}-143)] CL_{CSF} = 0.21 * [1 + 0.0047 * (DA - 178)] * [1 - 0.20 * (ET-6)]	7.25†	0.21		V_1	11.87†	NR	V_2	21.53	NR	V_{CSF}	0.039	42.94%	1.23%	82.46%	39.93%	55.09%	$\sigma_{1:CL}$ = 0.3† σ_{2CLCSF}= 0.34†

CL: clearance, CL_{CSF}: clearance from CSF compartment, V_1: central volume of distribution, V_2: peripheral volume of distribution, V_{CSF}: CSF volume of distribution, BSV: between-subject variability, RV: residual variability, WT: bodyweight, CLCR: creatinine clearance (mL/min/1.73m²), DA: Drainage amount, ET: elapsed time after administration, NR: not reported
† Refer to the respective article for more details
‡ Power model

Table 2. 8 Covariates that were included or evaluated for inclusion by the PopPK models included in this review

Study	Age	Bodyweight	Gender	Height	BMI	BSA	SCr	CL_{CR} (Cockroft– Gault)	GFR	Lean bodyweight	Cardio-pulmonary bypass	SOFA score	APACHE II score	SAPSII score	Shock	ECMO	CRRT	Albumin	CSF albumin	Bilirubin level	Total protein	AST	ALT	Sepsis	Ascites	Infection type	Type of blood pump in ECMO	Length of vancomycin administration	Hct	RBC	WBC	T-BIL	CRP	BUN	Underlying hematologic disease	Pre-existing renal insufficiency	Total daily dose	Concomitant drugs	Allo-HSCT conditioning	Neutropenia	Mode of ECMO	Liver cirrhosis	ICU admission	Resuscitation fluids	Early phase of treatment	Days post-neurosurgery	Serum cystatin C	Drainage amount	Elapsed time after administration	Neurosurgery	Neurosurgical patient	Hemodialysis	Polytrauma	Fibrinogen	proBNP	Mechanical ventilation	Diabetes	Glucose	renal replacement therapy	Osmolality	HVHF intensity	Fat-free mass
Adane et al. (1)	♦	✓	♦	♦	♦	♦		✓																																																						
Alqahtani et al. (14)	♦	✓	♦	♦	♦		♦	✓			♦							✓																																												
Bae et al. (15)	♦	✓	♦	♦				✓									✓	♦								♦								♦																		✓										
Bury et al. (16)	♦																																							✓																						✓
Chung et al. (2)	✓	✓	✓	♦			✓																															♦					♦				✓															
Deng et al. (3)	♦						♦	✓																																																						
Donadello et al. (17)	♦	♦	♦					♦				♦	♦		♦	♦	✓																																													
Escobar et al. (18)																																																													✓	
Goti et al. (19)	♦	♦	♦	♦			♦	✓																										♦									♦									✓								♦		
Hui et al. (20)										✓																																										✓		✓								
Ji et al. (4)	✓	♦	♦				♦	✓	♦[a]									♦																♦																												
Kim et al. (5)	♦	♦	♦				♦	✓										♦																				✓				✓	♦	♦	✓	♦					✓											
Li et al. (28)	♦	♦						♦											✓																																											
Li et al. (29)	♦	✓	♦					♦											✓																																											
Li et al. (30)	♦	♦	♦					✓											♦																													✓	✓													
Lim et al. (21)	✓	♦	♦	♦			♦	✓																																																						
Lin et al. (6)	♦	♦					♦	✓																										♦				♦																								
Liu et al. (7)	✓	✓							✓[b]																													♦												♦												
Mangin et al. (22)	♦	✓	✓				✓							✓																						♦																♦					✓					
Medellín-Garibay et al. (23)	✓	✓	♦	♦	♦	♦	♦	✓																														✓																								
Medellín-Garibay et al. (8)	♦	✓	♦	♦	♦	♦	♦	✓																																																✓		♦				
Moore et al. (24)	♦	✓	♦				♦	✓									♦																																										♦			
Okada et al. (25)	♦	✓	♦			♦	♦	✓										♦											♦	♦	♦	♦	♦	♦	♦			♦	♦																							
Purwonugroho et al. (26)	✓	♦	♦				♦	✓[a]	♦									♦		♦		♦	♦		♦									♦				♦																								
Roberts et al. (9)	♦	✓	♦		♦			✓				♦																																																		
Udy (31)	♦	♦	♦									♦	♦																																																	
Usman et al. (11)	♦	♦	♦				♦	✓																																																						
Wu et al. (12)	✓	♦	♦					✓										♦									♦														♦																					
Zaric et al. (27)	♦	♦	♦					✓[d]										♦		♦		✓[f]	♦	♦				♦					♦				✓[f]	✓[f]															✓[e]	✓[e]	♦							

Zhou et al. (13)	✓	✓	♦				♦	✓										♦		♦	♦	♦	♦											♦				♦

BMI: body mass index, BSA: body surface area, SCr: serum creatinine, , GFR: glomerular filtration rate, SOFA score: the sequential organ failure assessment score , APACHE II SCORE: the acute physiology and chronic health evaluation, SAPSII: the simplified acute physiology score, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CSF: cerebrospinal fluid, ECMO: extracorporeal membrane oxygenation, Hct: hematocrit , RBC: red blood cells, WBC: white blood cells, T-BIL: total bilirubin , CRP: C-reactive protein , BUN: blood urea nitrogen, proBNP: pro-brain natriuretic peptide, Allo-HSCT: allogeneic hematopoietic stem cell transplantation

✓tested and significant

♦tested but not significant

[a]tested other renal function descriptors, including at least a variation of modification of diet in renal disease MDRD4 (modification of diet in renal disease) equation

[b]using Hoek's equation based on cystatin C

[c]within 3 days of therapy initiation

[d]CL_{CR} was significant using MDRD4 and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in normal renal function group

[e]Significant in the group with normal renal function

[f]Significant within the impaired renal function group; aminoglycoside antibiotics are the significant concomitant drugs

Chapter 3

An Update on Population Pharmacokinetic Analyses of Vancomycin, Part II: in Pediatric Patients

This review is an update to a 2012 vancomycin review entitled “Vancomycin: A Review of Population Pharmacokinetic Analyses” by Amelie Marsot et al. An update was deemed necessary due to the large number of population pharmacokinetics analyses that were published following Marsot's original review. We split our update into two parts, adult and pediatrics. This article concerning pediatric was accepted at *Clinical Pharmacokinetics* “Aljutayli, Abdullah, Ibrahim El-Haffaf Amélie Marsot, and Fahima Nekka. "An update on population pharmacokinetic analyses of vancomycin, part II: in Pediatric Patients." *Clinical pharmacokinetics* (2021)”

3 Article II: An Update on Population Pharmacokinetic Analyses of Vancomycin, Part II: in Pediatric Patients

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Abstract

Vancomycin is widely used in pediatric patients. However, large inter- and intra-individual variability are observed in vancomycin pharmacokinetics, affecting proper therapeutic monitoring. This review aimed at providing a comprehensive synthesis of the population pharmacokinetic models of vancomycin in pediatric patients and identifying potential factors responsible for the variability observed in various subpopulations. We conducted a literature search on PubMed and EMBASE to obtain population pharmacokinetic studies for vancomycin published between January 2011 and January 2020. This search resulted in a total of 33 studies. Vancomycin pharmacokinetics was generally characterized using a one-compartment model (n=27), while a two-compartment model was used in six studies. The median (interquartile range) of the typical vancomycin clearance (CL) and the total volume of distribution adjusted to the median or mean body weight of the respective study was 0.103 (0.071-0.125) L/h/kg and 0.64 (0.59-1.03) L/kg, respectively. Median weight-adjusted CL between different children age groups, such as between infants and adolescents, did not appear to vary significantly, although the sample size for many age groups was very small. Examples of the conditions with relatively abnormal vancomycin pharmacokinetic values include renal insufficiency, sepsis, hematological and solid malignancy, and hypothermia treatment. Factors influencing pediatrics vancomycin pharmacokinetic after adjusting to size and maturation include various renal function descriptors and some case-specific variables such as dialysate flow rate, ultrafiltrate output, and hypothermia. This review was able to document possible variables explaining the high variability observed in certain subpopulations and contrast vancomycin pharmacokinetics in different pediatric subpopulations.

3.1 Introduction

Vancomycin is a large hydrophilic glycopeptide antibacterial effective against gram-positive organisms (1). Vancomycin clinical intravenous administration to pediatric patients was considered, previous to the recent advent of alternative antibiotics, as the drug of choice in the management of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections (2, 3). The 2020 revised vancomycin guideline reported concerns about the limited availability of prospective comparative outcome data evaluating vancomycin clinical and microbiological success (3). According to the revised guidelines, careful vancomycin therapeutic monitoring in pediatric patients is prudent (3). Despite the inconclusive data on vancomycin pharmacodynamic target in pediatric patients and based on the best of available retrospective and adult evidence, vancomycin monitoring was recommended to achieve a pharmacokinetic/pharmacodynamic (PK/PD) index of the ratio of area-under-the-curve (AUC) over 24 hours to minimum inhibitory concentration (MIC) by broth microdilution (AUC/MIC_{BMD}) of 400 to 600, assuming MIC of 1 mg/L. However, targeting an AUC/MIC of 400 might be preferable to reduce incidences of acute kidney injury (AKI), although an AUC value of 600 was considered tolerable. With such consideration, high or low therapeutic target within the 400-600 AUC/MIC range might be subject to clinical judgment (3).

Whereas adults' glomerular filtration might be directly related to vancomycin clearance while bodyweight could be related to vancomycin distribution volumes to some extent, vancomycin PK parameters in pediatric patients are subject, additionally, to the continual size and organ maturation changes (3, 4). Population pharmacokinetics (PopPK) approach using nonlinear mixed-effects models can potentially prove useful in explaining the PK variability in terms of the patient-specific characteristics (i.e. covariates), such as size-, maturation- and disease-related

changes (3). Accounting for patient-specific covariates should reduce the unexplained variability and aid in individualized dosing (5). It is worth mentioning that the remaining vancomycin random interindividual (IIV) clearance variability was reported to reach as high as 99.2% (6).

While we addressed adult vancomycin PopPK analyses in our first part (7), this second part concerns vancomycin therapeutic monitoring and optimal dosing in pediatric patients using a nonlinear mixed-effects approach. Driven by the updated 2020 vancomycin guidelines (3) and by the growing number of published population PK analyses, this part is an extension with the same objectives of providing a systematic and comprehensive overview of all pediatric analyses reported from January 1, 2011, to January 5, 2020, to improve vancomycin therapeutic monitoring and dose optimization. We also aimed to characterize vancomycin PK in different subpopulations and identify possible PK parameter alterations, accounting for varying study designs, model structures, and patient-specific characteristics. Therefore, a comprehensive review of such information might be warranted and might help its translation into a better-informed monitoring.

3.2 Data Source

3.2.1 Search strategy

We performed an electronic literature search of vancomycin population pharmacokinetics analyses using PubMed and EMBASE databases with time confinement from January 1, 2011, to January 5, 2020, using the same search term used in part 1 (7), and substituting adults with children, i.e. AND (child*). All relevant articles were retained, inspected, and evaluated for inclusion. We examined reference lists of the retrieved studies to identify any additional relevant materials.

3.2.2 Inclusion Criteria

We evaluated the retained studies for their inclusion eligibility according to predefined criteria; (i) studied population: children who received (ii) an intravenous treatment of vancomycin, and (iii) their vancomycin concentration-time profiles were modeled using a nonlinear mixed-effects pharmacokinetic modeling approach. Only (iv) original data and analysis (v) published in English were considered.

3.2.3 Exclusion Criteria

A three-point criterion was applied to exclude (i) any *in vitro* or animal study, (ii) any other reviews, meta-analysis, or methodology articles, (iii) or any applied methodology other than a nonlinear mixed-effects pharmacokinetic modeling approach.

3.2.4 Data Extraction

After applying the inclusion and exclusion criteria, we extracted all relevant information into data collection sheets. The extracted relevant information was discussed in detail in part 1 (7) and was, in brief, the authors, publication date, population demographics, clinical diagnoses, study design, vancomycin sampling frequencies and quantification methods, modeling approach, PK structural and statistical models, including vancomycin clearance (CL) and distribution volumes formulae, parameter estimates, and covariates information.

3.3 Results of Literature Search

3.3.1 Demographics and Study Characteristics

The conducted literature search, with the application of inclusion and exclusion criteria, resulted in 28 eligible studies. Reference screening added 5 more studies, summing to 33 different PopPK analyses. Patient demographics were summarized in Table 3.1. Vancomycin PK parameter estimates in certain ethnicities, races, and nationalities, relative to the others, were of interest in

five studies (8-12). In this review, we did not observe any systematic differences between different ethnicities, races, and nationalities. These analyses were conducted in the USA (n = 18), China (n = 6), and France (n = 3), while the remaining analyses (n=6) originated from five different other countries (Table 3.1). Three studies recruited less than 30 patients (13-15). The number of recruited patients per study spanned from 10 patients (i.e., Kato et al. and Ingrande et al.) to 702 patients (i.e., Le et al.) (13, 15, 16). It should be noted that while this review was dedicated to all pediatric patients, many analyses limited their patients to a specific children group, including preterm and term neonates in four studies (17-20), neonates in five studies (8, 13, 14, 21, 22), infants in a study (15), both neonates and young infants in three studies (9-11), and adolescents in two studies (23, 24), while the others did not limit their populations to specific age pediatric group (12, 16, 25-40). Figures in Supplementary Material 3.6 represent simulations of the age distribution for every study. Further, as summarized in Table 3.1, recruited children subscribed to varying combinations of age and/or clinical groups, such as neonates with late-onset sepsis (17). Other clinical diagnoses included renal disease, cancer, cardiac pathology, cystic fibrosis, obesity, critical illness, and extracorporeal membrane oxygenation (ECMO) administration (Table 3.1). Seven studies used control cohorts, including Le et al. (34) who used a matched case-control design (30, 34, 36-40).

3.3.2 Study Design and Protocol

All analyses collected therapeutic drug monitoring (TDM) data retrospectively (n = 29) or prospectively (n = 3), except for Sheng et al. (15) who conducted a clinical trial (Table 3.2). The main type of vancomycin administration was through intermittent infusion (Table 3.2). A continuous infusion was used in Guilhaumou et al. and Zhao et al. (22, 39), while both administration techniques (i.e., intermittent and continuous) were used in Germovsek et al. (11).

Vancomycin sampling frequency was at the discretion of the clinical teams in the TDM studies, which resulted in a varying number of samples per patient (Table 3.2). For instance, Kloprogge et al. reported withdrawing from two and up to 50 samples per patient (27). Sampling at steady-state conditions was reported in 18 studies (8, 10-12, 16, 17, 19, 25, 26, 28, 29, 34-37, 39, 40). In contrast, six studies stated the inclusion of pre-steady-state samples (9, 15, 21, 23, 24, 30), while the remaining analyses (n =9) did not report the steady-state status while sampling (13, 14, 18, 20, 22, 27, 31-33) (Table 3.2). Vancomycin quantification methods included a variety of immunoassays (n=27) and high-performance liquid chromatography, which was used in Zhang et al (40). The remaining five analyses did not specify the quantification method used (Table 3.3).

3.3.3 Population Pharmacokinetic Analysis

Vancomycin PopPK was largely described using one-compartment model (n = 27) (8, 10-14, 16-26, 28, 29, 33-40). A two-compartment model was used in the remaining analyses (n = 6) (9, 15, 27, 30-32). All studies performed model evaluations, including goodness-of-fit plots. Further, only six analyses validated their model externally (Table 3.4) (9-11, 18, 26, 27). In contrast, internal validation, such as the bootstrap procedure, was performed in most of the analyses (n = 27), as demonstrated in Table 3.4. In general, fitting vancomycin concentration-time profiles were carried using NONMEM software (Table 3.4). Other software packages, including Phoenix NLME, Monolix, and Pmetrics were used in three, one, and one analysis, respectively (Table3. 4).

3.3.4 Vancomycin Clearance

One challenge in writing this section was the lack of uniformity in reporting vancomycin CL (Table 3.5 and Table 3.6). The median (interquartile (IQ) range, range) of the typical vancomycin CL was 1.612 (0.429-3.403, 0.054-7.797) L/h, while the median (interquartile (IQ)

range, range) weight-adjusted typical CL to the respective study mean or median bodyweight was 0.103 (0.071-0.125, 0.0155-0.255) L/h/kg. This range suggests a 16-fold difference between the maximum and minimum weight-adjusted typical vancomycin CL. However, typical CL estimates did not appear to vary widely between age groups. Median CL values stratified by age groups, as reported in section 3.1, were 0.109, 0.095, 0.105, 0.103, 0.084, and 0.118 L/h/kg (i.e. 0.319, 0.276, 0.300,0.420, 6.323, 2.590 L/h) for preterm and term neonates (n=4), neonates (n=5), infants (n=1), both neonates and infants (n=3), adolescents (n=2), and all the others (n=18), respectively. Across all studies, estimated CL in the first quartile were reported for hematological malignancy children using cyclosporin, children with renal insufficiency, children administered ECMO therapy, very low birth weight neonates, preterm and term neonates, and infants undergoing open-heart surgery administered cardiopulmonary bypass (13, 15, 17, 18, 22, 31, 32, 37, 39, 40). In contrast, estimated CL within the fourth quartile was observed in hematological and solid malignancy children, children with cystic fibrosis, hypothermic children resuscitated from cardiac arrest, infants, neonates administered ECMO therapy, and general children (12, 14, 19, 25-30, 34).

Many maturation functions varying from a simple linear relation to a more complex sigmoidal function, were used to describe organ maturation in correlation with age in many studies (n=14), as shown in Table 3.5 and Table 3.6. Varying size scaling methods were used. These methods include allometric scaling using bodyweight or fat-free mass (FFM) to the theoretical power of 0.75 (n=17), an estimated power (n=10), or a power of 1 (n=2) with either standardizing to a bodyweight of 70 kg (n=8), FFM of 70 kg (n=2), standardizing to the study mean or median bodyweight (n=12), or without standardizing (n=7), as in Table 3.5 and Table 3.6. Three studies

did not size scale CL (13-15), while one study did not report CL formula (27). Cies et al. used an allometry scaling of the estimated glomerular filtration rate (eGFR) on CL (14).

3.3.5 Estimated Volume of Distribution

Estimated total volume of distribution (V_d) varied with a median (IQ range, range) of 0.64 (0.59-1.03, 0.32-5.89) L/kg. This V_d represents the volume of distribution for one-compartment models or the sum of the central and peripheral distribution volume for two-compartment models. Two studies reported a relatively elevated V_d, Zhao et al. for hematological malignancy and Moffett et al. for renal insufficient children, which brought the ratio between the highest and lowest V_d to 18-fold (28, 32). Excluding these two studies, the ratio between highest to the lowest V_d estimates was 5-fold only. Median V_d values stratified by age groups, as reported in section 3.1 were 0.778, 0.949, 0.47, 0.561, 0.681, and 0.663 L/kg for preterm and term neonates (n=4), neonates (n=5), infants (n=1), both neonates and infants (n=3), adolescents(n=2), and all the others (n=18), respectively. However, any conclusion about these values must be made with caution considering the limited sample size available for some groups. A relatively elevated V_d in the fourth quartile was observed in hematological and solid malignancy, PICU, very low birth weight neonates, renal insufficient children, and neonates undergoing ECMO, as well as infants and general children populations (8, 12-14, 19, 27, 28, 32, 39). In contrast, a relatively low V_d (within the first quartile) was reported in obese, renal insufficient children, infants undergoing open-heart surgery and cardiopulmonary bypass (CPB), and some neonates and general children (9-11, 15, 22, 23, 26, 34, 37). Size scaling methods varied, as well, on distribution volumes as six studies did not include weight in the V_d formula, two did not report the V_d formula, two included FFM, while the remaining introduced weight standardized to the study median (n=9), to 70 kg (n=6), or without standardization (n=8) (Table 3.5 and Table 3.6).

3.3.6 Modeling of the Random Effects

Vancomycin PK parameters appeared to vary extensively within some studies. For example, the IIV coefficient of variation (CV%) on the central volume of the distribution compartment (V_1) was 136% and 232% in Zane et al. and Kloprogge et al., respectively (27, 30). Further, the highest reported CV% of IIV on CL was 50.4% (27). All analyses modeled IIV using exponential models, whereas unexplained residual error was modeled using additive, proportional, and combined additive proportional models, (Table 3.5 and Table 3.6). Only Alsultan et al. (26) characterized inter-occasional variability.

3.3.7 Inclusion of Covariates

Collectively, the potential influence of 56 variables on explaining vancomycin PK variability was examined. Inclusion techniques were according to biological plausibility, *a priori* inclusion, and stepwise covariate modeling (Table 3.7). As discussed earlier in this text, frequently reported significant covariates were a variety of body weight and age. Renal function descriptors including serum creatinine (Scr), creatinine clearance (CL_{cr}), and GFR were significant in n=17, n=4, and n=3 studies, respectively (Tables 3.5, 3.6, and 3.7). All these studies size-adjusted the renal function, except (13) and (14), while nine adjusted to maturation (Tables 3.5 and 3.6). In contrast, these renal function descriptors (i.e. Scr, Cl_{cr}, and GFR) were reported not to be statistically significant covariates in (n=8) models, as shown in Table 3.7 (9, 11, 12, 19, 25, 26, 29, 39). A study reported a significant effect of concomitant drug usage with cyclosporin (39). Other non-frequent but significant covariates included blood urea nitrogen (BUN), albumin, ultrafiltrate output, and the volume of infusion (13, 31, 32). Some variables did not appear to be influential despite frequent testing, such as body surface area (BSA), height (HT), body mass index (BMI), PICU stay, and gender (Table 3.7).

3.4 Discussion

This review included 33 vancomycin PopPK analyses, published during the period from January 1, 2011, to January 5, 2020, using the nonlinear mixed-effects pharmacokinetic approach to characterize vancomycin concentration-time profiles in pediatric patients. Analyses included in the current review represented diverse clinical and children age groups. This review was meant to supplement part 1 (7), as well as to update an earlier review by Marsot et al. (1) which included 16 pediatric publications from 1986 to 2010. This apparent 2-fold increase in the rate of publication might suggest a growing interest in optimizing vancomycin therapeutic monitoring following the original vancomycin guidelines (41) and highlight the increasing popularity of population PK approaches.

Characterizing vancomycin concentration-time profiles in pediatric patients might be subject to increasing size and maturing organ functions (42). Size scaling using bodyweight, or other size predictors such as FFM, might be important for all children (42). Further, the maturation effect on CL can be accentuated in children younger than 2 y (4). In this review, maturation was always defined with age, except for Cies et al. (14) who used an allometric scaling of eGFR.

One complexity in writing this review was the lack of uniformity between studies in using size scaling methods, which included different allometry powers and standardizations. Overall, the median (IQ range, range) of CL per kg was slightly higher compared to values reported earlier in adults. It should be noted that the phenomenon of inflated CL expressed per kg in children compared to adults might not reflect a true higher CL (4). Despite this, once compared to adult values, no apparent systematic trend of varying vancomycin PK parameters in any clinical population was observed. It is worth mentioning that while we included varying CL and V_d statistics in this review to provide relativity, we would like to reemphasize that such comparison

should be viewed with caution due to differences between the studies, such as varying study designs, covariates, and parametrizations (7).

Vancomycin is cleared primarily through glomerular filtration, although tubular transport might play a role (1). This highlights the significance of quantifying renal function and its maturation in children. Kidney development (i.e. nephrogenesis) begins around 5-6 weeks into gestational age (GA) and continues until the 36-week GA (43). After birth, hemodynamic variations might result in faster GFR rates compared to the rate observed in adults, and GFR per surface area might take up to 6-12 months to reach adult levels (43). Quantifying GFR in clinical practice might be challenged by the impracticality of the gold standard inulin clearance, and the imprecision and variability of creatinine-based equations, especially for low mass patients and neonates younger than 72 hours, considering the confounding maternal Scr (10, 17). Despite this, the National Foundation of Kidney Function Disease Outcomes Quality Initiative recommends estimating GFR using creatinine-based equations in adults and children (17).

In our review, the influence of varying renal function descriptors was evaluated in many analyses, as shown in Table 3.7. For example, Bhongsatiern et al. evaluated the influence of various renal function descriptors that were calculated by varying methods such as the modified Schwartz, Counahan-Barrartt, and Leger formulae. They selected the modified Schwartz because of its simple bedside methods despite being developed in >1 y children with chronic kidney disease (17). This study further reported that Scr and CL_{cr} functioned similarly in explaining vancomycin CL variability (17). Mehrotra et al. reported that Scr accounted for 55% of vancomycin CL variability once weight in preterm and term neonates is taken into consideration (20). In contrast, in patients with renal insufficiency, Zhang et al. reported no correlation between vancomycin CL and CL_{cr} (40). Finally, preterm and term neonate serum creatinine-

based dosing might result in a higher number of patients achieving the therapeutic target compared to a fixed weight, postmenstrual age (PMA) and postnatal age (PNA) based dosing (20).

Many maturation models, including a simple linear relation to a more complex sigmoidal function, were used to describe organ maturation using varying age descriptors, such as PMA, PNA, PCA, and GA, in many studies (n=16), as shown in Tables 3.5, 3.6, and 3.7. In general, PMA and PCA might be preferable for neonates as it describes GA and PNA and accounts for before birth kidney development (4, 17, 20). For example, Moffett et al. reported that PMA, but not PNA, was a significant covariate on CL (33). Further, Mehrotra et al. reported that in preterm and term neonates, PMA accounted for 19% of IIV after accounting for weight (20). Finally, despite the potential capacity of such models to account for maturation, over parametrization and ill-conditioning were two factors that might have limited their implementations (17).

3.4.1 Preterm Neonates

Rapid physiological changes in the first weeks of life, including renal maturation and body water composition, coupled with the innate immunological immaturity, might predispose preterm neonates to further risks (13). For example, reports indicate that very low birth weight preterm neonates might have elevated sepsis-related mortality and morbidity rates (13, 44). Zhao et al observed larger variability in vancomycin concentrations in preterm compared to term neonates (22). Thus, various dosing regimens to optimize vancomycin administration were evaluated. Mehrotra et al. reported that a weight-based dose of 10 mg/kg every 8 hours resulted in the largest vancomycin concentration variations and the lowest percentage of patients in the therapeutic target range (it was identified as a trough of 5–15 mg/L) compared to PMA- or Scr-

based dosing (20). In contrast, Song et al. did not include Scr in their model, citing its limited utility as a marker of the glomerular filtration rate (9). Instead, Song et al. recommend a dosing algorithm that is based on birth bodyweight and PNA, which influence kidney function and growth. It should be noted that a strong correlation between body weight and both PNA and PMA, as well as a negative correlation between Scr and PMA in preterm neonates was reported (12). Despite this, a continuous infusion and a loading dose might be needed for rapid target achievement (11, 22).

3.4.2 Kidney Disease and Hemofiltration in Children

Given that vancomycin is primarily cleared through glomerular filtration, Le et al. aimed at studying the impact of renal insufficiency using a matched case-control design (37). Renal insufficiency (acute mild or moderate insufficiency) was reported to reduce vancomycin CL by 30% to 70% compared to the respective matched cohort having a normal renal function (37, 40). Another study estimated that impaired renal function could reduce vancomycin CL by up to 80% and 84% in normothermic and hypothermic patients resuscitated from cardiac arrest, respectively (30). This reduced vancomycin CL estimate in patients suffering mild and moderate renal insufficiency was reported to translate into an increased AUC by up to 2.8-fold, leading to a higher incidence of nephrotoxicity compared to normal patients (30, 40). In this review, renal insufficiency appears to result, generally, in a relatively lower vancomycin CL.

The impact of continuous venous-venous hemofiltration (CVVH) and its components, including ultrafiltration and dialysate flow rates, on children vancomycin PK was evaluated in Moffett et al. (32). This study incorporated dialysate flow rate, ultrafiltration rate, and BUN, as well as Scr due to their significant association with vancomycin CL (32). Although SCR and BUN are effectively cleared through CVVH, their levels might represent a residual renal function (32).

Estimated vancomycin CL in this study appeared to be relatively low compared to other studies (32). On the other hand, reported V_d of this study was among the largest in this review, which was attributed to the potential poor characterization of V_d as a result of the sparse sampling nature of the study, large priming volume used for the CVVH circuit, and fluid overload in many patients (32). This study reported that allometrically scaling the PK parameters using FFM resulted in a better model fit compared to using bodyweight, and no other covariates influenced the distribution volumes in this study (32).

3.4.3 Children on Extracorporeal Membrane Oxygenation

Several patient- and circuit-specific factors involved in ECMO administration might provoke the hypothesis that ECMO support can alter vancomycin PK (31). Additionally, evidence exists suggesting that the target vancomycin concentrations were not obtained in ECMO patients (45). However, consistent with our previous observations in adults, vancomycin PK parameters of patients undergoing ECMO therapy did not seem to be systematically different compared to other clinical populations, although vancomycin CL and V_d estimates in Cies et al. were relatively high compared to all other studies in this review (7, 14, 31). Further, ultrafiltrate volume and urine output were not reported to be strongly associated with vancomycin CL (31). Although Moffett et al. aimed at characterizing the variability in circuit priming, fluid balance, and pathophysiology changes, this was not achievable due to the sparse sampling nature of the study (31). The study of Moffett et al. used Quadrox oxygenators and Rotaflow centrifugal pumps (Maquet Holding B.V & Co, Rastatt, Germany) (31). On the other hand, the study by Cies et al. aimed at characterizing vancomycin PK during ECMO administration using the contemporary ¼-inch Quadrox-iD Pediatric oxygenator (Maquet Cardiovascular, LLC) (14).

Vancomycin CL reported by Cies et al. was extremely larger than the CL estimate reported by Moffett et al. (14, 31).

3.4.4 Obese Children

Weight-based dosing might raise concerns of AKI in obese patients (3). Two studies in this review aimed at characterizing vancomycin PK in obese children. Similar to the earlier report in adults, PK parameter estimates adjusted to the size did not appear very different compared to the non-obese patients (7, 24, 34). Using a matched case-control study, Le et al. reported a slightly lower vancomycin weight-adjusted CL and V_d by 10.8% and 2.2% compared to the non-obese cohort (34). Despite this, the study concluded that this difference was unlikely to translate into a clinical significance (34). The influence of varying body size descriptors on CL, such as actual weight, BMI, allometric weight, and BSA, were evaluated (24, 34). Le et al. used allometric weight scaling according to the allometric theory due to its practicality despite BSA slightly outperforming it, while Moffett et al used FFM (24, 34).

3.4.5 Children with Cystic Fibrosis

Vancomycin therapy in cystic fibrosis (CF) might be of great relevance considering that a reported 50% of CF patients were infected with *S. aureus*, while 23% were infected with MRSA (29). Further, MRSA might possess a tissue-damaging virulence factor, and MRSA patients might have an increased mortality rate and a higher airway obstruction, needing thus aggressive antibiotic treatments, and more frequent hospitalizations compared to patients infected with methicillin-sensitive S. aureus (MSSA) (46-48). Despite this, the influence of CF and its associated pathophysiological changes on vancomycin PK might be poorly understood (29). In this review, Stockman et al did not report a significant difference in PK estimates between CF and non-CF children (29).

3.4.6 Children with Critically Illness or Sepsis

In this review, three studies evaluated vancomycin PK in critically ill children (8, 21, 38). In critically ill children, augmented renal clearance (ARC) can be suspected due to a hyperdynamic state that can lead to increased cardiac output and renal blood flow (38). Avedissian et al. reported an augmented vancomycin CL by 50 mL/min/1.73 m^2 in patients with ARC compared to those without ARC, which was observed in one in every ten patients (38). Further, chances of augmented vancomycin CL were reported to be higher in children ≥ 7.9 y compared to younger kids (17% vs 4.6%) (38). However, Avedissian et al. reported no statistically significant difference in doses administered to the groups of patients with or without ARC, as well as in the estimated AUC (38). Admission to the neonatal intensive care unit (level III) was evaluated in Frymoyer et al. (21). Overall, typical vancomycin PK values of these three studies did not appear to differ significantly from other studies in this review (8, 21, 38).

Late-onset neonatal sepsis can be defined as at least one positive culture ≥ 72 h after birth or after the first week of life (17). For low birth weight neonates (i.e. <1500 g), late-onset sepsis might warrant careful attention given the estimated 15% mortality rate that might be attributed to their compromised immunity and high risk of infection (e.g. use of catheters) (17, 49). Three studies evaluated vancomycin PK in late-onset septic pre-term and term neonate and sepsis in infants (11, 17, 22). It should be noted that 20% of (22) patient populations were diagnosed with sepsis. Overall, a trend of a relatively low estimated vancomycin CL and/or V_d was noticed in every study (11, 17, 22). In contrast, in our previous review concerning adults, this trend of low estimated CL and/or V_d was not observed (7). According to Monte Carlo simulations conducted by Bhongsatiern et al., 50% of their simulated neonates achieved an AUC ≥ 400 (17). Overall,

further investigation might be warranted and many suggested that continuous infusion might be needed (3, 11, 22).

3.4.7 Therapeutic Hypothermia after Resuscitation from Cardiac Arrest and Cardiac Surgery

Therapeutic Hypothermia (TH) and normothermia (NT) might be applied to improve long-time neurological outcomes following resuscitation from cardiac arrest and hypoxic-ischemic encephalopathy (30). Zane et al. aimed at elucidating the potential effect TH and NT on vancomycin PK, given the potential for many pathophysiological conditions, such as reduced organ perfusion, organ dysfunction, transient renal impairment, renal failure in 12-28% of the patients, and consequently altered GFR that might not accurately reflect vancomycin CL (30, 50). Further, Zane et al developed a PopPK model with a body temperature variable that predicted that extreme hypothermia might result in a reduced vancomycin CL by 25% in patients with normal kidney function (30). Impaired renal function children might experience reduced vancomycin CL by 80% and 84% in NT and HT, respectively (30).

Children undergoing cardiac surgery might experience an increased incidence of AKI due to low cardiac output syndrome, venous congestion, and reduced end-organ perfusion resulting from inflammations of the CPB (15). Also, it might be suspected that priming volumes involved in the CPB procedure in addition to the altered fluid status from diuretics administration might alter vancomycin PK (15). However, Ingrande et al. reported no significant effect of CPB on vancomycin PK, although estimated CL and V_d were within the first quartile relative to other studies in this review (15). This CL observation did not seem to be consistent with the previous observation in adults undergoing open-heart surgery (7).

3.4.8 Children with Hematological and Solid Malignancy

Risk of life-threatening infection, bacterial resistance, compromised immunity, and concomitant nephrotoxins use might warrant optimal vancomycin dosing in children with hematological and solid malignancies (25, 39). Further, MRSA isolates might be prevalent among malignancy patients (25). Guilhaumou et al. reported that vancomycin CL correlated with cyclosporin coadministration and tumor pathology (solid or hematological malignancy) (39). Further, a relatively lower estimated CL in hematological patients treated with cyclosporin for bone marrow transplantation of 3.49 L/h was observed compared to a CL value of 4.66 L/h in hematological malignancy patients not administered cyclosporin, and 4.97 L/h in solid malignancy patients (39). It is worth mentioning that Scr levels were significantly higher, yet stable, in patients who administered cyclosporin and were not retained as a significant variable in this PK model (39). Other nephrotoxins used for bone marrow transplant including amphotericin b, foscavir, and acyclovir were not identified as significant variables, as well (39). Further, concomitant chemotherapeutic agents did not seem to affect PK (25). Zhao et al. studied children with hematological malignancy and reported elevated PK parameters (i.e. CL and V_d) that were among the highest in this review (28). The estimation of vancomycin CL in Abdel Hadi et al. was relatively elevated as well (25). In contrast, while Guilhaumou et al. V_d estimate was relatively elevated, its vancomycin CL was relatively low (i.e. in the first quartile) compared to other studies in this review (39). It is worth mentioning that the median estimated creatinine clearance in Zhao et al. was 191 ml/min (28).

3.5 Conclusion

This review included 33 PopPK analyses on vancomycin in various children subpopulations. Despite the evaluation of the influence of 56 covariates, only a few were retained in the models

after adjusting for size and maturation. Estimation of vancomycin CL and V_d varied widely across the studies included in this review. The highest reported CV% of IIV on CL was 50.4%. The TDM nature of most studies might have attributed to a relatively elevated CV% of IIV on V_1, as high as 232%. While we could identify some factors as those mentioned here that may alter vancomycin PK in this review, additional research might be required before advocating for vancomycin dosing regimen changes.

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Table 3. 1 Demographic Summary

Study	Publication year	Country	Patients	N (male/female)	Age (y)[a] PNA	PMA	GA	Body and birth weight (kg)[a]	Scr (mg/dL)[a]
Abdel Hadi et al. (1)	2016	Jordan	Cancer	49 (27/22)	6 ± 2.46	NR	NR	19.6 ± 6.95	0.406 ± 0.118
Alsultan et al. (2)	2018	Saudi Arabia	General pediatric patients	76 (44/32)	5.8 ± 2.9	NR	NR	18.1 ± 8.5	0.38 ± 0.12
Avedissian et al. (3)	2019	USA	Critically ill	221 (107/114)	9.0 (3.0-14.2)[b]	NR	NR	26.4 [14.6-50.0][b]	0.40 [0.30–0.6][b]
			Critically ill with augmented renal clearance	29 (15/14)	11.3 (8.7-13.8)[b]	NR	NR	41.8 [25.8-53.9][b]	0.33 [0.30–0.4][b]
Bhongsatiern et al. (4)	2015	USA	Neonates with late-onset sepsis	152 (88/64)	PNA: 23 (15-41)[b] days	33.0 (28.5-39.4)[b] weeks	NR	1.5 (0.88-2.7)[b]	0.44 (0.33-0.6) [0.1-3][b]
Chen et al. (5)	2018	China	Neonates and young infants	213*	26 [6-59][c] days	39.8 [28-47.9][c] weeks	36.9 [25-42] weeks[c]	Birth weight: 2.53 [0.7-4.7][c] Body weight: 2.73 [0.88-5.1][c]	0.28 [0.11–0.72][c]
Cies et al. (6)	2017	USA	Neonates on ECMO	12 (7/5)	9.5 [0-28] days[c]	NR	39 [36-41] weeks[c]	3.1 [2.2-4.41][c]	NR
Dao et al. (7)	2019	Switzerland	Full term and preterm Neonates	405 (231/174)	12.3 [0-146][c] days	32 [24.6-61.0] weeks[c]	29 [24-42.1] weeks[c]	1.1 [0.462-5.660][c]	54 (31-68)[c, e]
Frymoyer et al. (8)	2014	USA	Neonates	249 (128/121)	19 [0-173][c] days	39 [24-54] weeks c	34 [22-42] weeks c	Birth weight: 2.0 [0.4-4.4] c Body weight: 2.9 [0.5-6.3][c]	0.4 (0.3-0.6)[b]
Germovsek et al. (9)	2019	England	Neonates and infant	54*	30 [1-156][c] days	NR	29 [23.7-41.9] weeks c	NR	31.0 [18-98][c, e]
Guilhaumou et al. (10)	2016	France	Hematological malignancies	61 (30/31)	9.1 ± 5.7	NR	NR	31.6 ± 18.6	32.8 ± 20.1[e]
			Solid malignancies	60 (24/36)	7.1 ± 5.4	NR	NR	25.0 ± 16.4	28.3 ± 14.7[e]
Ingrande et al. (11)	2019	USA	Infants undergoing open-heart surgery with CPB	10 (4/6)	3.075 months	NR	NR	4.63	NR
Kato et al. (12)	2017	Japan	Low birth weight neonates	10 (7/3)	19.7 ± 6.7 [11-28] days	NR	26.8 ± 3.0 [23.4-31.6] weeks	Birth weight: 0.78 ± 17 [0.57-1.11] Body weight: 0.97 ± 0.23 [0.69-1.43]	0.62 ± 0.33 [0.29-1.34]
Kloprogge et al. (13)	2019	England	General pediatrics (13.3 % experienced nephrotoxicity)	616*	61 [0.03-255] months	NR	NR	19 [0.742-95]	39 [5-892][e]
Lanke et al. (14)	2017	USA	Adolescent patients with suspected sepsis	463 (266/197)	15.6 (14.0-17.5)[b]	NR	NR	58.9 (45.8-72.2)[b]	0.62 (0.50-0.79)[b]
Le et al. (15)	2013	USA	General pediatric patients	25 (18/7)	50.2 ± 17.0 (21-81)	NR	NR	22.8 (12.6-46.0)[b]	0.48 ± 0.33 (0.3-0.6)
Le et al. (16)	2014	USA	Children with renal insufficiency	63 (40/23)	13 ± 6	NR	NR	52 ± 26	1.3 ± 0.5
			Control: general pediatric patients	63 (31/32)	13 ± 6	NR	NR	50 ± 25	0.6 ± 0.2

Study	Publication year	Country	Patients	N (male/female)	Age (y)[a] PNA	PMA	GA	Body and birth weight (kg)[a]	Scr (mg/dL)[a]
Le et al. (17)	2014	USA	General pediatric patients	138 (72/66)	6.1 (2.2-12.2)[b]	NR	NR	22.2 (13.2-37.9)[b]	0.37 (0.30-0.50)[b]
Le et al. (18)	2014	USA	Control: general pediatric patients	635 (341/294)	6.8 [2.4-13.6][b]	NR	NR	23 [12.8-47.3][b]	0.4 (0.3-0.5)[b]
			General pediatric patients who experienced nephrotoxicity	45 (20/25)	5.1 [1.5-14.3][b]	NR	NR	23.4 [12.9-42.4][b]	0.3 (0.2-0.6)[b]
Le et al. (19)	2015	USA	Overweight and obese	87 (44/43)	10.0 (4.8-15.2)[b]	NR	NR	44.0 (23.4-78.1)[b]	0.51 ± 0.22 (0.34-0.67)
			Control: normal weight children	87 (42/45)	10.2 [4.5-14.8][c]	NR	NR	31.3 (16.8-47.1)[b]	0.48 ± 0.20 (0.30-0.60)
Li et al. (20)	2018	China	Critically ill Chinese neonates	80 (54/26)	32.3 ± 24.1 [4-126] days	39.4 ± 3.60 [29-47.1] weeks	34.7 ± 4.31 [25.7-41.1] weeks	2.87 ± 0.89 [1.4-5.6]	23.2 ± 10.4 [5.85-61.6][c, e]
Liu et al. (21)	2017	China	General pediatric patients	54 (23/31)	124.30 [1.29 – 541.4] weeks	NR	NR	10.36 [1.4-33.5]	0.39 [0.15-1.32]
Mehrotra et al. (22)	2012	USA	Full term and preterm neonates	134 (72/62)	26.8 ± 24.3 [1-121] days	36.5 ± 5.2 [24.6–44] weeks	32.7 ± 5.7 [23-41] days	2.5 ± 1.1 [0.6-5.3]	0.6 ± 0.38 [0.2-2.5]
Moffett et al. (23)	2018	USA	ECMO	93 (48/45)	0.64 (0.07-6.7)[b]	NR	NR	7.6 (3.7-21.9)[b]	0.56 (0.32–1.01)[b]
Moffett et al. (24)	2019	USA	Cardiac surgical population	261 (157/104)	0.31 (0.07-0.77)[b]	NR	NR	4.8 (3.4-7.4)[b]	0.32 (0.25-0.41)[b]
Moffett et al. (25)	2019	USA	CVVHDF	138 (63/75)	4.9 [1.0, 14.5][c]	NR	NR	31.0 ± 25.8	0.72 (0.41-1.29)[b]
Moffett et al. (26)	2019	USA	Large pediatric patients: obese (75%) and overweight (13.8%)	196 (135/61)	15.9 [9.3-18.9][c]	NR	NR	91.8 ± 20.6	0.90 ± 0.48
Sheng et al. (27)	2017	China	Infants	61 (34/27)	0.08 [0.003-0.97][c]	37.86 [26.00-41.43][c] weeks	NR	3.15 [0.95-16.0][c]	32.3 [10.4 – 109][c]
Song et al. (28)	2017	China	Neonates and infants	316 (201/115)	24 [0-60]c days	NA	37 [28-41][c] weeks	3.95 [1.25-5.38][c]	28.6 [12-151][c, e]
Stockman et al. (29)	2013	USA	Children with Cystic fibrosis	67 (27/40)	13.9 (8-17)[b]	NA	NA	41.2(25.5-56.8)[b]	NR
Zane et al. (30)	2017	USA	Hypothermic children resuscitated from cardiac arrest	11*	43 [4-211][c] months	NR	NR	16.4 [7-88.3][c]	0.2 [0.1-2.0[c]
			Normothermic children resuscitated from cardiac arrest	41*	23 [1.75-210][c] months	NR	NR	12 [3.8-77.5][c]	0.4 [0.1-3.9][c]
Zhang et al. (31)	2016	China	Normal renal function	66 (43/23)	8.0 [1.1-23.9][c] months	NR	NR	8.2 ± 2.4	0.3 ± 0.1
			Mild renal insufficiency	24 (17/7)	6.5 [1.0-24.0][c] months	NR	NR	8.0 ± 3.3	0.5 ± 0.1

Study	Publication year	Country	Patients	N (male/female)	Age (y)[a] PNA	PMA	GA	Body and birth weight (kg)[a]	Scr (mg/dL)[a]
			Moderate renal insufficiency	20 (14/6)	3.0 months [1.1-24.0][c]	NR	NR	6.6 ± 3.0	0.7 ± 0.2
			Total	110 (74/36)	6.0 months [1.0-24.0][c]	NR	NR	7.9 [5.0-11.2]	NR
Zhao et al. (32)	2013	France	Neonates	116 (59/57)	26 ± 25 [1-120] days	33.8 ± 5.3 [24.4-49.4] weeks	NR	Birth weight: 1.331 ± 0.839 [0.510-3.930] Body weight: 1.700 ± 0.964 [0.460-5.680]	48 ± 33 [5-228][c]
Zhao et al. (33)	2014	France	Malignant hematological disease	70 (41/29)	6.8 ± 4.8 [0.3-17.7]	NR	NR	25.7 ± 15.5 [5.6-71.0]	32 ± 17 [10-141][c]

ARC augmented renal clearance, BMI body mass index, CPB cardiopulmonary bypass, CL_{CR} creatinine clearance, CVVHD continuous venovenous hemodialysis, ECMO extracorporeal membrane oxygenation, GA gestational age, ICU intensive care unit, NR not reported, PCA postconceptual age, PMA postmenstrual age, PNA postnatal age, Scr serum creatinine,

[a] Values are expressed as mean ± standard deviation [range] (interquartile range)

[b] Values are expressed as median (interquartile range)

[c] Values are expressed as median [range]

[d] Values are expressed in mL/min

[e] Values are expressed in µmol/L

* Gender was not reported

Table 3. 2 Summary of the clinical protocols for studies included in this review

Study	Design	Vancomycin administration	Samples			
		Dosage	Samples per patient	Total samples	Sampling only at steady state	Sampling scheme
Abdel Hadi et al. (1)	Retrospective	Initial: 205 [100–460][a] mg/day	2.45*	120	At least 51.5% at steady-state	Peak and trough
Alsultan et al. (2)	Retrospective	Initial: 61.5 ± 9.5[a] mg/kg/d	2	122	Yes	Peak and trough
Avedissian et al. (3)	Retrospective	45 (39.97-58.61)[b] mg/kg/d 16.63 (12.81–16.16)[b] mg/kg/dose	2.632*	658	Yes	94.4% were trough
Bhongsatiern et al.(4)	Retrospective	33.2 ± 17.6[a] mg/kg/d	3.5*	528	Yes	Peak and trough
Chen et al. (5)	Retrospective	Initial for bacteremia: 10 mg/kg q 8 or 12 h over 1 h IV infusion Initial for meningitis: 15 mg/kg q	1.55*	330	Yes	Peak (35%) and trough (65%)

Study	Design	Vancomycin administration	Samples			
		Dosage	Samples per patient	Total samples	Sampling only at steady state	Sampling scheme
		8 or 12 h over 1 h IV infusion				
Cies et al.(6)	Retrospective	Per standard of care at the respective hospital	7.7 [3-19][a]	108	NR	Trough
Dao et al. (7)	Retrospective	13.7 (10-16.1)[b] mg/kg	4.5[b]	1831	NR	Peak, trough, and random
Frymoyer et al. (8)	Retrospective	Initial:15 mg/kg q 12	6.84*	1702	No	Peak and trough
Germovsek et al. (9)	Retrospective	Initial: 15 mg/kg followed by IV infusion based on Scr levels	Intermittent: 2.61* Continuous: 4.34*	81 102	Yes	Peak and trough
Guilhaumou et al. (10)	Prospective	Initial: Loading dose of 10 mg/kg followed by 30 mg/kg continuous infusion	2.5*	301	Yes	NR
Ingrande et al. (11)	Prospective	A single dose of 15 mg/kg	[5-7][a]	57	No	Peak, trough, and random
Kato et al. (12)	Retrospective	26.2 ± 3.0[a] mg/kg/day	2.6*	26	NR	NR
Kloprogge et al. (13)	Retrospective	Per the standard of care at the respective hospital	7 [2-50][a]	4137	NR	NR
Lanke et al. (14)	Retrospective	48 (38-60)[b] mg/kg/day	2.4[a]	1107	No	Peak, trough, random
Le et al. (15)	Retrospective	45 ± 12[a] mg/kg/day	2.36*	1660	Yes	Peak, trough, random
Le et al. (16)	Retrospective	Renal insufficiency group: 38 ± 14 [a] mg/kg/day Control: 42 ± 13[a] mg/kg/day	2.53*	319	Yes	Mostly trough concentrations
Le et al. (17)	Retrospective	44 (39-47)[b] mg/kg/day	5.2*	712	Yes	Peak, trough, random
Le et al. (18)	Retrospective	46.7 ± 11.6[a] mg/kg/day	2.32*	1576	Yes	Trough
Le et al. (19)	Retrospective	Control: 47.4 ± 13.0 (39.9–53.3)[a] mg/kg/d Obese: 41.9 ± 12.0 (33.4–50.1)[a] mg/kg/d	2.27*	389	Mostly at steady state	Peak, trough, and random
Li et al. (20)	Retrospective	45 ± 16[a] mg	2.5*	165	Yes	Peak (n = 90) and trough (n = 75)
Liu et al. (21)	Retrospective	Per standard of care at the respective hospital	2.4*	128	Yes	Peak and trough
Mehrotra et al. (22)	Retrospective	Per standard of care at the respective hospital	2*	267	NR	Peak and trough
Moffett et al. (23)	Retrospective	14.6 ± 1.9[a] mg/kg/dose	4	433	NR	Time after dose: 13.2 ± 10.7 [a] h
Moffett et al. (24)	Retrospective	14.5 ± 1.7[a] mg/kg/dose	2.21*	578	NR	Time after dose: 8.9 ± 3.8 [a] h
Moffett et al. (25)	Retrospective	14.3 ± 1.6[a] mg/kg/dose	6 (2-12)[b]	828*	NR	Time after dose: 13.6 ± 8.4 [a] h
Moffett et al. (26)	Retrospective	13.3 ± 2.2[a] mg/kg/dose 1,192 ± 205[a] mg	1 (1-3)[b]	555	No	Time after dose: 7.9 h (0.0-112.4 h)[b]
Sheng et al. (27)	Retrospective	42.91 ± 13.74[a] mg/kg/d	1.18*	72	Yes	Peak and trough
Song et al. (28)	Retrospective	36.7 (13.7-73.5)[c] mg/kg/d	1.33*	421	No	Peak, trough, and random
Stockman et al. (29)	Retrospective	17.4 ± 4.4[a] mg/kg over 1 h infusion	7.25*	486	Yes	Peak and trough
Zane et al. (30)	Retrospective	Hypothermic children: 10 [5-20][c] mg/kg Normothermic children: 10 [10-20][c] mg/kg	2.96*	154	No	Trough
Zhang et al. (31)	Retrospective	39.6 [35.1-45.0][c] mg/kg/d	2*	253	Yes	Peak and trough
Zhao et al. (32)	Prospective	Hospital 1: Initial: 10 or 15 mg/kg with a maintenance dose of 15 to 35 mg/kg/day Hospital 2: Initial: 15 mg/kg with a maintenance dose of 30 mg/kg/day Hospital 3: 20 or 30 mg/kg/day	1.8*	207	NR	Time after dose: 26.8 h [9.8–137.8 h][c]
Zhao et al. (33)	Prospective	13.0 ± 3.4[a] mg/kg	1.4*	98	Yes	NR

NR not reported, PMA postmenstrual age, PNA postnatal age, Scr serum creatinine, TDM therapeutic drug monitoring

*Estimated

[a] Values are expressed as mean ± standard deviation [range] (interquartile range)

[b] Values are expressed as median (interquartile range)

[c] Values are expressed as median [range]

Table 3. 3 Reported vancomycin quantification methods

Study	Assay	LLQ -ULQ (mg/L)	Instrument
Abdel Hadi et al. (1)	NR	NR	NR
Alsultan et al. (2)	Chemiluminescent microparticle immunoassay	NR	NR
Avedissian et al. (3)	Fluorescence polarization immunoassay	2.0-100	AxSYM (Abbott Laboratories, Abbott Park, IL)
Bhongsatiern et al. (4)	Fluorescence polarization immunoassay	2.0-100	AxSYM (Abbott Laboratories, Abbott Park, IL)
Chen et al. (5)	Enzyme multiplied immunoassay	2.0-50	Viva-E (Siemens Healthcare Diagnostics, Eschborn, Germany) Siemens Healthcare Diagnostics
Cies et al.	Method 1: fluorescence polarization immunoassay	NR	Roche Integra 800 analyzer (Roche Diagnostics, Manheim, Germany)
	Method 2: chemiluminescent microparticle immunoassay	NR	ARCHITECT i System (Abbott Labs, Abbott Park, IL)
Dao et al. (7)	Fluorescence polarization immunoassay	0.74	Cobas Integra 400+, Roche Diagnostics)
Frymoyer et al. (8)	Particle-enhanced turbidimetric inhibition immunoassay	0.8-50	Dimension clinical chemistry system (Siemens Healthcare Diagnostics)
Germovsek et al. (9)	Enzyme multiplied immunoassay	1.7-80.0	Cobas 702 platform

Study	Assay	LLQ -ULQ (mg/L)	Instrument
			(Roche Diagnostics)
Guilhaumou et al. (10)	Fluorescence polarization immunoassay	2.00	Cobas Integra 400+ (Roche Diagnostics, Mannheim, Germany)
Ingrande et al.(11)	Particle-enhanced turbidimetric inhibition immunoassay	0.8	Siemens RxL analyzer (Siemens Healthcare Diagnostic, Newark, DE)
Kato et al. (12)	Enzyme multiplied immunoassay	1.7	Roche Diagnostics K., K., Tokyo, Japan
Kloprogge et al. (13)	Quantitative microsphere system immunoassay	2.0-100	Indiko Plus
Lanke et al. (14)	Immunoassay	1.1-100	Abbott Architect System
Le et al. (15)	Method 1: direct chemiluminescence technology	0.67-90	Advia Centaur System (Siemens Medical Solution, Deerfield, IL)
	Method 2: fluorescence polarization immunoassay	2.0-100	AxSYM (Abbott Laboratories, Abbott Park, IL).
Le et al. (16)	Fluorescence polarization immunoassay	2.0-100	AxSYM (Abbott Laboratories, Abbott Park, IL).
Le et al. (17)	Method 1: direct chemiluminescence technology	0.67-90	Advia Centaur System (Siemens Medical Solution, Deerfield, IL)
	Method 2: fluorescence polarization immunoassay	2.0-100	AxSYM (Abbott Laboratories, Abbott Park, IL).
Le et al. (18)	Fluorescence polarization immunoassay	2.0-100	AxSYM (Abbott Laboratories, Abbott Park, IL).
Le et al. (19)	NR	NR	NR
Li et al. (20)	Fluorescence polarization immunoassay	3.0-50	ARCHITECT i2000SR (Abbott Laboratories, Chicago, IL, USA).
Liu et al. (21)	Fluorescence polarization immunoassay	7-75	TDx FLX assay system (Abbott Laboratories, Irving, TX, USA).
Mehrotra et al. (22)	NR	NR	NR
Moffett et al. (23)	Enzyme multiplied immunoassay	5.0-50	VITROS 5600 (Ortho Clinical Diagnostics, Raritan, NJ) Integrated System
Moffett et al. (24)	Enzyme multiplied immunoassay	5.0-50	VITROS 5600 (Ortho Clinical Diagnostics, Raritan, NJ) Integrated System
Moffett et al. (25)	Enzyme multiplied immunoassay	5.0-50	VITROS 5600 (Ortho Clinical Diagnostics, Raritan, NJ) Integrated System
Moffett et al. (26)	NR	NR	NR
Sheng et al. (27)	Chemiluminescence microparticle immunoassay	3.0-NR	ARCHITECT i1000 system (Abbott Laboratories, Abbott Laboratories, Chicago, IL, USA)
Song et al. (28)	Fluorescence polarization immunoassay	1.0-NR	NR
Stockman et al. (29)	Fluorescence polarization immunoassay	2.0-100	AxSYM (Abbott Laboratories, Abbott Park, IL).
Zane et al. (30)	NR	NR	NR
Zhang et al. (31)	HPLC	0.9–117.3	Agilent HPLC
Zhao et al. (32)	Method 1: fluorescence polarization immunoassay	0.74-NR	Cobas Integra system (Roche Diagnostics, Meylan, France)
	Method 2: immunoturbidimetric assay	2.0-NR	
Zhao et al. (33)	Fluorescence polarization immunoassay	0.74-NR	Cobas Integra 400 plus system (Roche Diagnostics, Meylan, France)

CV coefficient of variation, HPLC high-performance liquid chromatography system, LLQ lower limit of quantification, NR not reported, RUV residual unexplained variability, ULQ upper limit of quantification

Table 3. 4 Population pharmacokinetic modeling methods and techniques used by the studies included in the review

Study	Compartments	Modeling		
		Software	Validation	Covariate modeling
Abdel Hadi et al. (1)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P \leq 0.05$) and backward elimination ($P \leq 0.005$))
Alsultan et al. (2)	One-compartment	Monolix 4.3	External (n = 16)	SCM
Avedissian et al. (3)	One-compartment	NONMEM 7.2	Internal: bootstrap	SCM (forward inclusion ($P \leq 0.05$))
Bhongsatiern et al. (4)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000) and NPDE	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Chen et al. (5)	One-compartment	NONMEM VII	Internal: bootstrap (n=1000); external (n=57)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Cies et al. (6)	One-compartment	Pmetrics	NR	SCM
Dao et al. (7)	One-compartment	NONMEM 7.3	Internal: bootstrap and NPDE; external (n=78)	NR
Frymoyer et al. (8)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=2000) and NPDE	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Germovsek et al. (9)	One-compartment	NONMEM 7.3	External (n=34)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Guilhaumou et al. (10)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	Biological plausibility and SCM
Ingrande et al.(11)	Two-compartment	NONMEM 7.3	Internal: bootstrap (n=1000)	General additive model
Kato et al. (12)	One-compartment	Phoenix NLME	Internal: bootstrap (n=200) and NPDE	SCM (forward inclusion and backward elimination ($P < 0.01$))
Kloprogge et al. (13)	Two-compartment	NONMEM 7.3	Internal: bootstrap (n=1000) and NPDE; external (n=169)	A priori selection and backward elimination
Lanke et al. (14)	One-compartment	NONMEM 7.3	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Le et al. (15)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$))
Le et al. (16)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$))
Le et al. (17)	One-compartment	NONMEM 7.2	NR	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$))
Le et al. (18)	One-compartment	NONMEM 7.2	Internal: bootstrap	SCM ($P < 0.05$)
Le et al. (19)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000) and NPDE	A priori selection and SCM
Li et al. (20)	One-compartment	NONMEM 7.4	Internal: bootstrap (n=2000) and NPDE	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$))
Liu et al. (21)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=2000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$))
Mehrotra et al. (22)	One-compartment	NONMEM V	NR	SCM (forward inclusion ($P < 0.001$) and backward elimination ($P < 0.001$)) elimination
Moffett et al. (23)	Two-compartment	NONMEM 7.3	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Moffett et al. (24)	One-compartment	NONMEM 7.3	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Moffett et al. (25)	Two-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Moffett et al. (26)	One-compartment	NONMEM 7.3	Internal: bootstrap (n=1000) and NPDE	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.001$))
Sheng et al. (27)	One-compartment	NONMEM 7.3	Internal: bootstrap (n=500)	SCM (forward inclusion ($P < 0.005$) and backward elimination ($P < 0.001$))
Song et al. (28)	Two-compartment	Phoenix NLME 1.3	Internal: bootstrap (n=2000); external (n=19)	SCM (forward inclusion ($P < 0.01$) and backward elimination ($P < 0.001$))
Stockman et al. (29)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.01$) and backward elimination ($P < 0.001$))
Zane et al. (30)	Two-compartment	NONMEM 7.2	NR	A priori selection and backward elimination
Zhang et al. (31)	One-compartment	Phoenix NLME 1.2	Internal: bootstrap (n=1000)	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.01$))
Zhao et al. (32)	One-compartment	NONMEM VI	Internal: bootstrap (n=500) and NPDE	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$))
Zhao et al. (33)	One-compartment	NONMEM 7.2	Internal: bootstrap (n=500) and NPDE	SCM (forward inclusion ($P < 0.05$) and backward elimination ($P < 0.005$)) and

Study	Compartments	Modeling		
		Software	Validation	Covariate modeling
				biological plausibility

SCM stepwise covariate modeling; NR not reported; NPDE prediction distribution error

Table 3. 5 Population pharmacokinetic models (one-compartment)

Study	CL (L/h)			V_d (L)			IIV		RUV	
	Formula	Parameter	Value	Formula	Parameter	Value	CL (%)	V_d (%)	Proportional (%)	Additive (mg/L)
Abdel Hadi et al. (1)	$\theta_2 \times ALWT$	θ_2	0.381	$\theta_1 \times WT$	θ_1	0.663	44	Not characterized	-	CV = 33%
Alsultan et al. (2)[a]	$\theta \times (WT/20)$	θ	2.99	-	θ	9.55	15[a]	11.6	11.90%	-
Avedissian et al. (3)	$\theta_{CLwt} \times WT \times (e^{(\theta_{CLwtSCr} \times (Scr - 0.40))}$	θ_{CLwt}	0.118	$\theta_{vwt} \times WT$	θ_{vwt}	0.624	38.7	34.9	21%	2.96
		$\theta_{CLwtSCr}$	-1.13							
Bhongsatiern et al. (4)	$\theta_1 \times (WT/1.5)^{\theta_3} \times (CL_{CR}/36)^{\theta_4} \times (PMA/33)$	θ_1	0.095	$\theta_2 \times (WT/1.5)$	θ_2	0.905	19.2	23.5	-	17.5
		θ_3	0.585							
		θ_4	0.72							
Chen et al. (5)	$\theta_1 \times (WT/70)^{0.75} \times (PMA^{\theta_4}/PMA^{\theta_4} + \theta_3^{\theta_4}) \times (Scr/0.28)^{\theta_3}$	θ_1	4.87	$\theta_2 \times (WT/70)$	θ_2	40.7	26.8	0 Fixed	23.9%	0.688
		θ_3	34.5							
		θ_4	4.61							
		θ_5	-0.221							
Cies et al.(6)	θ x ([eGFR/eGFR$_{median}$])$^{0.75}$	Θ	3.48	NR	V_d	1.2 L/kg	NR	NR	NR	NR
Dao et al. (7)	$\theta_1 \times (WT/WT_{median})^{\theta_2} \times (Scr/Scr_{median})^{\theta_3} \times MF$	θ_1	0.268	$\theta_4 \times WT/WTmedian$	θ_4	0.629	22.6	Not characterized	CV = 0.236%	CV = 1.98%
	$MF = PMA^{Hill}/(PMA^{Hill} + T50^{Hill})$	θ_2	0.438							
		θ_3	0.483							
		Hill	3.57							
		T50	46							
Frymoyer et al. (8)	$\theta_1 \times (WT/2.9\ kg)^{0.75} \times F_{mat} \times (1/SCr_{mg/dl})^{\theta_2}$	θ_1	0.345	$\theta_3 \times (WT/2.9\ kg)$	θ_3	1.75	21.6	10.9	20.5%	1.3
	Where $F_{mat} = 1/(1+ [PMA_{wk}/TM_{50}])^{\theta_{Hill}}$	TM_{50}	34.8							
		Hill	4.53							
		θ_2	0.267							
Germovsek et al. (9)	$\theta_1 \times MF \times (WT/70)^{0.632}$ Where $MF = PMA^{Hill}/(PMA^{Hill} + T50^{Hill})$	θ_1	5.7	$\theta_2 \times (WT/70)$	θ_2	39.3	0.1	0.1	0.09	-
Guilhaumou et al. (10)	$\theta_{CL} \times (WT/70)^{0.75}$	$\theta_{CL:hemato\ without\ CsA}$	4.66	θ_V	θ_V	34.8	31.1	60.9	0.238	4.45
		$\theta_{CL:hemato\ with\ CsA}$	3.49							
		$\theta_{CL:solid}$	4.97							
Kato et al. (11)	θ_1 x $(Scr/0.59)^{-0.80} \times (Volume\ of\ infusion/159.3)^{0.98}$	θ_1	0.054	θ_2	θ_2	1.19	14.8	29.4	-	0.3
Lanke et al.	$\theta_1 \times (WT/58.9)^{\theta_3} \times (CLCR/108.1)^{\theta_4}$	θ_1	4.85	$\theta_2 \times (WT/58.9)^{\theta_5}$	θ_2	31.0	27.9	24.9	20.7%	CV = 37.1%

(12)	θ_3	0.84		θ_5	0.52					
	θ_4	0.78								
Le et al. (13) $\theta_2 \times WT^{0.75} \times (0.48/Scr)^{\theta 3} \times [\ln(Age)/7.8]^{\theta 4}$	θ_2	0.248	$\theta_1 \times WT$	θ_1	0.636	35	18	29%	-	
	θ_3	0.361								
	θ_4	0.995								
Le et al. (14) $\theta^2 \times WT^{0.75} \times (0.64/SCr)^{\theta 3} \times [\ln(DOL)/8.6]^{\theta 4}$	θ_2	0.235	$\theta_1 \times WT$	θ_1	0.564	39	Not characterized	28%	-	
	θ_3	0.407								
	θ_4	1.090								
Le et al. (15) $\theta^1 \times WT^{0.75} \times (0.4/SCr)^{\theta 2} \times [\ln(Age)/7.7]^{\theta 3}$	θ_1	0.258	$\theta_4 \times WT$	θ_4	0.644	41	12	32%	-	
	θ_2	0.431								
	θ_3	0.808								
Le et al. (16) $\theta_{CL} \times WT^{0.75} \times (0.39/SCr)^{\theta CL\_SCr} \times [\ln(Age)/3.4]^{\theta CL\_AGE}$	θ_{CL}	0.105	$\theta_V \times WT$	θ_V	0.628	34	22	26.40%	1.29	
	$\theta_{CL\ SCr}$	0.457								
	$\theta_{CL\ AGE}$	1.12								
Le et al. (17) $\theta 2 \times ALWT \times (0.4/Scr)^{\theta 3} \times (\ln[Age]/8.3)^{\theta 4}$	θ_2	0.286	$\theta_1 \times WT$	θ_1	0.574	30	29	24%	-	
	θ_3	0.29								
	θ_4	0.755								
Li et al. (18) $\theta 1 \times (WT/2.9)^{\theta 2} \times (23.3/SCr)^{\theta 3}$	θ_1	0.309	$\theta_4 \times (WT/2.9)^{\theta 5}$	θ_4	2.63	37.9	Not characterized	37.5%	-	
	θ_2	1.55		θ_5	1.05					
	θ_3	0.337								
Liu et al. (19) $\theta_1 \times [PNA^{\theta 2}/(PNA^{\theta 2} + 33.3^{\theta 2})] \times (WT/70)^{0.75}$	θ_1	11.75	$\theta_3 \times WT/70$	θ_3	54.49	36.2	67.11	32.15%	0.62	
	θ_2	0.4672								
Mehrotra et al. (20) $\theta_1 \times (WT/2.5)^{0.75} \times (0.42/Scr)^{\theta 2} \times (PMA/37)^{\theta 3}$	θ_1	0.18	$\theta_4 \times (WT/2.5)$	θ_4	1.7	25.3	21.8	16	1.5[b]	
	θ_2	0.7								
	θ_3	1.4								
Moffett et al. (21) $\theta_1 \times (WT/70)^{0.75} \times (CL_{CR}/84)^{\theta 2} \times (1/[1 + (PMA/50)^{\theta 3}])$	θ_1	7.86	$\theta_4 \times (WT/70)$	θ_4	63.6	17.4	25.5	19.90%	-	
	θ_2	0.9								
	θ_3	-0.285								
Moffett et al. (22) $\theta_1 \times (FFM/70)^{0.75} \times \theta 2^{(Scr/0.67)}$	θ_1	18.6	$\theta_3 \times (FFM/70)$	θ_3	102	32.6	40.5	21.70%	-	
	θ_2	0.582								
Sheng et al. (23) $\theta_1 \times e^{0.0193} \times (WT/3.22)^{\theta 3} \times (PNA/0.1)^{\theta 4}$	θ_1	0.449	θ_2	θ_2	4.45	ω = 0.0193	0 fixed	0 Fixed	0.281	
	θ_3	0.643								
	θ_4	0.289								
Stockman et al. (24) $\theta_{CL} \times (WT/70)^{0.75}$	θ_{CL}	5.57	-	V_d	44.1	7	16	CV=0.29%	CV =351%	
Zhang et al. (25) $\theta_{CL} \times (WT/7)^{\theta WT\_CL} \times (GFR/108)^{\theta GFR}$	θ_{CL}	0.83	$\theta_{Vd} \times (WT/7)^{\theta WT\_Vd}$	θ_{Vd}	4.22	28.2	21.6	-	0.01	
	$\theta_{WT\ CL}$	0.97		$\theta_{WT\ Vd}$	0.93					
	θ_{GFR}	0.42								
Zhao et al. (26) $\theta_3 \times (WT/1416)^{\theta 4} \times (\text{birth weight}/1010)^{\theta 5} \times (1 + \theta_6 \times (PNA/17)) \times (1/(SCr/42)^{\theta 7})$	θ_3	0.0571	$\theta_1 \times (WT/1416)^{\theta 2}$	θ_1	0.791	17.9	40.1	20.30%	2.28	
	θ_4	0.513			0.898					
	θ_5	0.599								
	θ_6	0.282								
	θ_7	0.525								
Zhao et al (27) θ_3 x $(WT/20.2)^{\theta 4}$ x RF $RF = (CL_{CR}/191)^{\theta 5}$	θ_3	4.37	θ_1 x $(WT/20.2)^{\theta 2}$	θ_1	119	34.8	77	5.30%	1.17	
	θ_4	0.677		θ_2	0.838					
	θ_5	1.03								

ALWT allometric body weight, CL clearance, CL_{CR} creatinine clearance, FFM fat-free mass, GFR glomerular filtration rate, IIV interindividual variability, MF maturation function, PMA postmenstrual age, PNA postnatal age, RF renal function, RUV residual unexplained variability, SCr serum creatinine, V_d Volume of distribution, WT body weight

[a] Intercessional variability on CL of 9.40%
[b] for data with LOQ of 5 mg/L, the additive error was 5 mg/L

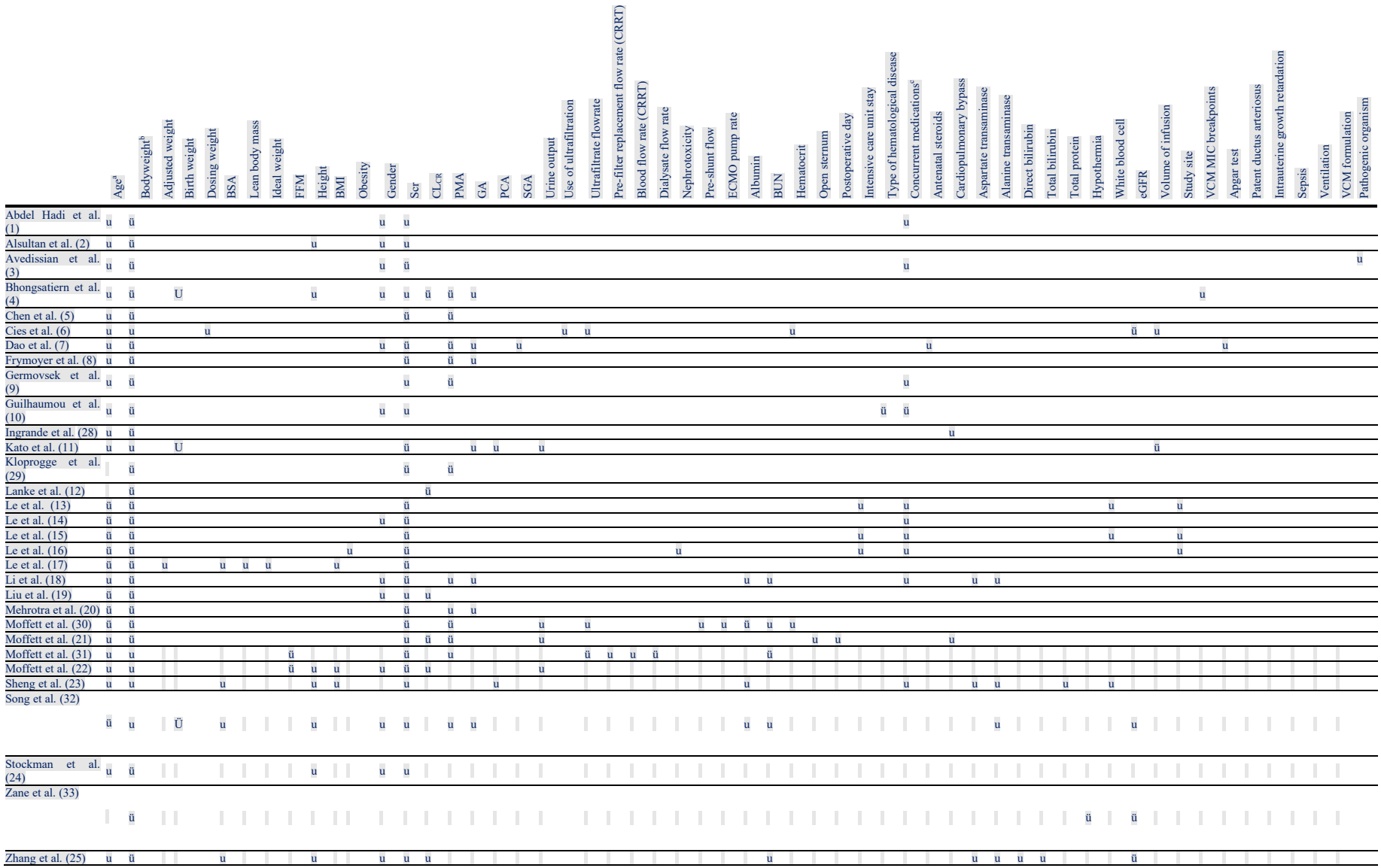
Table 3. 6 Population pharmacokinetic models (two-compartment)

Study	CL (L/h)			V_1 (L)			V_2 (L)			IIV			RUV	
	Formula	Parameter	Value	Formula	Parameter	Value	Formula	Parameter	Value	CL (%)	V_1 (%)	V_2 (%)	Proportional (%)	Additive (mg/L)
Ingrande et al.(28)	θ_3	θ_3	0.03	θ_1- θ_5 x WT	θ_1 θ_5	1.43 0.178	θ_2	θ_2	1.55	NR	NR	NR	NR	NR
Kloprogge et al. (29)	NR	CL	4.84	NR	V_1	39.9	NR	V_2	37.8	50.4	232	Not characterized	-	0.243
Moffett et al. (30)	θ_1 x (WT/70)$^{0.75}$ x (0.56/Scr)θ_2 x (1/[1 + (PMA/43)θ_3]	θ_1 θ_2 θ_3	3.96 0.809 -0.949	θ_4 x (WT/70) x $\theta_5^{(AGE/0.64)}$	θ_4 θ_5	25.2 0.932	θ_6 x θ_6 (WT/70) x $\theta_7^{(2.9/ALB)}$		32.4	28.8	94.8	-	19.40%	-
Moffett et al. (31)	θ_1 x (FFM/70)$^{0.75}$ x $\theta_2^{LN(SCr/0.56)}$ x $\theta_3^{LN(BUN/30)}$ x $\theta_4^{(CRRTUF/500*05\text{^}(DILYSTE/600))}$	θ_1 θ_2 θ_3 θ_4 θ_5	2.24 0.535 0.92 1.88 1.12	θ_6 x (FFM/70)	θ_6	81	θ_7 x θ_7 (FFM/70)		550	32.30%	27.50%	-	20.50%	-
Song et al. (32)	θ_1 x (BWT/3.22)$^{\theta 2}$ x (PNA/29)$^{\theta 3}$	θ_1 θ_2 θ_3	0.42 0.888 0.449	-	θ_4	1.27	Θ_5	Θ_5	2.2422	ω = 0.317	-	-	-	2.187
Zane et al. (33)	θ_1 x (WT/70)$^{0.75}$ x (GFR/90)$^{\theta 2}$ x (Temp/37)$^{\theta 3}$	θ_1 θ_2 θ_3	4.48 1.01 1.96	θ_4 x (WT/70)	θ_4	12.7	θ_5 x θ_5 (WT/70)		35.5	49.70%	136%	32.60%	20.90%	-

ALB albumin, BWT birth body weight, BUN blood urea nitrogen, CL clearance, CRRTUF continuous renal replacement therapy ultrafiltrate flow, DILYSTE dialysate flow rate, FFM fat-free mass, GFR glomerular filtration rate, PMA postmenstrual age, PNA postnatal age, RUV residual unexplained variability, IIV interindividual variability, SCr serum creatinine, Temp temperature, V_1 central volume of distribution, V_2 peripheral volume of distribution, WT body weight

Table 3. 7 Included or evaluated variables

Study	Variables


Age[a]
Bodyweight[b]
Adjusted weight
Birth weight
Dosing weight
BSA
Lean body mass
Ideal weight
FFM
Height
BMI
Obesity
Gender
Scr
CLCR
PMA
GA
PCA
SGA
Urine output
Use of ultrafiltration
Ultrafiltrate flowrate
Pre-filter replacement flow rate (CRRT)
Blood flow rate (CRRT)
Dialysate flow rate
Nephrotoxicity
Pre-shunt flow
ECMO pump rate
Albumin
BUN
Hematocrit
Open sternum
Postoperative day
Intensive care unit stay
Type of hematological disease
Concurrent medications[c]
Antenatal steroids
Cardiopulmonary bypass
Aspartate transaminase
Alanine transaminase
Direct bilirubin
Total bilirubin
Total protein
Hypothermia
White blood cell
eGFR
Volume of infusion
Study site
VCM MIC breakpoints
Apgar test
Patent ductus arteriosus
Intrauterine growth retardation
Sepsis
Ventilation
VCM formulation
Pathogenic organism
Abdel Hadi et al. (1)
Alsultan et al. (2)
Avedissian et al. (3)
Bhongsatiern et al. (4)
Chen et al. (5)
Cies et al. (6)
Dao et al. (7)
Frymoyer et al. (8)
Germovsek et al. (9)
Guilhaumou et al. (10)
Ingrande et al. (28)
Kato et al. (11)
Kloprogge et al. (29)
Lanke et al. (12)
Le et al. (13)
Le et al. (14)
Le et al. (15)
Le et al. (16)
Le et al. (17)
Li et al. (18)
Liu et al. (19)
Mehrotra et al. (20)
Moffett et al. (30)
Moffett et al. (21)
Moffett et al. (31)
Moffett et al. (22)
Sheng et al. (23)
Song et al. (32)
Stockman et al. (24)
Zane et al. (33)
Zhang et al. (25)

Zhao et al. (26)	ü	ü		Ü										ü		u																				u															u	u	u	u	u	
Zhao et al. (27)	u	ü												u	ü																				u																					
Summary																																																								
ü Frequency	**8**	**27**	**0**	**2**	**0**	**0**	**0**	**0**	**2**	**0**	**0**	**0**	**0**	**17**	**4**	**8**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**3**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
u Frequency	**20**	**6**	**1**	**2**	**1**	**4**	**1**	**1**	**0**	**7**	**3**	**1**	**13**	**12**	**3**	**5**	**7**	**2**	**1**	**4**	**1**	**2**	**1**	**1**	**0**	**1**	**1**	**1**	**3**	**4**	**2**	**1**	**1**	**3**	**1**	**10**	**1**	**2**	**3**	**4**	**1**	**1**	**1**	**0**	**3**	**1**	**1**	**3**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Sum	**28**	**33**	**1**	**4**	**1**	**4**	**1**	**1**	**2**	**7**	**3**	**1**	**13**	**29**	**7**	**13**	**7**	**2**	**1**	**4**	**1**	**3**	**1**	**1**	**1**	**1**	**1**	**1**	**4**	**5**	**2**	**1**	**1**	**3**	**2**	**11**	**1**	**2**	**3**	**4**	**1**	**1**	**1**	**1**	**3**	**4**	**2**	**3**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**

BMI body mass index, BSA body surface area, BUN blood urea nitrogen, BWT birth bodyweight, CL_{CR} creatinine clearance, CRRT continuous renal replacement therapy, eGFR estimated glomerular filtration, FFM fat-free mass, GA gestational age, GFR glomerular filtration rate, PCA postconceptional age, MIC minimum inhibitory concentration, PMA postmenstrual age, PNA postnatal age, SCr serum creatinine, SGA: small for gestational age status, VCM vancomycin

□Variable that significantly improved model fit

□Variable that did not result in a significantly improved model fit

[a] Includes PNA

[b] Includes a priori inclusion of allometric weight

[c] Tested but not significant concurrent medications include aminoglycoside, amphotericin B, ceftriaxone, dexamethasone, furosemide, gentamicin, ibuprofen, inotrope, meropenem, sirolimus, and tacrolimus

3.6 Supplementary Material 3.1

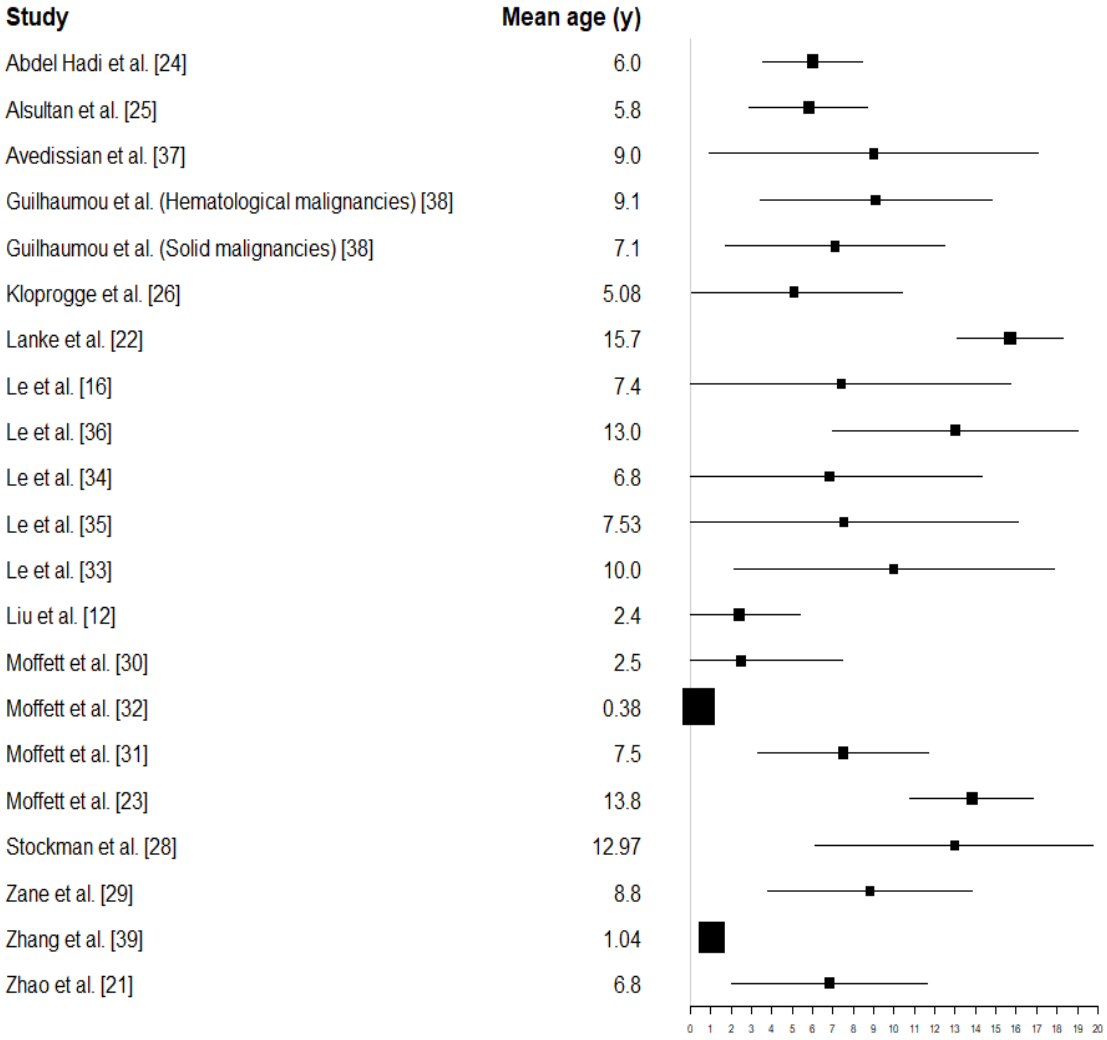


Figure S3.1. Simulation of the age distribution for the studies reported age in years assuming a truncated normal distribution. Mean age was estimated based on this assumption.

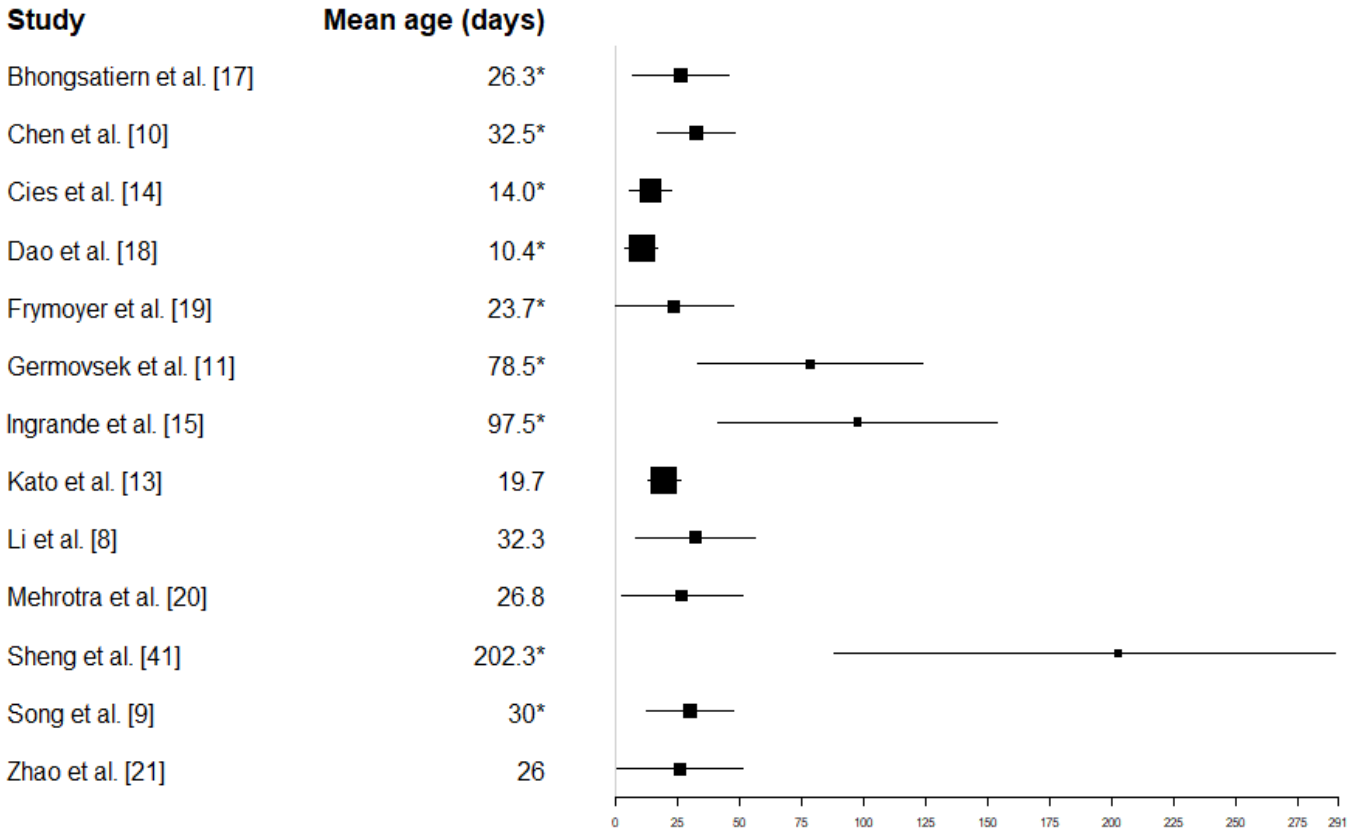


Figure S3.2. Simulation of the age distribution for the studies reported age in days assuming a truncated normal distribution. *Mean ages were estimated based on this assumption.

Table S3. 8 Representation of age groups per study.

Study	Age group				
	Preterm	neonates (0-27 days)	Infants (28 days to 23 months)	Young Children (2-11 years)	Adolescents (>11 years)
Abdel Hadi et al. (1)				■	
Alsultan et al. (2)				■	
Avedissian et al. (3)		■	■	■	■
Bhongsatiern et al. (4)	■	■			
Chen et al. (5)		■	■		
Cies et al. (6)		■			
Dao et al. (7)	■	■			
Frymoyer et al. (8)		■			
Germovsek et al. (9)		■	■		
Guilhaumou et al. (10)				■	■
Ingrande et al.(28)			■		
Kato et al. (11)		■			
Kloprogge et al. (29)		■	■	■	
Lanke et al. (12)					■
Le et al. (13)		■	■	■	■
Le et al. (14)				■	■
Le et al. (15)		■	■	■	■
Le et al. (16)		■	■	■	■
Le et al. (17)				■	■
Li et al. (18)		■			
Liu et al. (19)			■	■	
Mehrotra et al. (20)	■	■			
Moffett et al. (30)		■	■	■	
Moffett et al. (21)		■	■		
Moffett et al. (31)				■	■
Moffett et al. (22)					■
Sheng et al. (23)	■	■	■		
Song et al. (32)		■	■		
Stockman et al. (24)				■	■
Zane et al. (33)				■	■
Zhang et al. (25)		■	■		
Zhao et al. (26)		■			
Zhao et al. (27)				■	■

The shaded area represents the presence of this age group in the respective study population

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Chapter 4

Pharmacokinetics Equations Versus Bayesian Guided Vancomycin Monitoring: Pharmacokinetic Model and Model-Informed Precision Dosing Trial Simulations

In light of the revised vancomycin monitoring guidelines, we aimed at exploring the predictive performance of the new monitoring methods in varying clinical scenarios. This chapter might help clinicians optimize vancomycin therapeutic monitoring.

4 Article III Pharmacokinetics Equations Versus Bayesian Guided Vancomycin Monitoring: Pharmacokinetic Model and Model-Informed Precision Dosing Trial Simulations

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Conflict of interest statement

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Keywords

vancomycin, vancomycin population PK, vancomycin therapeutic monitoring, model-informed precision dosing, clinical trial simulation

Abstract

The recently released revised vancomycin consensus guideline endorsed area under the concentration-time curve (AUC) guided monitoring. Means to AUC-guided monitoring includes first-order analytic equations and Bayesian software programs, with the latter approach being preferable. We aimed to evaluate the predictive performance of these two methods when monitoring using a trough or a peak and a trough at varying single or mixed dosing intervals (DI), as well as evaluate the significance of satisfying underlying assumptions of steady-state and model transferability. Methods included developing a vancomycin population pharmacokinetic model and conducting model-informed precision dosing clinical trial simulations. A one-compartment pharmacokinetic model with linear elimination, exponential between-subject variability, and mixed (additive and proportional) residual error model resulted in the best model fit. Conducted simulations demonstrated that Bayesian-guided AUC might, potentially, outperform that of equation-based AUC predictions. Our simulations might support rapid Bayesian monitoring using data as sparse and early as troughs at 1st DI. Depending on the quality of model transferability diagnostics and met assumptions, to a certain extent, Bayesian-guided AUC prediction performance using a trough from the 1st dosing interval was equivalent to the performance of PK equations using two measurements (peak and trough) from the 5th DI. However, a strong relation between model transferability diagnostics with predictive performance could not be established. Sampling from the 4th and/or 5th DI did not seem to have a significant effect. This study illustrates cases and conditions at which the most reliable AUC predictions can be obtained, which can help optimize vancomycin therapeutic monitoring.

4.1 Introduction

Vancomycin is widely used for suspected and confirmed serious invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections (1). Recently, the revised consensus guideline abandoned the previously recommended use of vancomycin trough concentrations as surrogates to estimate the ratio of the area under the concentration-time curve over 24 hours to minimum inhibitory concentration (AUC/MIC) (1, 2). Instead, the revised guideline recommended therapeutic target attainment through the means of AUC-guided dosing (1). This AUC-guided dosing should be achieved by employing a) first-order analytic equations or b) Bayesian software programs, with the latter approach being preferable (1). This preference was attributed to reports suggesting that Bayesian approaches can provide rapid and reliable AUC estimations while requiring as few as one vancomycin measurement that is not necessarily obtained at steady-state (1, 3). Rapid achievement of the target AUC can be vital for effective therapy (1). In contrast, valid use of first-order analytic equations requires at least two post-distributional vancomycin measurements (preferably at the same dosing interval [DI]) obtained at or near steady-state (1). The revised guideline, however, acknowledges difficulties determining steady-state conditions in clinical practice, being subject to variables such as changing renal function and loading dose (1). Trough monitoring might be preferred in certain settings according to a Canadian perspective on the revised guideline (4).

Utilizing pharmacokinetic and/or pharmacodynamic (PK/PD) models to optimize, guide, and individualize dosing using patients' covariates and drug concentrations is referred to as model-informed precision dosing (MIPD), Bayesian forecasting, or model-based precision dosing (5-7). Reports exist suggesting MIPD, for example, using Bayesian programs, might outperform clinician judgment in recommending vancomycin dosing regimens (3, 8). In principle, Bayesian

programs incorporate prior knowledge and experiments, such as a developed PK model and its parameter values. This prior component is combined with the patients' observed vancomycin concentrations to yield Bayesian posterior parameter distribution (5, 6, 9).

Despite the potentials of Bayesian-guided monitoring, equation-based AUC estimation was reported to result in an equivalent or better accuracy and bias compared to using five Bayesian programs (10). Further, recent reports indicated that few hospitals in the united states implemented AUC-guided dosing (11, 12). For example, a recent survey indicated that 70.3% (n = 202) of hospitals did not implement AUC-guided dosing with 43% of which had no plan to adopt it soon (12). Bayesian-guided monitoring was implemented in only 12% of hospitals surveyed (12). This low rate of implementation might be attributed, partly, to clinicians' unfamiliarity with Bayesian monitoring (11-13)

While both methods, *i.e.,* equations and Bayesian, were suggested in the revised guideline, a comprehensive analysis of their performances in predicting AUC under different real-life scenarios yet seems to be lacking. Using population PK (PopPK) modeling approach and MIPD clinical trial simulations, the first of our three-fold objective is to compare the predictive performance of equation- and Bayesian-based AUC estimation under different conditions (*e.g.,* variations of near and confirmed steady-state intervals using two vancomycin measurements per the guideline recommendations), as depicted in Figure 4.1. We also aim at evaluating Bayesian-guided AUC prediction when using two compared to one measurement, since the latter was only moderately recommended (1). Additionally, to increase familiarity with Bayesian monitoring, we aim at discussing proper Bayesian priors' selection including the influence of using sparsely sampled PK-fitted models as priors, and the relative significance of satisfying underlying assumptions.

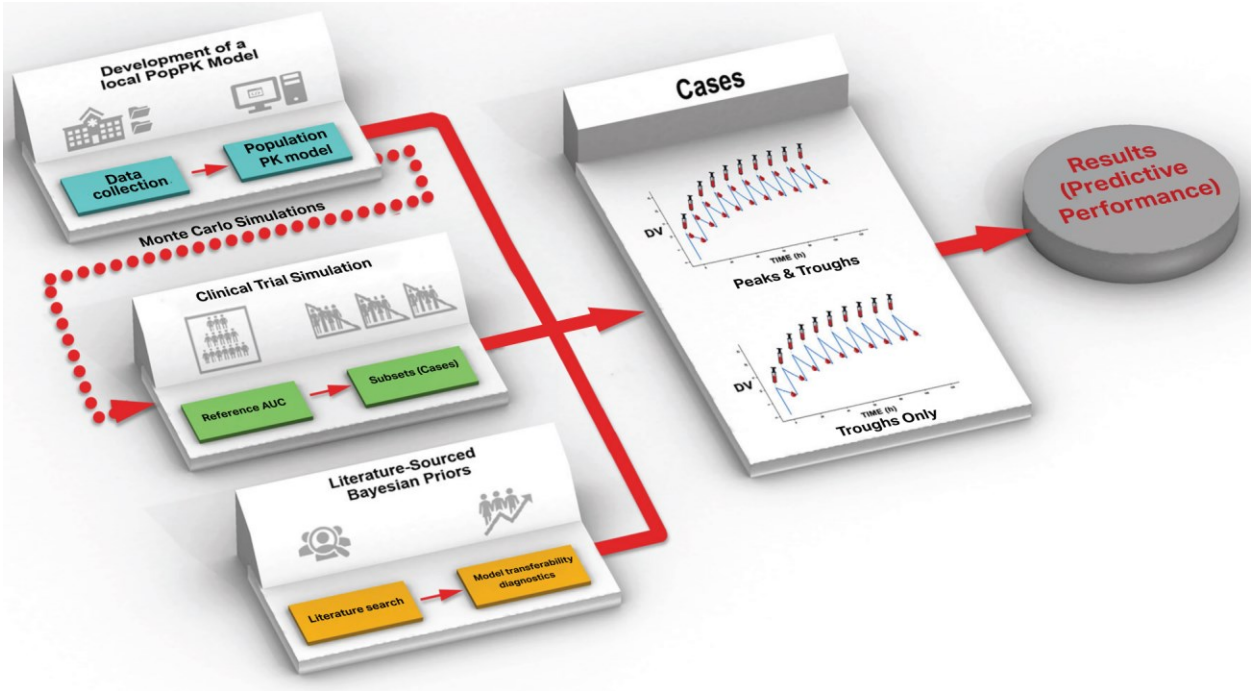

Figure 4. 1 Schematic roadmap of our study illustrating predictive performance, based on accuracy and bias calculations of two cases of peak and trough or trough only, each at six varying dosing intervals using the two main methods of 1st order PK equations and Bayesian methods. This roadmap shows two parallel processes of selecting Bayesian priors, either obtained through the literature or the PopPK model developed here.

4.2 Methods

4.2.1 Study Design

Adult patients admitted at the McGill University Health Center (MUHC)-Royal Victoria Hospital during 2016 and 2017 were screened for this single-center retrospective study. Included patients received at least four vancomycin Intravenous administrations and had at least one measured plasma concentration. Exclusion criteria were one or more of the following: acute kidney failure, renal replacement therapy, extracorporeal support membrane oxygenation (ECMO), end-stage renal disease, and intravenous fluids larger than 2 L within the last 4 vancomycin doses. Variables collected include vancomycin dosage and administration records, patients' demographics, the main indication for vancomycin, co-morbidities (*e.g.,* obesity,

neutropenia, liver disease, renal insufficiency), admission to the intensive care unit (ICU), laboratory, biochemistry, and microbiology data. This study was approved by the MUHC Institutional Review Board.

4.2.2 Vancomycin and Serum Creatinine Quantification

Vancomycin and serum creatinine were quantified using Beckman Coulter AU5800 (Beckman Coulter Inc., Brea CA, USA) with a quantification range of 2.5 - 100.0 mg/L and 4.4 - 4420 µmol/L for vancomycin and serum creatinine, respectively. We used QMS® Vancomycin (VANCO) assay (Thermo Fisher; Microgenics Corp., Fremont, CA, USA) and creatinine enzymatic assay (Olympus OSR61204).

4.2.3 Population Pharmacokinetic

Our first goal was to develop a local vancomycin PopPK model for the collected MUHC data. Vancomycin PopPK parameters were estimated using NONMEM (Version 7.4; GloboMax LLC, Hanover, MD, USA) within PsN toolkit (14). We used the first-order conditional estimation method with interaction (FOCE-I) to fit vancomycin concentration-versus-time profiles to a base one- and two-compartment model, while assuming log-normal between-subject variability (BSV) distribution on the typical parameter estimates. Multiple residual unexplained variability (RUV) models were tested, including additive, proportional, and mixed (additive and proportional) models. Allometric scaling of the effect of weight on vancomycin PK parameters was evaluated using the allometric theory (15).

Biologically plausible variables, including the collected patients' demographics (e.g. weight, body mass index, and serum creatinine) and co-morbidities (e.g. obesity, neutropenia, liver diseases, renal insufficiency, and admission to the intensive care unit (ICU)), were selected for multivariate analysis using stepwise covariate modeling (SCM) (16). We used ggplot2 in R

(www.r-project.org) to produce all the plots (17). Bootstrap analysis of 1000 replicates was conducted to evaluate uncertainty and 95% confidence intervals (CI) around model parameters. Further PopPK modeling details are presented in Supplementary Material, Section 4.5.1.

4.2.4 Individual Reference AUC

Based on the PopPK model developed in the previous section, we conducted Monte Carlo simulations of 1000 virtual patients to obtain individual steady-state AUC (AUC_i) (18). This simulated dataset will be referred to here as the reference dataset. Conditions of this simulation are presented in Supplementary Material, Section 4.5.2.

4.2.5 Prediction of Reference AUC

In this section, our goal was to predict AUC_i at steady-state from using concentrations from different DIs (*i.e.* not AUC_{tau} of the respective interval) using methods suggested in the revised guideline and detailed below (1).

4.2.5.1 First-Order Analytic Equations

As suggested in the revised guidelines, this method should be used with at least two measurements (peak and trough), obtained near steady-state (1). The equations (given in Supplementary Material, Section 4.5.3) were coded in R and used in Section 4.2.6.

4.2.5.2 Bayesian Estimation

Bayesian estimation was performed using two approaches and algorithms: a conventional Bayesian using the FOCE algorithm and a full Bayesian using Markov chain Monte Carlo (MCMC) algorithm. These two approaches are fundamentally different and a discussion about Bayesian analysis can be found in (9, 19), as well as in Supplementary Material, Section 4.5.4.

4.2.6 Selection of PopPK Models to Serve as Bayesian Priors

The goal of this step was to identify and systematically evaluate well-established PopPK models from the literature having similar study design and patient characteristics as MUHC data, to serve as Bayesian prior components. This assumes both subpopulations, of MUHC and the literature model, were derived from one population with similar study designs (20, 21). Based on these assumptions, we conducted a literature survey to identify proper original or recycled models published from inception and up to January 2020 using the methodology detailed in (22). These models were coded in NONMEM and evaluated according to the quality criteria discussed in (20), including ranking by the objective function (OFV), Akaike Information Criterion (AIC), and the visual overlap between individual η_i distribution densities with the theoretical η-distribution $N(0, \omega^2)$, as well as simulation-based diagnostics, such as prediction-corrected visual predictive check (pcVPC) and normalized prediction distribution errors (NPDE). These models, in addition to our PopPK model developed above, will serve, each in turn, as Bayesian priors to drive AUC predictions in Section 4.2.6.

4.2.7 MIPD Clinical Trial Simulations

In this step, our goal was to estimate AUC_i under multiple realistic clinical scenarios. Using the reference dataset simulated in Section 4.2.4, 14 subsets were created in R with each subset representing realistic clinical cases, Figure 4.1. These scenarios represent either couple of peaks and troughs or only troughs, obtained from single or mixed DIs, spanning from the first to the fifth DI, as well as at a steady-state (*i.e.* SS=1 in NONMEM). Using these scenarios and assuming a MIC value of 1 mg/L, three different clinical trials were conducted.

4.2.7.1 MIPD Clinical Trial A: Using Literature-Sourced Bayesian Priors

The goal of this trial was to compare the predictive performance of simple PK equations to Bayesian methods using Bayesian priors obtained from the literature. This trial simulation aimed at mirroring the implementation of Bayesian programs in clinical practice.

4.2.7.2 MIPD Clinical Trial B: Using Locally Constructed PK Model as Bayesian Prior

In Trial B, we used our local model, *i.e.,* MUHC PopPK model, as a Bayesian prior for subsequent analyses. This is to isolate the influence of Trial A model transferability assumptions, while examining and attributing results to the other remaining components, such as estimation methods and varying DIs.

4.2.7.3 MIPD Clinical Trial C: Sampling from Different Dosing Intervals

The goal of this trial was to study the effect of sampling from two different DIs. Using R, we randomly selected individual peaks and troughs from near steady-state intervals (*i.e.,* the 4^{th} and/or 5^{th} DI). This trial investigates the guideline preference of using peaks and troughs from the same dosing interval versus different DI when the PK equations are applied (1).

4.2.8 Performance Metrics

The predictive performance was evaluated in terms of relative bias (rBias) using relative mean percentage prediction error (rMPE) and relative mean absolute percentage prediction error (rMAPE) to assess accuracy, and using relative root mean squared error (rRMSE) to assess precision. The equations are given in Supplementary Material, Section 4.5.5. Considering the narrow vancomycin AUC/MIC range for therapeutic effect, a very conservative range of rMPE to fall within ± 20% was considered tolerable bias. For example, for an AUC_i value of 500, a prediction within 400-600 will result in a tolerable rMPE. Cases that result in smaller rRMSE values were considered more favorable if the rMPE 95% confidence interval includes zero.

4.2.9 Additional Verification of Results

For additional verification of results, we repeated steps 2.4 to 2.7 but with simulation from Colin *et al*. (23), a well-established PopPK model containing 8300 vancomycin measurements from 2554 patients across 14 centers. Trial simulations B and C and were not repeated and the MCMC algorithm was not used here due to its intensive computational demand.

4.3 Results

4.3.1 Patients

We included 116 patients, who satisfied the study criteria, having 326 measurements. Table 4.1 and Table S4.1 in Supplementary Material summarize the demographics and patient diagnosis of our MUHC data.

Table 4. 1 Baseline demographics and clinical characteristics of MUHC participants.

Variable	Value
Study size (n)	116
Male/female (n)	83/33
Vancomycin observations (n)	326
Trough measurements (%)	88%
Patients with one vancomycin observation (%)	40%
Patients with one or two vancomycin observations (%)	60%
Age* (years)	67.8 ± 11
Weight* (kg)	72 ± 8.6
Height* (cm)	167.9 ± 4.9
BMI* (kg/m^2)	24.2 ± 3.1
Serum creatinine* (mg/dL)	1.0 ± 0.5
Liver disease (n)	5
Neutropenia (n)	6

* Data presented as mean ± SD (SD: standard deviation).

4.3.2 Population Pharmacokinetic Modeling

A one-compartment model with linear elimination resulted in the best model fit, probably due to the sparse nature of our therapeutic drug monitoring (TDM) data (*i.e.,* 88% troughs and 40% of patients had one measurement). Exponential and mixed (additive and proportional) models best

described BSV and RUV, respectively. Introducing CL_{CR} on CL significantly reduced the objective function (*i.e.,* ΔOFV −118.34 at $p < 0.01$), and therefore was included in the final model. Model and values of typical parameter estimates are shown in Table 4.2. The diagnostic plots for the final model are presented in Supplementary Material, Figures S4.3 to S4.6. The final model had successful minimization and covariance.

Table 4. 2 MUHC vancomycin population PK model and the corresponding parameter estimates of the final model, as well as its bootstrap results.

PK Parameter	Final Model Estimates	% RSE[a]	Bootstrap Value (n=1000)[b]		
			Mean	2.5th Percentile	97.5th Percentile
CL (L/h) = Θ_1 * (CL_{cr}/84)					
Θ_1	4.16	4.1	4.16	3.84	4.53
V (L) = Θ_2 * (WT/70)					
Θ_2	102.46	9.7	102.95	82.3	125.0
Interindividual variability (IIV)					
ω_{CL}[c] (%)	34.12	11.2	34.0	26.68	42.07
ω_V[c] (%)	51.83	16.8	51.48	30.51	66.56
Residual unexplained variability (RUV)					
$\sigma_{Proportional}$[c] (%)	13.95	29.9	13.59	4.41	21.6
$\sigma_{Additive}$ (mg/L)	3.04	19.7	2.92	1.58	4.03

[a]Relative standard error; [b]95% success; [c]Expressed as a coefficient of variation (CV); CL: Clearance; V: Volume of distribution; Θ: NONMEM fixed-effect PK parameter; ω: standard deviation of the interindividual variation (*i.e.,* ηi); *σ: proportional or additive residual variability; concentrations (ε); CL_{cr}: Creatinine clearance.*

4.3.3 Literature-sourced Bayesian Priors

Seven vancomycin PopPK models were retained from the literature as Bayesian priors for subsequent analyses (23-29). Due to their TDM nature, literature-sourced models bared varying degrees of resemblances in design and population to the MUHC data. Nevertheless, we assumed a negligible influence arising from these differences on vancomycin PK parameter estimates that were not accounted for using model transferability diagnostics (22). We produced diagnostic

plots including pcVPC and NPDE (Supplementary Material, Table S 4.2). Models were ranked according to OFV, AIC, and visual overlap between individual ηi density distribution with the theoretical distribution (Supplementary Material, Table S4.3, and Figure S4.7). Results suggested that two models might be appropriate for MUHC data, namely Colin *et al.* and Yamamoto *et al.* (23, 27). Other models resulted in varying degrees of some systematic under- or over-prediction or misfit. It should be noted that Colin *et al.* model was slightly modified per MCMC run requirements (23, 30).

4.3.4 Clinical Trial Simulation

4.3.4.1 MIPD Clinical Trial A: Using Literature-Sourced Bayesian Priors

Results of MIPD Trial A using literature-sourced Bayesian priors are presented in Figure 4.2 and Supplementary Material, Figures S4.8 to S4.10. Trial A might suggest varying degrees of improved predictive performance moving from the 1st DI to steady-state, as can be seen with the percentage of patients within ± 20% rMPE in Figure 4.2. The trend of improved predictive performance was not observed for two Bayesian priors (*i.e.,* Usman *et al.* and Kim *et al.*) used with the conventional Bayesian method (25, 28). Two models (*i.e.,* Zhou *et al.* and Staatz *et al.*) had a relatively long half-life, which might explain the drastic improvement in predictive performance at confirmed steady-state intervals (26, 29). The estimated half-life for other models ranged from 5.77 to 9 h (Supplementary Material, Table S 4.3). Considering rMPE 95% CI and rRMSE, this trend was observed, to a certain extent, for some Bayesian priors, although 95% CI for most cases did not include zero except for most of Colin *et al.* (23) using the conventional-Bayesian approach and Adane *et al.* (24) using the full-Bayesian approach (Supplementary Material, Figure S4.14).

In Trial A, Bayesian prediction using two samples compared to one sample demonstrated a very comparable or slightly better overall predictive performance. Yet, this difference did not seem systematic or significant. Predictive performance of the Bayesian approach was better overall than the performance of PK equations in pre-steady-state DIs (*i.e.* 1 to 3), except for Yamamoto *et al.*(27) using the full-Bayesian and Kim *et al.*(28) using the conventional-Bayesian. Once near or at steady-state, no similar conclusion could be made. Results of Trial A did not support any generalized conclusion comparing the full- to conventional-Bayesian approach. For example, a higher percentage of patients within ± 20% rMPE, particularly at steady-state, was observed when using full-Bayesian compared to the respective conventional-Bayesian cases with Usman *et al.* (25) and Kim *et al.* (28). In contrast, Yamamoto *et al.* (27) showed better predictive performance and a significantly higher percentage of patients within ± 20% rMPE using the conventional Bayesian approach. In terms of rRMSE, Bayesian priors that consistently achieved a relatively low rRMSE were Colin *et al*. (23), and Adane *et al.* (24) in the cases of peaks and trough using full-Bayesian, and Zhou *et al*. (26) as well as Yamamoto *et al.* (27) in the cases of peaks and trough using conventional-Bayesian. Overall, peaks and troughs with conventional Bayesian resulted in a higher number of points with low rRMSE (defined as below 75 rRMSE).

Conducted model transferability diagnostics (Section 4.3.3) might suggest an overall relation to the predictive performance that was not as strong as we expected. For example, despite Yamamoto *et al.* (27) model having better transferability diagnostic plots compared to other models, and similar clinical population and design as our MUHC study, only 2% of patients were within ± 20% rMPE in the case of full-Bayesian monitoring at the 1st DIs, being the lowest among all results in our study, Figure 4.2. In contrast, Adane *et al.* (24) transferability diagnostic plots suggested incompatibility while its population was limited to extremely obese, unlike most

of the MUHC population. Yet, the overall predictive performance was one of the best. It is worth mentioning that Adane *et al.* (24) was included as a prior as the MUHC population had obese patients and based on the premise that obese vancomycin CL might not be significantly different from non-obese (22).

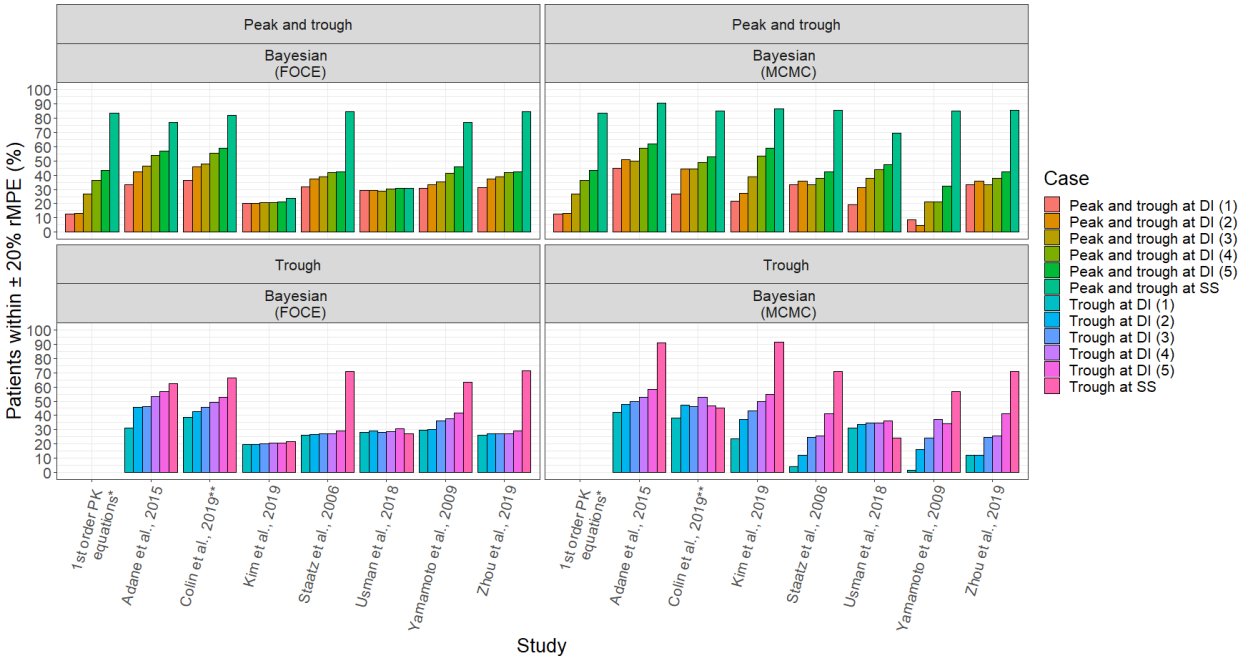

Figure 4. 2 Bar Plot of the percentage of patients within the tolerable rBias range of ± 20% rMPE from MIPD clinical trial simulation A. Each subplot represents a combination of using a peak and a trough or a trough only at varying dosing intervals (DI) (*i.e.,* the 1st,2nd,3rd,4th,5th, and at steady state [SS]) with the full-Bayesian and the conventional Bayesian approach. For reference, results using the 1st order PK equations were plotted. Each color represents a case. *For reference as the 1st order PK equations should be used with near or at steady-state samples. **Colin *et al.* model was modified for MCMC runs.

4.3.4.2 MIPD Clinical Trial B: Using Locally Constructed PK Model as Bayesian Prior

Trial B results are shown in Figure 4.3 and Supplementary Material, Figures S4.11 to S4.13. Unlike some cases in Trial A, Trial B showed an overall systematic and incremental gain in predictive performance (increased accuracy and precision and reduced bias) progressing between intervals towards steady-state. In Trial B, Bayesian approaches with peaks and troughs consistently outperformed using only troughs, which translated into 2% to 15% more patients

achieving ± 20% rMPE when using peaks and troughs. Using local Bayesian priors resulted in, overall, a much better predictive performance compared to using literature-sourced priors (*i.e.,* Trial A).

The Bayesian approach used in Trial B consistently outperformed the respective cases using first-order PK equations, with 20-25% more patients within the desired ± 20% rMPE target at the third, fourth, or fifth DIs. Further, using the first-order PK equations performed very poorly at the first and second DIs, as expected, in which less than 13% were within ± 20% rMPE target, compared to 45% to 53% using Bayesian methods at the respective cases of Trial B. Bayesian methods used in Trial B appeared more precise and accurate compared to the first-order equations, as indicated clearly by rRMSE and rMAPE results. Further, first-order equations resulted in a systematic bias as indicated by the persistent underprediction in every non-steady-state interval as explained in (31); a trend that was not observed for the respective cases using Bayesian methods. Finally, rMPE 95% CI favored Bayesian-guided AUC estimation over the corresponding cases using first-order PK equations. These observations extend as well to Bayesian approaches with a trough only, as Bayesian methods resulted in 15% to 35% more patients within the ± 20% rMPE target in every non-steady-state DI, compared to the respective cases using first-order PK equations.

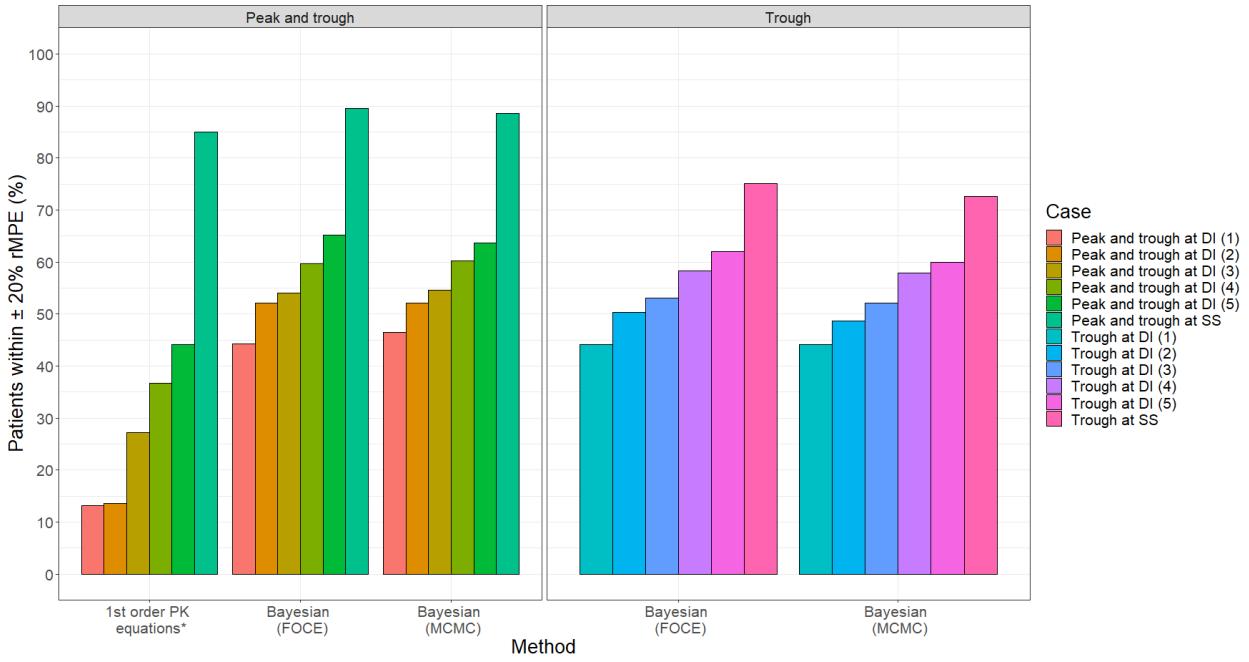

Figure 4. 3 Bar Plot of the percentage of patients within the tolerable rBias range of ± 20% rMPE from MIPD clinical trial simulation B. Each subplot represents either the case of a peak and a trough or a trough only at varying dosing intervals (DI) (*i.e.,* the 1st,2nd,3rd,4th,5th, and at steady state [SS]) with the full-Bayesian and the conventional Bayesian approach. For reference, results using the 1st order PK equations were plotted. Each color represents a case. *For reference as 1st order PK equations should be used with steady-state samples.

4.3.4.3 MIPD Clinical Trial C: Sampling from Different Dosing Intervals

Results of using the first-order PK equations with two levels from the 4th and/or 5th DIs were consistent with the trend of incremental gain in predictive performance progressing between intervals towards steady-state, as shown in Figure 4.4 and Supplementary Material, Figures S4.15 to S4.17. In contrast, using Bayesian approaches with two levels from the 4th and/or 5th DIs did not show a similar trend but rather showed comparable results to using only the 4th or the 5th DI.

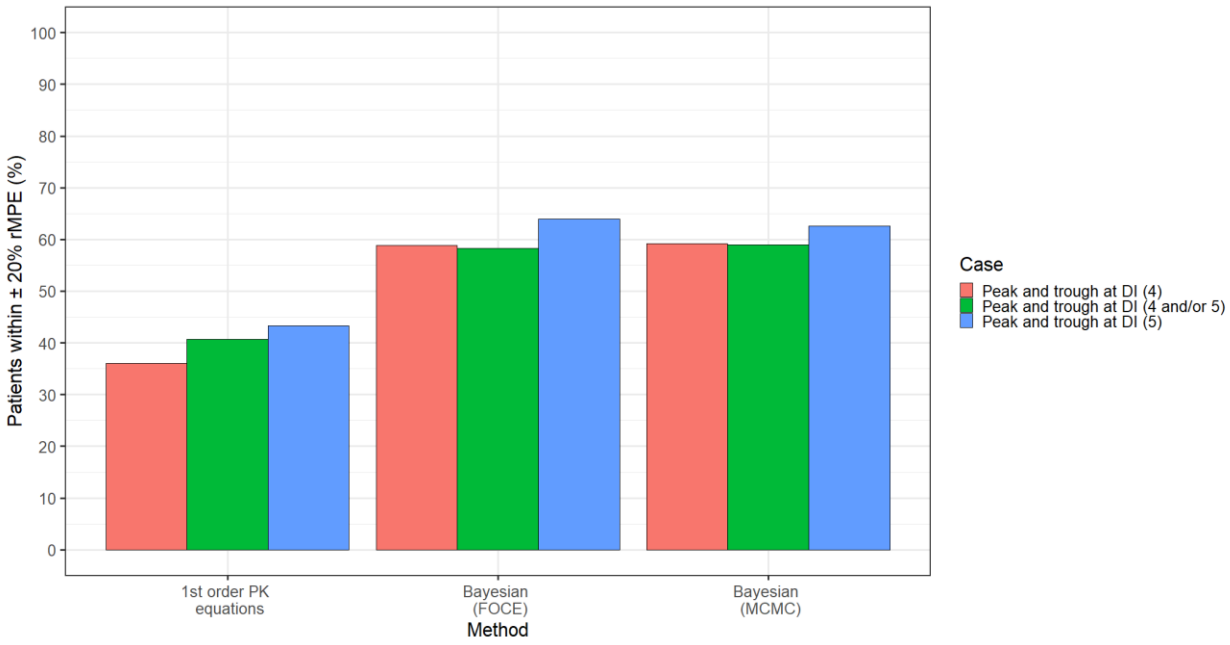

Figure 4. 4 Bar Plot of the percentage of patients within the tolerable rBias range of ± 20% rMPE from MIPD clinical trial simulation C, representing a peak and a trough obtained from varying dosing intervals (*i.e.,* 4th, 5th, or both) with the full-Bayesian, the conventional Bayesian approaches, and 1st order PK equations. The revised guidelines recommendation of sampling within the same dosing interval was for the 1st order PK equation.

4.3.5 Additional Verification of Results

Predictive performance of simulations from Colin *et al*. (23), instead of the MUHC model, seemed to support general observations reported in section 3.4.1, comparing Bayesian to PK equations, Figure 4.5. This might suggest that our results extend beyond the quality of MUHC data and model structure (one- versus two-compartment).

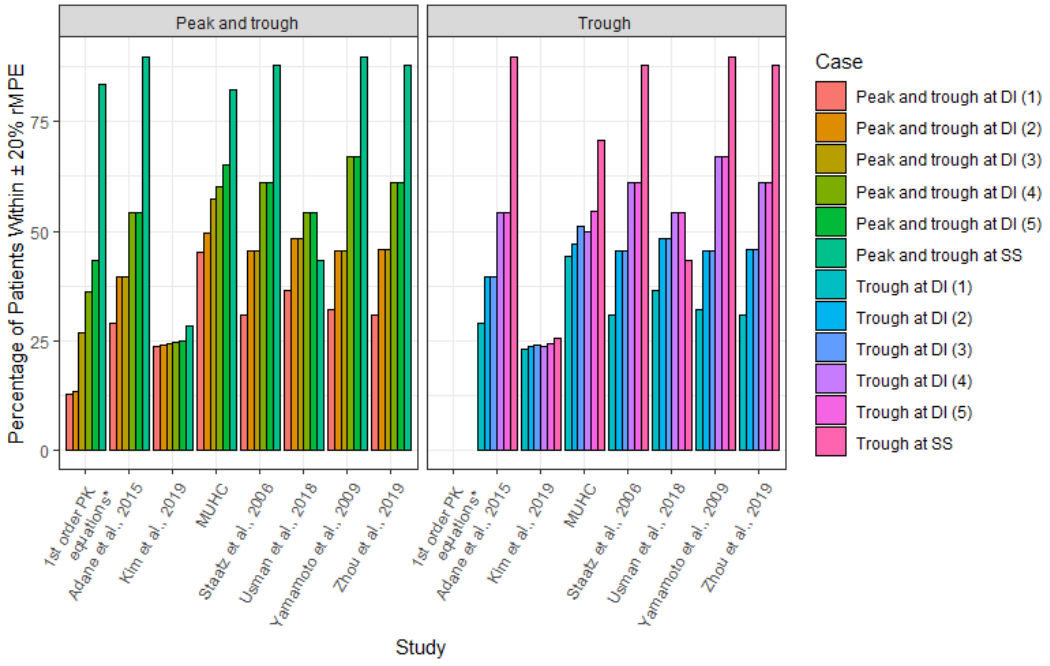

Figure 4. 5 Bar Plot of the percentage of patients within the tolerable rBias range of ± 20% rMPE from MIPD clinical trial simulation A, but with data simulated from *Colin et al*. Each subplot represents using a peak and a trough or a trough only at varying dosing intervals (DI) (*i.e.,* the 1st,2nd,3rd,4th,5th, and at steady state [SS]). For reference, results using the 1st order PK equations were plotted. Each color represents a case. *For reference as the 1st order PK equations should be used with near or at steady-state samples.

4.4 Discussion

In this study, the predictive performance of the two recommended AUC-guided monitoring methods (1) was compared in an array of realistic clinical cases, ranging from a practical early trough to late peaks and troughs sampling near or at steady-state. Results varied significantly depending on a combination of the estimation method, case, and the relative influence of not satisfying assumptions required for PK equations and PopPK model transferability. Further, we presented the possible negligible impact of sampling from mixed versus single near steady-state DIs.

We aimed to assess Turner *et al.* conclusion that equation-based AUC predictions resulted in an equivalent or better accuracy and bias compared to using five Bayesian software programs (10).

Trial A (using MUHC and Colin *et al.* model-based simulations, one- and two-compartment models, respectively) did not seem to support a generalized conclusion, unlike Trial B that showed monitoring using Bayesian methods with troughs only as early as the 1st DI showed comparable results to near steady-state monitoring using PK equations (*i.e.,* peak and trough at the 5th DI), which resulted in 43% of the patients within this study desired rMPE limits. These results as well as the desired rapid achievement of the therapeutic target and the ability to update current knowledge might favor Bayesian-guided monitoring (1, 6). A three-year clinical trial demonstrated that significant performance improvements can be made when new knowledge is progressively added (32).

We included results that violated steady-state assumptions essential for PK equations in order to gain insights into the prospective impact of violating such assumptions and for relative comparison with Bayesian methods. The revised guidelines highlighted the difficulty in determining steady-state conditions in practice and stated the strong preference for the two measurements to be near steady-state (1).

Part of our simulations might support rapid Bayesian vancomycin monitoring using sparse data, as sparse as only a trough that is obtained as early as at the 1st DI. MIPD Trial B showed that peaks and troughs compared to trough-only Bayesian monitoring were not very different. For example, the percentage of patients within ± 20% rMPE at the 1st DI was 46% and 44% for the peak and trough and trough only cases, respectively. Waiting to the 5th DI increased the percentage of patients within our desired ± 20% rMPE target to roughly 64%.

Bayesian-guided AUC monitoring might be affected by the quality of data used to build the prior (6, 9). The revised guideline only recommended Bayesian programs that implemented richly sampled Bayesian priors, (1), yet, the availability of such models in the literature might be

limited for many patient populations (22, 33). This can be attributed to previous TDM practices comprised of trough-only monitoring that resulted in many PopPK-fitted models using sparse samples (22, 33). Most priors used in our study were fitted using sparsely sampled TDM data, including our MUHC model. This sparse nature and our conservative rBias limits, might explain the capping of the percentage of patients within ±20 rMPE at 65% and 90% for the 5th and confirmed steady-state DI, respectively.

Implementing MIPD using literature-sourced Bayesian priors might require a systematic model evaluation and validation and expertise, as performed by some of the Bayesian TDM programs (6, 20, 34, 35). The results of conducted systematic model evaluation varied with DIs, the number of measurements, and the algorithm used and did not seem to suggest strong relation with predictive performance (Trial A). This assumes little influence of unsatisfied underlying assumptions (*i.e.,* populations driven from one population and similar study design) (20, 21). One can argue, having collected local data, that developing local PopPK models for subsequent local studies can be more efficient and less assumption-demanding compared to adopting and validating varying vancomycin PopPK models, as demonstrated in Trial B (local prior) compared to Trial A (literature-sourced priors). Ideally, however, all previous experiments could be incorporated in the Bayesian prior components. Also, other approaches such as automated model selection or model averaging algorithms can be used (5, 20).

Despite the simulation nature of AUC in this study (the gold standard real AUC was not available), key points seem relevant to clinical practice and can help optimize vancomycin TDM. Although the performance of some priors might be limited to MUHC and it might be expected that others report different or similar results (34, 36), the premise of this manuscript was not to advocate for a specific prior but to increase familiarity with important aspects of AUC-guided

monitoring, uncover its case-specific performance and limitations, such as when using sparse non-optimally sampled TDM data, and help transition into AUC-guided monitoring. The additional simulations from a well-established model did not seem to contradict our general observations despite that predictive performance can be expected to vary depending on many conditions, such as the relatively long average half-life of MUHC models that exceeded the DI length, the type and magnitude of the PopPK error model used, the narrow sampling window, the varying levels of biased parameter estimates. Finally, this work was based on the premise that improved AUC prediction might yield improved outcomes and focused only on evaluating methodology. Therefore, the gold standard PopPK modeling software NONMEM seemed more suitable to use rather than a commercially available TDM program with specific pre-built PopPK models.

In conclusion, this study will likely contribute to better vancomycin clinical monitoring and precision dosing by understanding contexts that might impact AUC predictions in TDM settings. It shows that Bayesian-guided AUC monitoring has the potential to outperform equation-based AUC monitoring, although not necessarily in all conditions. This study also supports rapid vancomycin Bayesian AUC-guided monitoring using only a trough that was obtained as early as at the 1st dosing interval.

Study Highlights

1. What is the current knowledge on the topic?

   AUC-guided vancomycin monitoring was, recently, recommended using first-order PK equations or Bayesian software programs. Additionally, vancomycin trough-only monitoring was abolished.

2. What question did this study address?

   Are there any predictive performance differences between first-order PK and Bayesian software programs, between Bayesian-guided troughs versus Bayesian-guided troughs and peaks, and between monitoring at varying single or mixed pre- or at-steady-state dosing intervals?

3. What does this study add to our knowledge?

   Bayesian-guided AUC estimation has the potential to outperform equation-based AUC estimation, although not necessarily in all conditions.

   Rapid vancomycin Bayesian AUC-guided monitoring using only a trough that was obtained as early as at the 1st dosing interval was quite supported by this study under certain conditions.

   Incremental improvements in AUC estimation accuracy and precision and reduction in bias were generally observed progressing between intervals from the 1st dosing interval towards steady-state.

   Sampling from different dosing intervals (i.e. the 4th and 5th) did not seem to have a detrimental impact on the AUC prediction.

4. How might this change clinical pharmacology or translational science?

   This study will likely contribute to better vancomycin clinical monitoring and precision dosing by understanding contexts that might impact AUC estimation.

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4.5 Supplementary Material for Pharmacokinetics Equations Versus Bayesian Guided Vancomycin Monitoring: Pharmacokinetics Model and Model-Informed Precision Dosing Trial Simulations

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4.5.1 PopPK Modeling

Accepted modification on the hierarchical models was defined by a 3.84 reduction in the objective function (p-value < 0.05 for 1 degree of freedom). All collected variables (*i.e.,* gender, age, weight, high, bacteremia, cellulitis, endocarditis, meningitis, osteomyelitis, pneumonia, sepsis, wound infection, obesity, neutropenia, liver disease, renal insufficiency, admission to ICU, serum creatinine levels, and type of pathogen) were tested for their influence. Several renal function descriptors were evaluated, such as creatinine clearance (CL_{cr}) eGFR (calculated using

Cockcroft-gault), and GFR estimated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (CKD-$EPI_{creatinine}$) or Modification of Diet in Renal Disease (MDRD) equation (37, 38). Further, the influence of renal function change from the start of therapy was evaluated. We used a stepwise covariate modeling (forward inclusion (p-value < 0.05) and backward elimination (p-value < 0.005)). Introducing CL_{CR} on CL significantly reduced the objective function (*i.e.,* ΔOFV of −118.34 at $p < 0.01$), and therefore was included in the final model. No other covariates were significant. ηCL-shrinkage (%) for our model was 17.2%. The whole process of model selection was guided by model diagnostics, model selection criteria (such as objective function, Akaike information criterion [AIC], and Bayesian information criteria [BIC]), successful minimization, the precision of parameter estimates, the magnitude of between- and unexplained random variability, and graphical diagnostics.

4.5.2 Simulation Conditions

Simulation conditions were as follows. A standard dosage of 15 mg/kg every 12 h was given to all patients, as recommended in the revised guideline (1). Moreover, doses were rounded to the nearest multiple of 250 mg to mirror clinical practice. The administered course of therapy was up to six days. Dense vancomycin sampling was performed consisting of 15 samples per dosing interval. A peak was defined as a concentration level obtained within 2 h from the end of infusion, while a trough as a concentration level obtained within 3 h just at the end of the dosing interval (*i.e.,* before the administration of the subsequent dose).

Covariates were simulated having the same underlying distributions as those of MUHC data. Based on these simulations, individual reference AUC was approximated using the trapezoidal rule in R (*i.e.* trapz function) (39) and according to:

$$AUCi = Dosei/CLi$$

where *i* refers to a virtual individual, i=1,…, 1000.

As vancomycin CL remains constant with increasing concentration, calculated AUC_{tau} represents steady-state for a given interval at repeated dosing administrations. This calculated reference AUC was assumed to be ideal for subsequent analyses. In our simulations, we did not include cases of loading doses or irregular dosing intervals due to the limited space available in this article. We assumed a MIC of 1 mg/L across all simulations for simplicity.

4.5.3 First-order Analytic PK Equations

$$K_e = \frac{\ln\left(\frac{C1}{C2}\right)}{t2-t1} \quad (1)$$

$$t_{1/2} = \frac{0.693}{k_e} \quad (2)$$

$$\text{Cmax} = \frac{\text{Cp0}}{\text{e}^{-k(t-tinf)}} \quad (3)$$

$$\text{Cmin} = \text{Cmax} * \text{e}^{-k(t-tinf)} \quad (4)$$

$$Vd = \frac{\text{Dose}/T_{inf}*(1-e^{-k*T_{inf}})}{k*(C_{max}-(C_{min}*e^{-k*T_{inf}}))} \quad (5)$$

$$C_{peak} = \frac{\text{Dose}*(1-e^{-K_{el}*T_{inf}})}{T_{inf}*Vd*K_{el}*(1-e^{-K_{el}*Tau})} \quad (6)$$

$$CL = Vd * K_{\text{el}} \quad (7)$$

$$AUC_i = Dose_i/CL_i \quad (8)$$

4.5.4 Bayesian Methods

In the "conventional" Bayesian approach, a previously developed PopPK model and its parameters are combined with the present dataset to produce individual conditional parameter estimates. The second approach (*i.e.*, "full" Bayesian) incorporates, as well, a prior model and its

parameters which is combined with the present dataset to produce individual parameter posterior probability distribution. Full-Bayesian using MCMC algorithm seeks the entire posterior distribution rather than point estimates, as FOCE does (19, 30). Despite that we obtained the entire posterior distributions of the individual parameters, we used the *maximum a posteriori* (*i.e.* mode) of these distributions to simply compare this full Bayesian to the conventional Bayesian approach. The large load of information the MCMC algorithm produces deems it computationally expensive with less statistical power relative to FOCE (19). However, such information should be ideally well utilized, and Figure S4.1 provides an example of prior, likelihood, and posterior probability distributions.

Informative prior values and variances, as well as their degrees of freedom, were supplied to the $Prior statement according to the NONMEM manual (19, 30). For every individual, we obtained the parameters posterior probability distribution using the required verbatim code (30). For the full-Bayesian approach, we used $EST BAYES and PRIOR statements in NONMEM along with the MCMC algorithm. The default NONMEM MCMC estimation settings were used (i.e., AUTO=1), which specify 4000 iterations for the burn-in phase. However, iterations of the stationary distribution phase were limited to 1000 iterations (instead of the default 10,000 iterations) due to a large number of runs (*i.e.* 96 MCMC runs) and limited resources (*i.e.* available memory space and computational power), especially, when running on 3 independent Markov chains (30). While the predictive performances using either conventional or full-Bayesian were very comparable, run times were very different. For example, the run time was 17.3 seconds for the conventional approach with FOCE compared to 389 seconds using the fully Bayesian approach with the MCMC algorithm.

For efficient use of the MCMC algorithm, codes were re-written according to NONMEM requirements for MU referencing, which refers to a process in which fixed effects parameters are only involved in describing the mean (MU) obtained from the normal population distribution of individual parameters (19, 30). In addition, we assumed constant CL_{cr} values for every individual across the study to satisfy the MCMC requirement (30). However, variable CL_{cr} did not appear to have a noticeable impact on the results per small-scale analysis (results not presented).

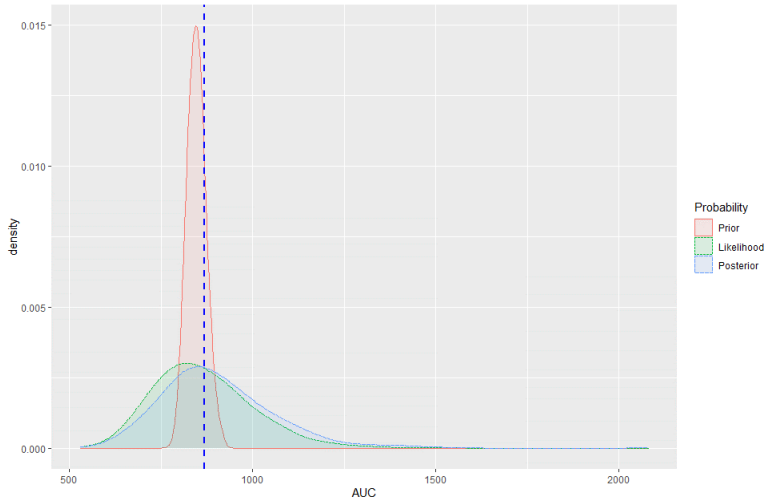


Figure S4.1. Informative prior, likelihood (*i.e.,* data), and posterior AUC distributions for one virtual subject (ID=43), compared to reference AUC (dashed blue line) for MIPD Trial B at the 5th dosing interval. Although in this article we calculated predictive performances in respect to the MAP, Bayesian must be thought of as a probability distribution rather than a point estimate (*e.g.,* mode). For this individual, the probability of being 400-600 AUC over 24 h was very low. Conditioned on his medical diagnosis, a decrease in dosage might be warranted.

4.5.5 Performance Metrics

Formula

$$rMPE(\%) = \frac{1}{N} \cdot \sum_{i=1}^{N} \left(\frac{AUC_{i\_subset} - AUC_{i\_Reference}}{AUC_{i\_Reference}} \right) \times 100 \quad (9)$$

$$\text{rMAPE (\%)} = \frac{1}{N} \cdot \sum_{i=1}^{N} \left| \frac{AUC_{i\_subset} - AUC_{i\_Reference}}{AUC_{i\_Reference}} \right| \times 100 \quad (10)$$

$$rRMSE = \sqrt{\frac{1}{N} \cdot \sum_{i=1}^{N} \left(\frac{AUC_{i\_subset} - AUC_{i\_Reference}}{AUC_{i\_Reference}} \right)^2} \quad (11)$$

Percentage of Patients within ± 20%

The additional presentation of our results in a form of the percentage of patients within a ± 20% rMPE was to provide relativity to clinical settings. In our study, we chose a relatively conservative ± 20% rMPE limits due to the 400 to 600 AUC/MIC therapeutic target. Yet, wider desirable limits (*e.g.,* ± 30%) revealed a relatively proportional improvement in the number of patients within the desirable limits for almost all methods and cases, Figure S4.2 below. For example, for peak and trough at the 5th dosing interval using our MUHC model as a prior, 50%, 65%, 74%, and 80% of patients were within the rMPE desirable limits of ± 15, 20, 25, and 30%, respectively. Although different desirable levels might influence the rationale for clinical decisions, general trends, described here, appeared to persist across different desirable limits.

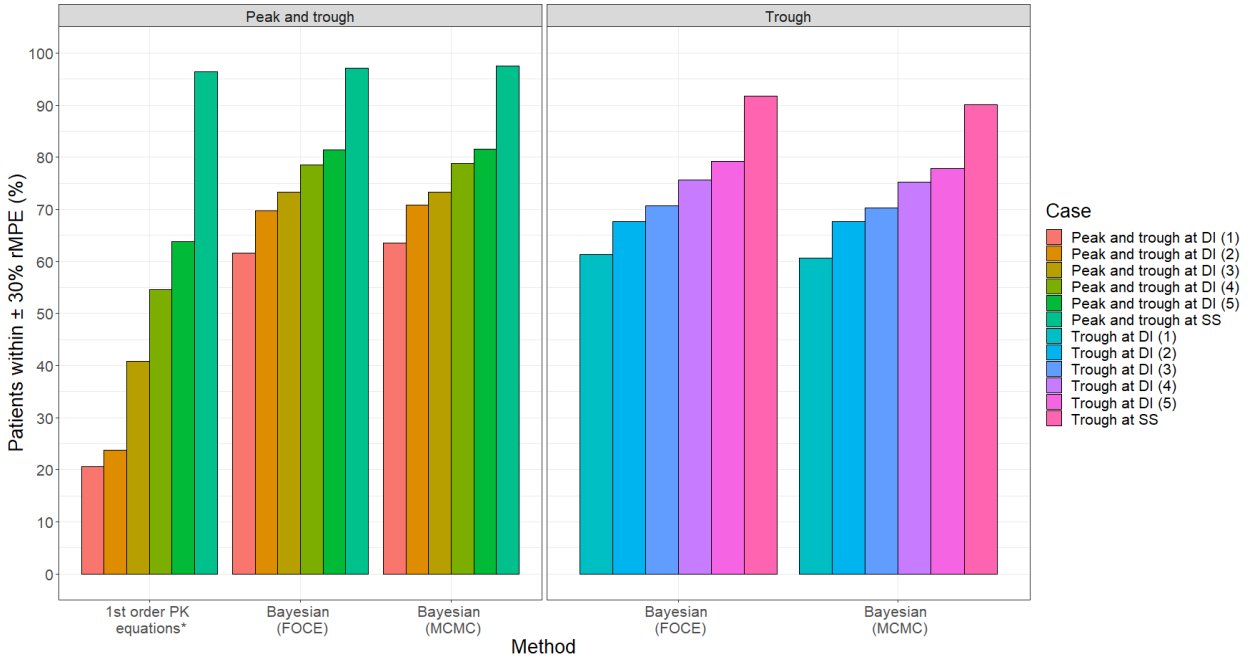


Figure S4.2. Bar Plot of the percentage of patients within tolerable rMPE range of ± 30 MPE from MIPD clinical trial simulation B. Each subplot represents either the case of a peak and a trough or a trough only at varying dosing intervals with the fully Bayesian and the conventional Bayesian approaches. Also, rBias of estimating AUC using 1st order PK equations with a peak and a trough were plotted. Each color represents a case. Pre-steady state dosing interval violates PK equation underlying assumptions.

Table S4.1. Diagnosis and indication for MUHC participants. Dosage and vancomycin concentration were ordered per the standards of clinical care at the MUHC.

Diagnosis	**Number of Patients**
Bacteremia	14
Cellulitis	17
Wound Infection	10
Sepsis	7
Pneumonia	4
Osteomyelitis	6
Meningitis	6
Endocarditis	7
Not reported	51
Indication	
Empirical vancomycin /Confirmed MRSA	101/15

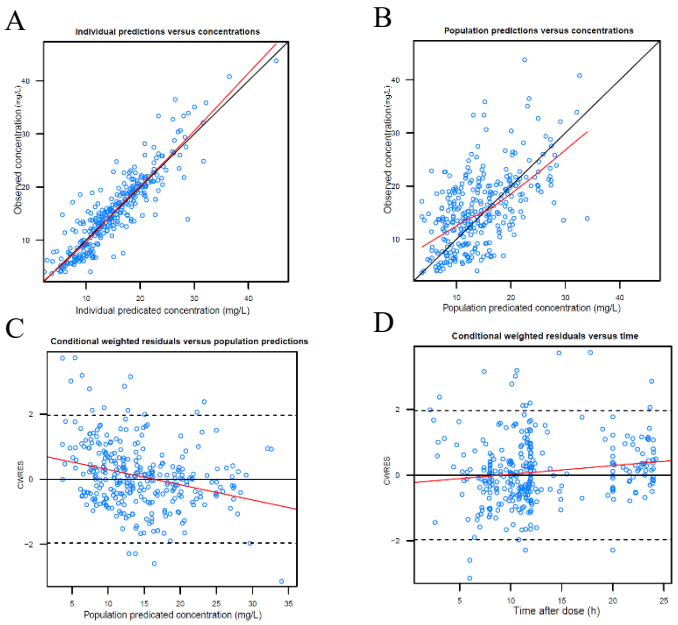


Figure S4.3. Graphical model diagnostic of MUHC final model, showing an adequate description of the observed data. Panels A and B show individual and population predictions versus observed concentrations, respectively. Panels C and D show conditional weighted residuals versus population predicted concentrations and time, respectively.

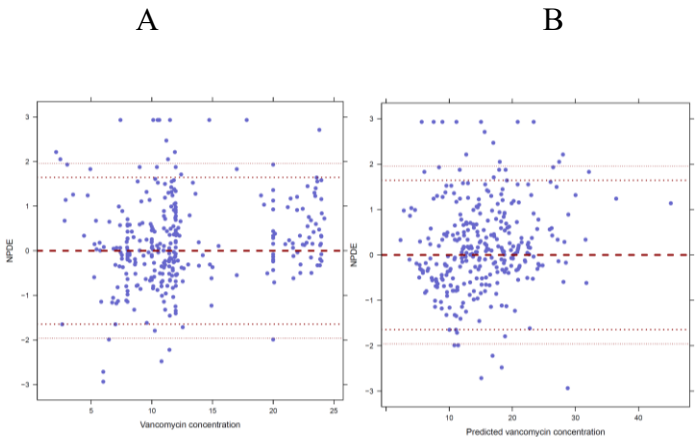


Figure S4.4. Panels A and B show normalized prediction distribution errors (NPDE) versus observed and predicted concentrations (mg/L), respectively.

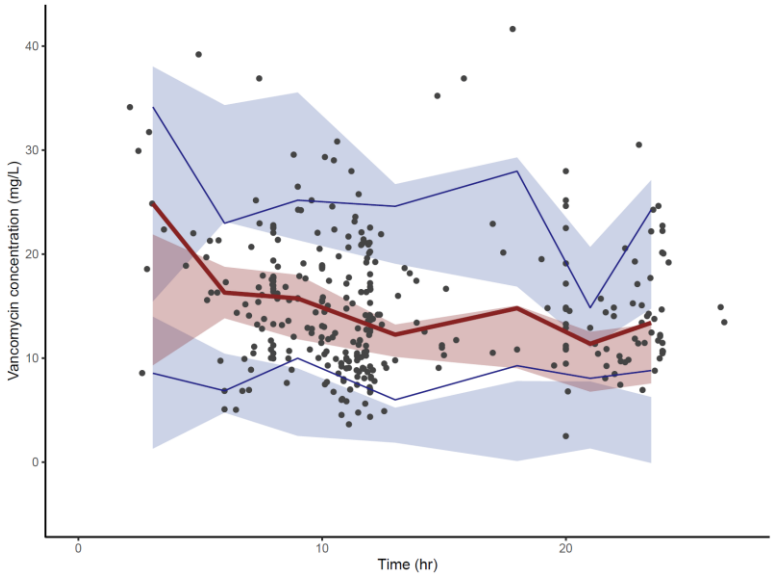


Figure S4.5. Simulation-based model diagnostics of MUHC data which includes prediction corrected visual predictive check (pcVPC) for vancomycin concentration observations versus time (n = 1,000). The solid red line represents the 50th percentile, while the solid blue lines show the 10th and 90th percentile of the observed data. The corresponding shaded regions represent the 90% CI around the 10th, 50th, and 90th percentiles of the simulated data. Observed concentrations are represented by black circles.

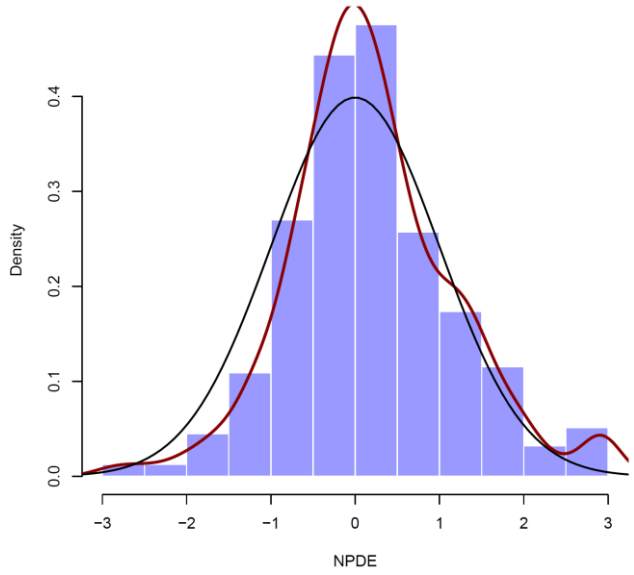
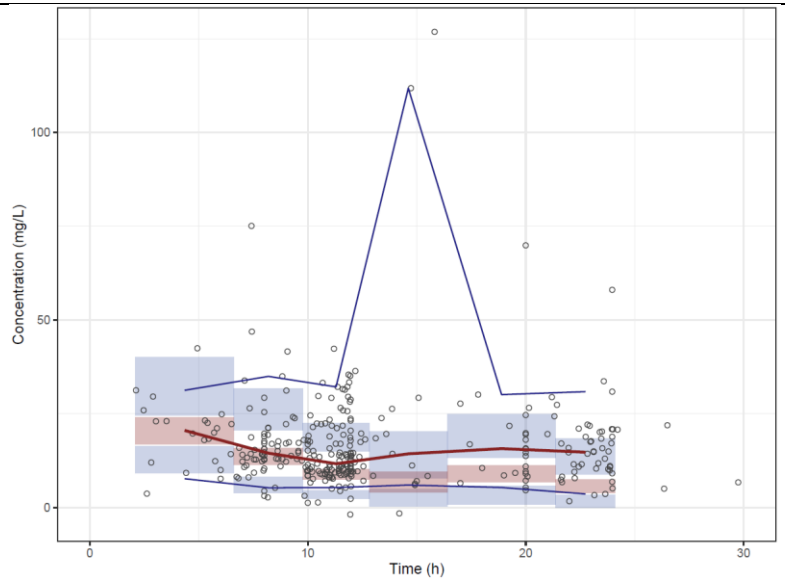
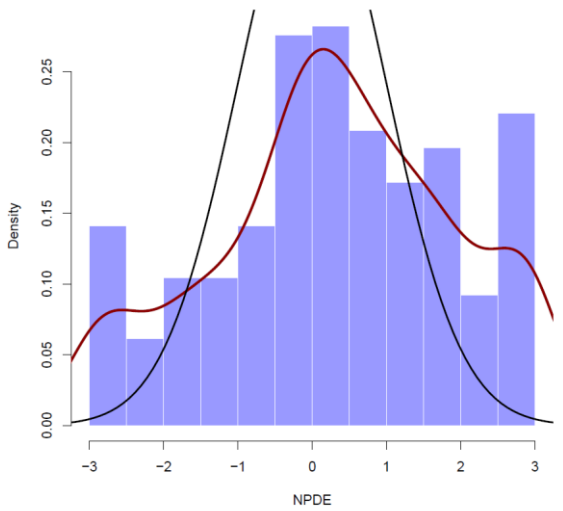


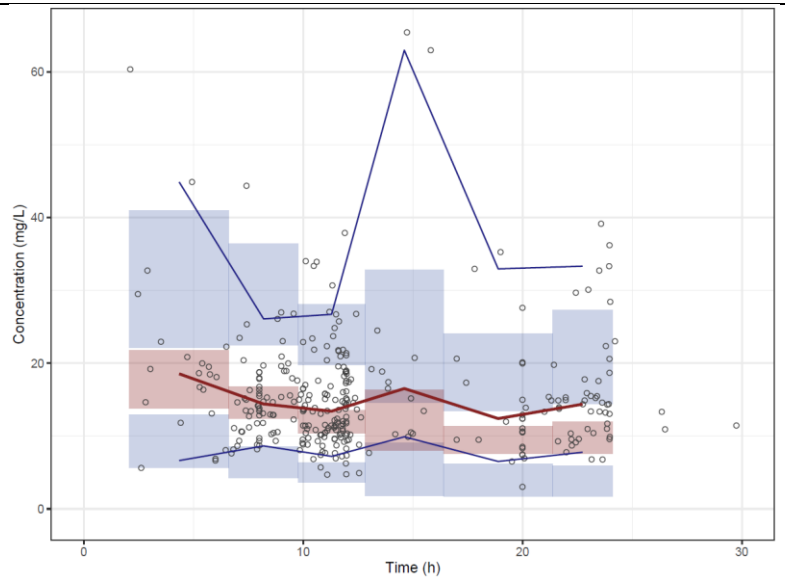
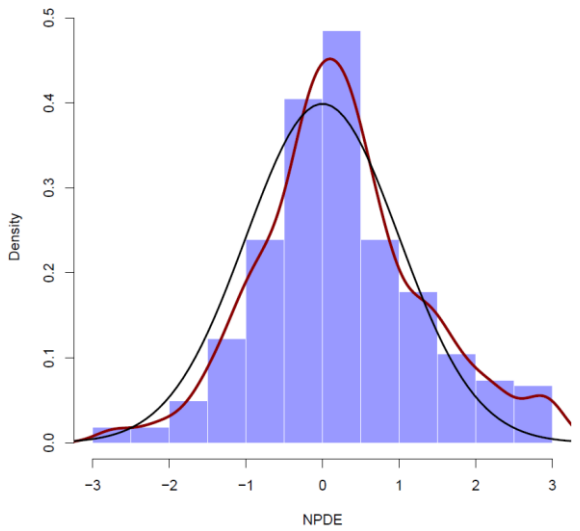
Figure S4.6. Normalized prediction distribution errors (NPDE) density plot of predicted and observed concentrations.

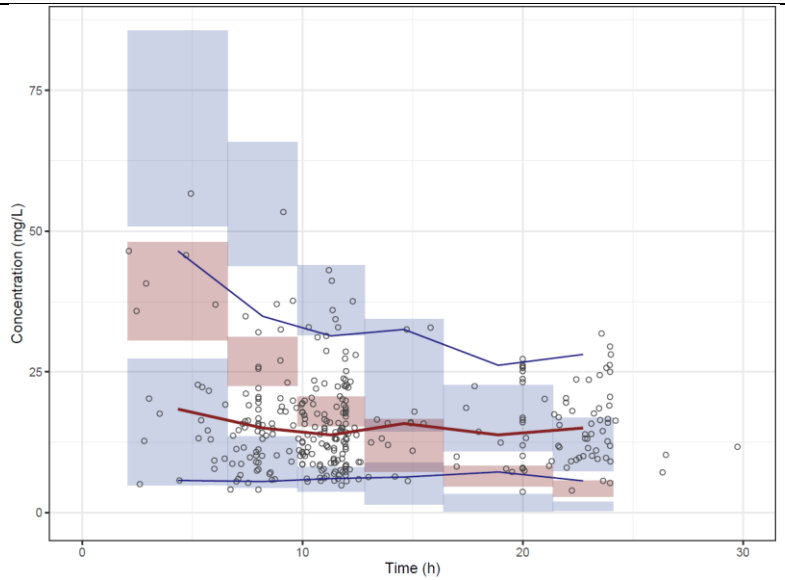
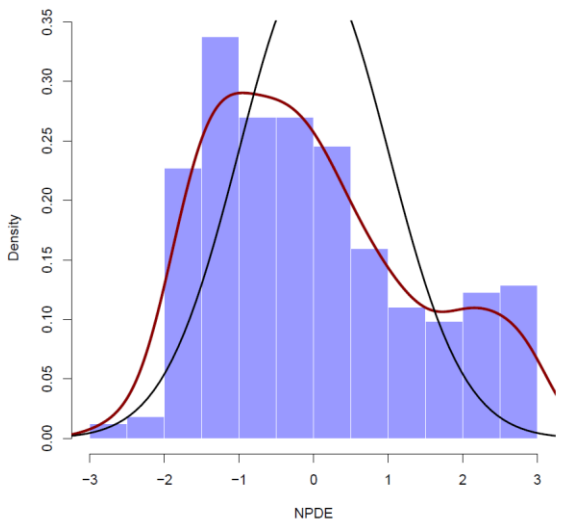
4.5.6 Simulation-based Model Diagnostics

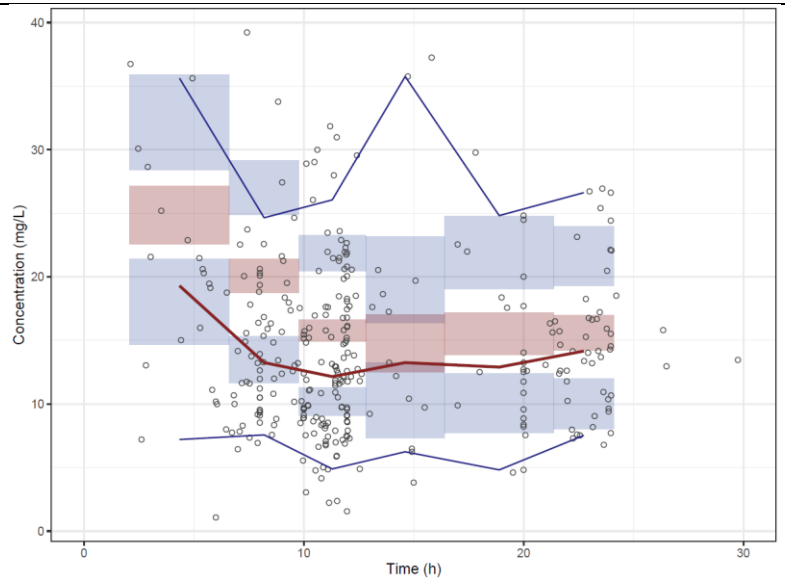
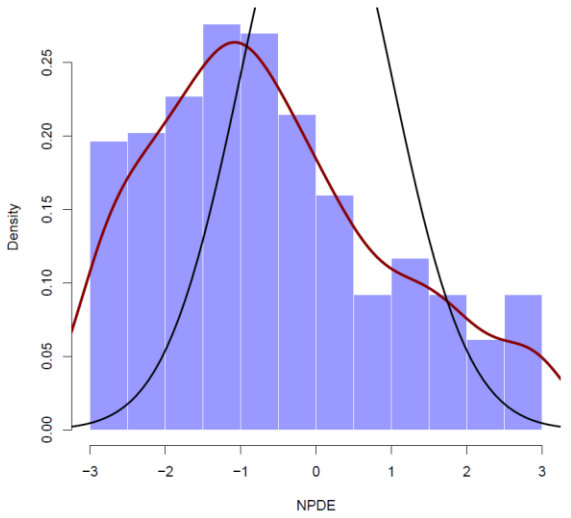
Table S4.2. Simulation-based model diagnostics of literature-sourced Bayesian priors which include prediction corrected visual predictive check (pcVPC) for vancomycin concentration observations versus time (1,000 Monte Carlo simulations). The solid red line represents the 50th percentile, while the solid blue lines show the 10th and 90th percentile of the observed data. The corresponding shaded regions represent the 90% CI around the 10th, 50th, and 90th percentiles of the simulated data. Observed concentrations are represented by black circles. Table S 4.2 includes as well normalized prediction distribution errors (NPDE) density plots of predicted and observed concentrations. To test if the NPDE results followed a normal distribution, we used Wilcoxon signed-rank t-test (t-test), Fischer test for variance (F test), and Shapiro-Wilk test (S-W) at a 95% confidence level and a theoretical distribution $N(0,1)$.* Indicates that the NPDE results are significantly different from the $N(0,1)$ distribution.

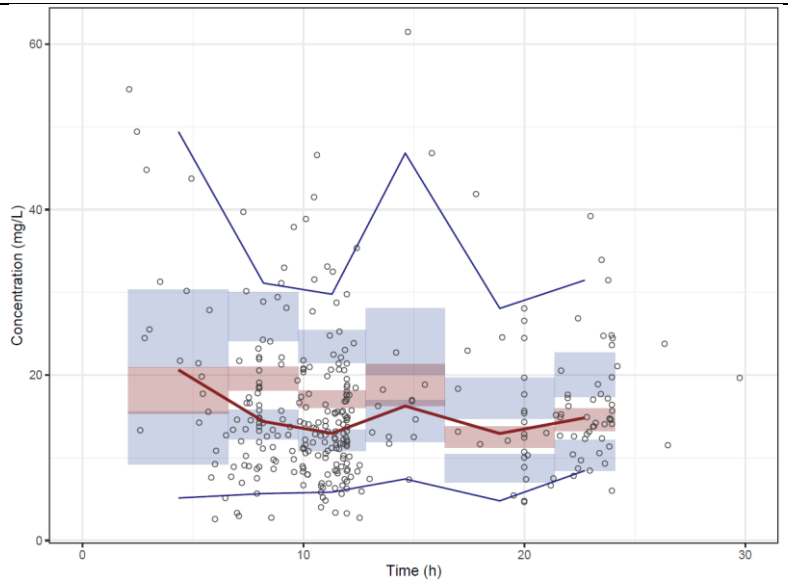
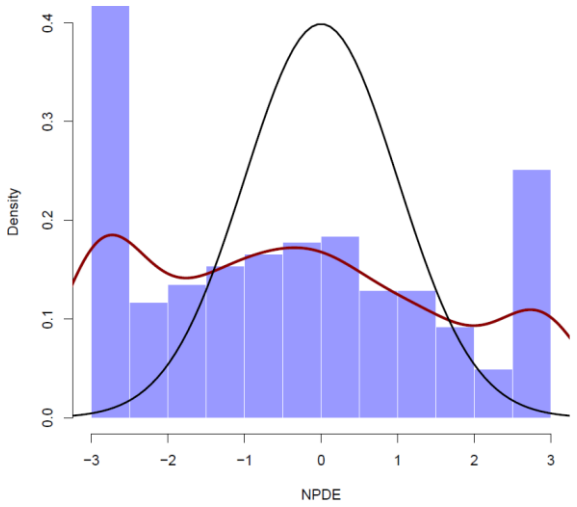
Model	pcVPC	NPDE

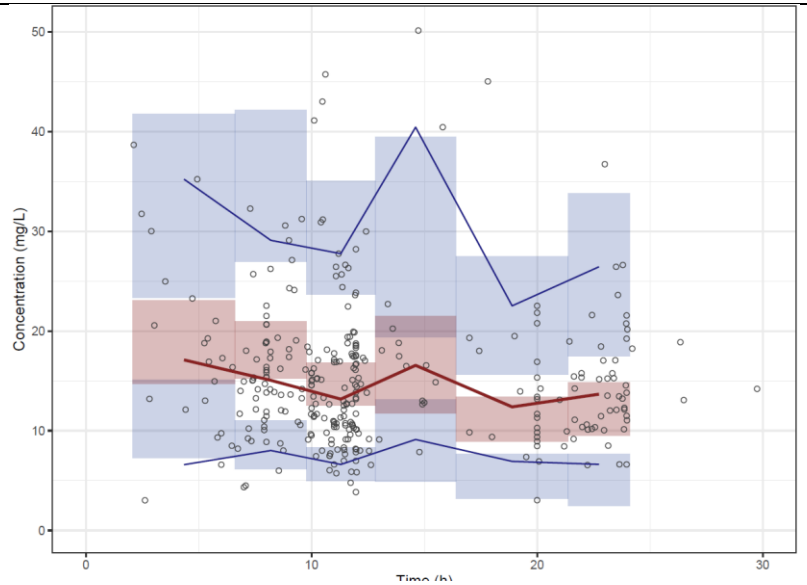
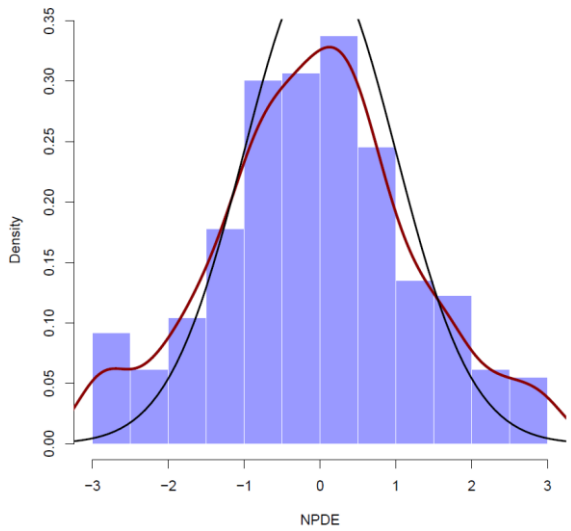
Adane et al. (1)		 t-test: 0.0043* F test: < 0.0000* S-W: < 0.0000*

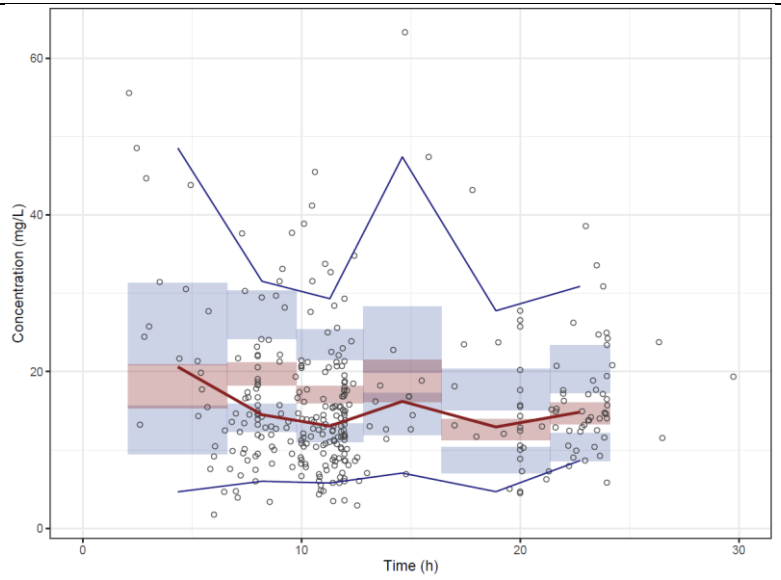
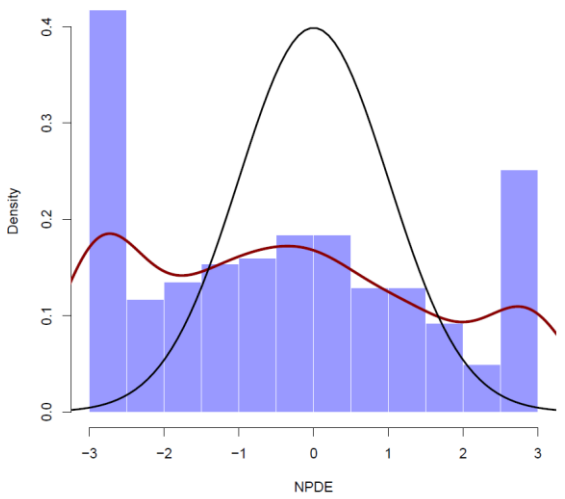
Colin *et al.* (2)		 t-test: 0.03571* F test: 0.4502 S-W: 0.0008*

Usman *et al.* (3)		 t-test: 0.07805 F test: < 0.0000* S-W: < 0.0000*

Kim *et al.* (4)		 t-test: < 0.0000* F test: < 0.0000* S-W: < 0.0000*

Staatz *et al.* (5)		 t-test: 0.0002* F test: < 0.0000* S-W: < 0.0000*

Yamamoto *et al.* (6)			t-test: 0.2352 F test: < 0.0000* S-W: 0.01273*

Zhou *et al.* (7)		 t-test: 0.0002* F test: < 0.0000* S-W: < 0.0000*

Comment

Prediction corrected VPC plots suggested that Yamamoto *et al.* (and to some extent Colin *et al.*) models might be suitable to predict MUHC vancomycin observed concentrations (2, 6). The pcVPC plots of the other models indicated varying degrees of model

misspecification, and ranking these models based on their pcVPC plots could not be established (1, 3-5, 7). Difficulties ranking some models based on their VPC plots were reported in (8). Means and variances of NPDE results were significantly different from the theoretical distribution $N(0,1)$, except for the variance of Colin *et al.* and means of Yamamoto *et al.* and Usman *et al.* (2, 3, 6). The distributions of the NPDEs were significantly different from the normal distribution.

4.5.7 Model Diagnostics

Table S4.3. Model diagnostics including objective function values (OVF), Akaike information criterion (AIC), and ηCL-shrinkage with MAXEVAL = 0, and the percentage of patients within ±20% rMPE target, as well as the half-time for the respective models.

Model	**OVF**	**AIC**	**η_{CL}-shrinkage (%)**	**5th DI (OVF)**	**5th DI (AIC)**	**Patients on Target at 5th DI**	**Half-time**
Colin *et al.* (1)	1487.6	1523.7	22.7	11033.0	11067.1	60	7 h[a]
Adan *et al.* (2)	1806.0	1816.0	-14.0	12924.3	12934.5	58	8 h[b]
Usman *et al.* (3)	1985.9	1995.9	-48.9	13910.5	13920.5	30	5.77 h[a]
Zhou *et al.* (4)	3698.2	3710.7	-81.9	21748.6	21760.6	43	43.3 h[c]
Staatz *et al.* (5)	3695.4	3707.4	-81.5	21725.6	21737.7	42	19.5 h[c]
Yamamoto *et al.* (6)	1628.5	1650.4	24.9	13974.0	13996.7	48	9 h[a]
Kim *et al.* (7)	1940.8	1960.7	73.8	19781.5	19801.5	20	8.8 h[a]

[a] Calculated using 0.693/β
[b] Reported
[c] Calculated using 0.693/kel
CL: clearance; DI: dosing interval

Comment

Model ranking based on the least OVF values suggested that Colin *et al*., Yamamoto *et al.*, and Kim *et al.* were the most compatible prior models, Using AIC, the most compatible prior models were Colin *et al.*, Yamamoto *et al.,* and Adan *et al.* Both OVF and AIC suggested

potential poor compatibility of Staatz *et al.* and zhou *et al.* priors with our data (4, 5). ηCL-shrinkage values indicated potential compatibility of colin *et al.* and Yamamoto *et al*. (1, 6) Negative shrinkage values might indicate potential model misspecification and might be a result of a parameter variance smaller than the true value (8). In our study, using these metrics, collectively, was a predictor of the percentage of patients within ±20% rMPE although a strong relationship could not be established.

4.5.8 Clearance formula for the Typical Patient

Table S4.3. Clearance formula for the typical patient

Model	**CL Formula for the Typical Patient**
Colin *et al.* (1)	$CL = \theta_1 \times (V1/\theta v1)^{0.75} \times F_{Mat} \times F_{Decline} \times F_{SCR} \times (1 \times \theta_{Cancer})$
Adan *et al.* (2)	$CL = \Theta \times (Clcr/125)$
Usman *et al.* (3)	$CL = \Theta * (1 + \theta_{Clcr} \times CLcr - CLcr_{median})$
Zhou *et al.* (4)	$CL = \Theta * (CLcr/56.28)^{\theta CLcr}$
Staatz *et al.* (5)	$CL = \theta_1 * (1 + \theta_2 * CLcr - CLcr_{median})$
Yamamoto *et al.* (6)	$SWIT = 0$ $CL1 = \theta_1$ $CL2 = \theta_2 \times CLcr + \theta_3$ $CL = CL1 \times SWIT + CL2 \times (1 - SWIT)$
Kim *et al.* (7)	$CL = \theta_1 * (\theta_{Base}/eGFRiBASE) + (eGFRi\ at\ time\ /\ eGFRmedian)$

CL: clearance; V_1: central volume of distribution; F_{Mat}: maturation function; $F_{Decline:}$ Decline function; F_{SCR}: serum creatinine function; CLcr: creatinine clearance; eGFR:

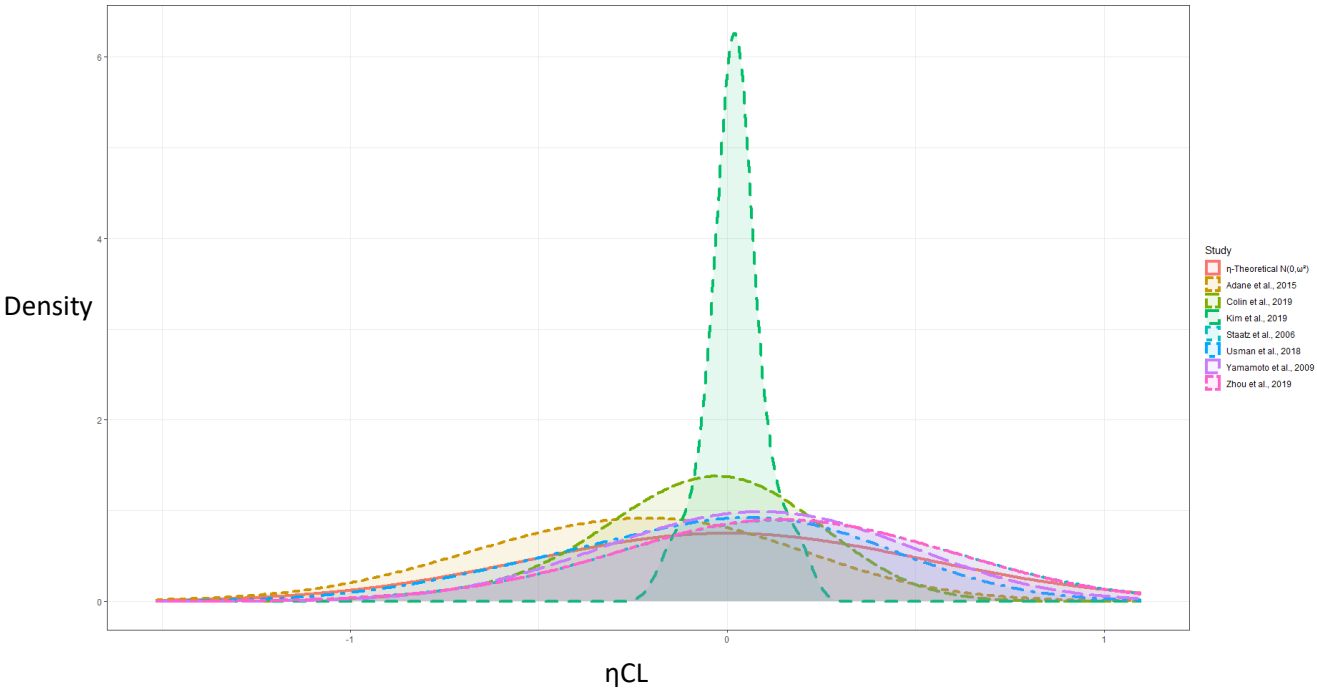


Figure S4.7. ETA_{CL} distribution of all literature-based models compared to our theoretical distribution of N (0, 0.116). Overlap with the theoretical distribution indicated proper Bayesian prior.

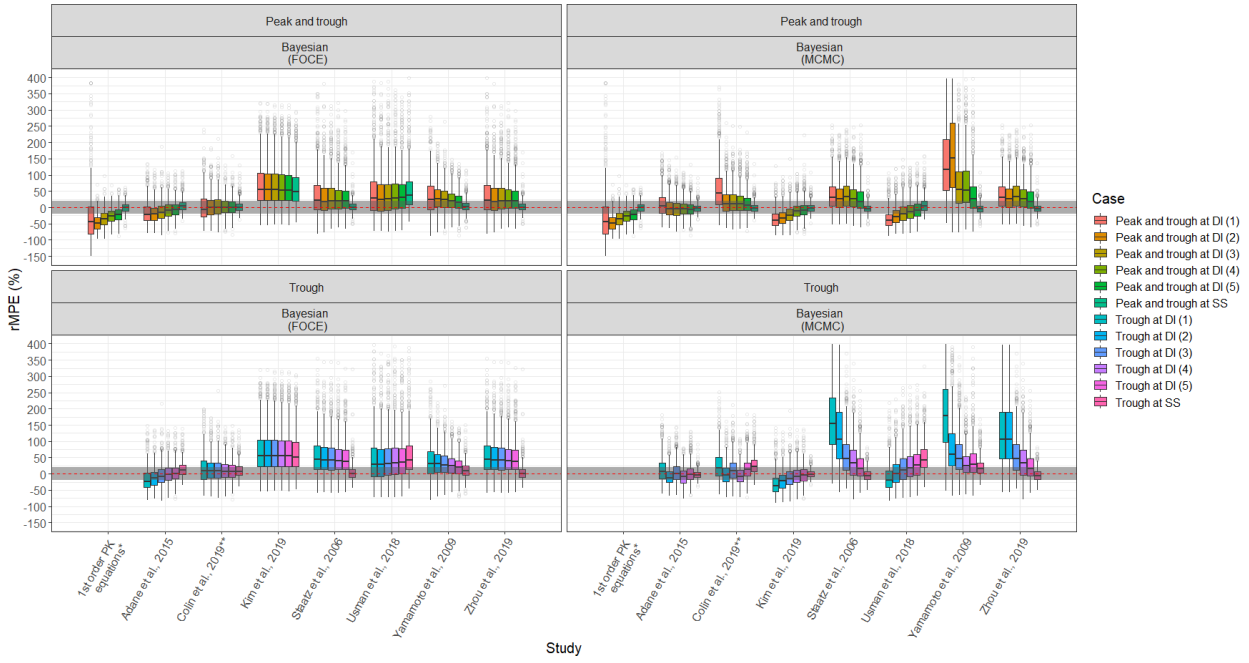


Figure S4.8. Box plot representing rMPE results of MIPD clinical trial simulation A. Each subplot represents a combination of using a peak and a trough or a trough only at varying dosing intervals (DI) with the fully Bayesian and the conventional Bayesian approaches. Also, rBias of estimating AUC using 1st order PK equations and a peak and a trough were plotted. Each color represents a case. The shaded area represents ± 20% rMPE, and the red dashed line is at y=0. *Pre-steady state dosing interval violates the underlying assumptions. **Model was modified for MCMC algorithm requirements.

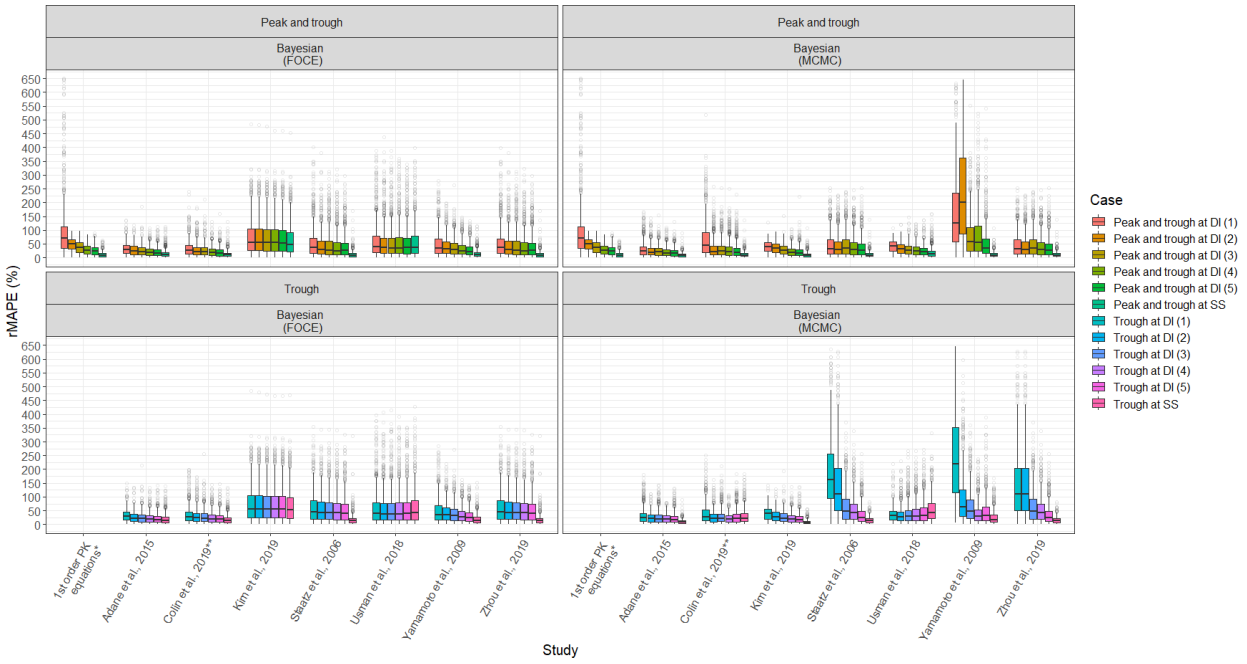


Figure S4.9. Box plot representing rMAPE results of MIPD clinical trial simulation A. Each subplot represents different cases representing a combination of a peak and a trough or a trough only at varying doing intervals with the full-Bayesian and the conventional Bayesian approaches. Also, rMAPE of estimating AUC using 1st order PK equations and a peak and a trough were plotted. *Pre-steady state dosing interval violates the underlying assumptions. **Model was modified for MCMC algorithm requirements.

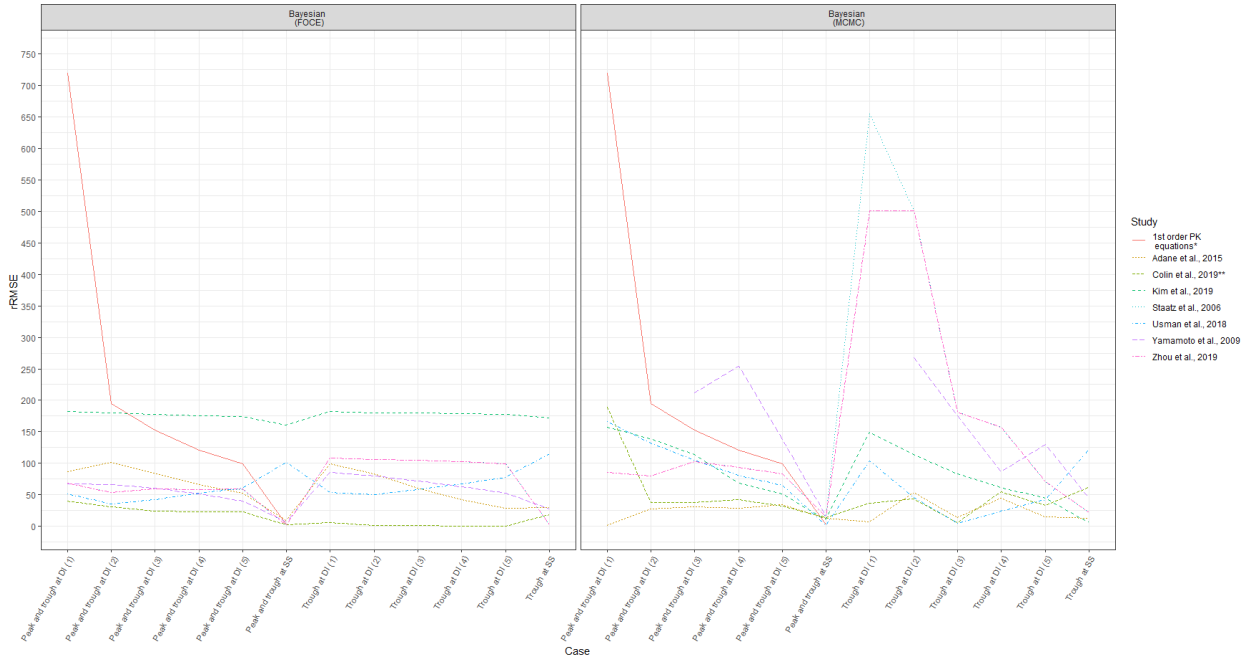


Figure S4.10. Line plot of RMSE result of MIPD Trial A. Each subplot represents Full-Bayesian or the conventional Bayesian approach. Each color represents using a Bayesian prior model. *Pre-steady state dosing interval violates the underlying assumptions. **Model was modified for MCMC algorithm requirements.

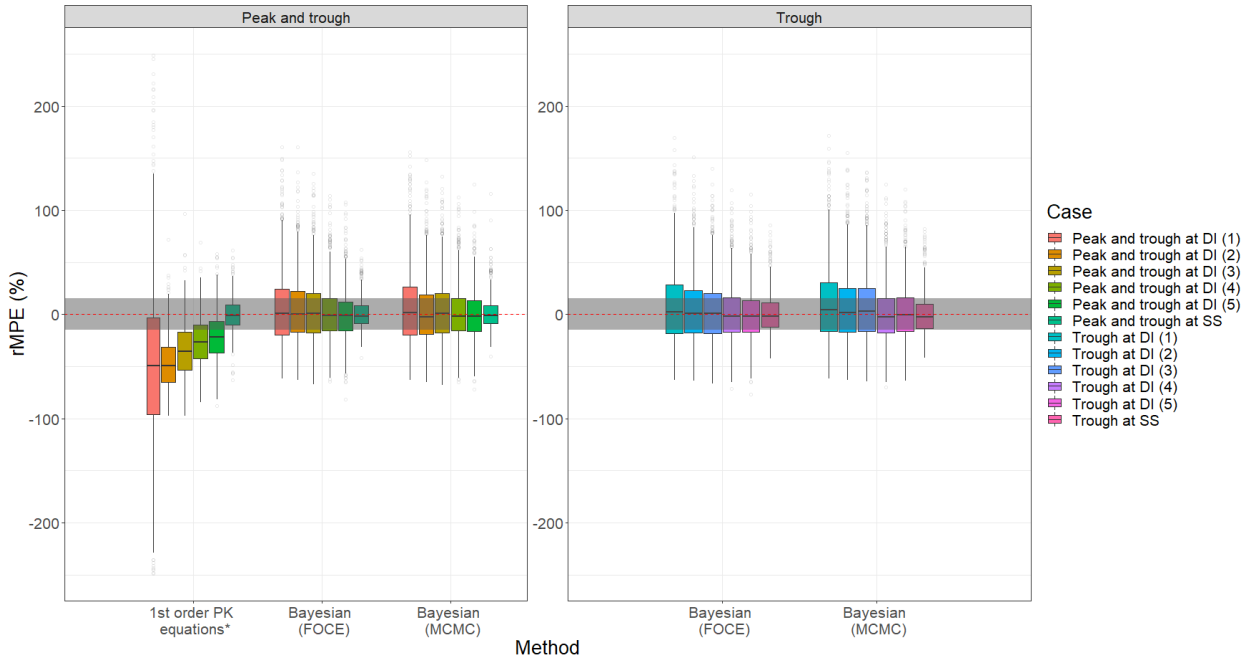


Figure S4.11. Box plot representing rMPE results of MIPD clinical trial simulation B. Each subplot represents either the case of a peak and a trough or a trough only at varying doing intervals with the full Bayesian and the conventional Bayesian approaches. Also, rBias of estimating AUC using 1st order PK equations and a peak and a trough were plotted. Each color represents a case. The shaded area represents ± 20% rMPE, and the red dashed line is at y = 0. Pre-steady state dosing interval violates PK equations underlying assumptions.

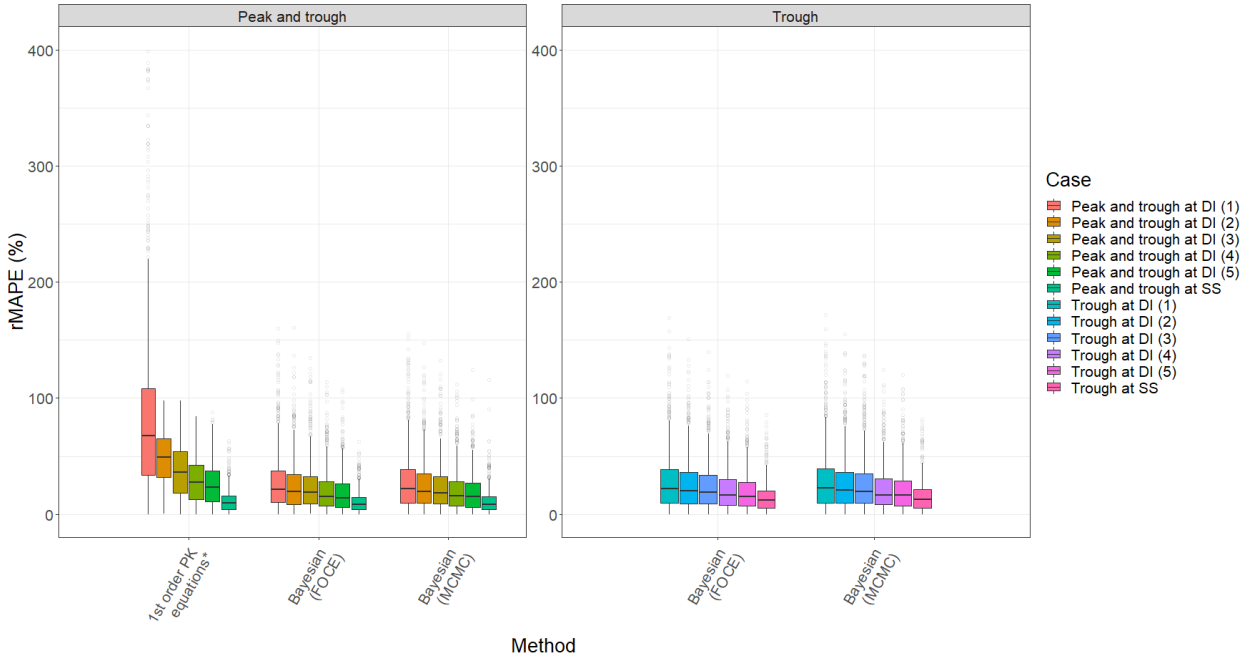


Figure S4.12. Box plot representing rMAPE results of MIPD clinical trial simulation B. Each subplot represents cases of a peak and a trough or a trough only at varying doing intervals with the full-Bayesian and the conventional Bayesian approaches. Also, rMAPE of estimating AUC using 1st order PK equations and a peak and a trough were plotted.

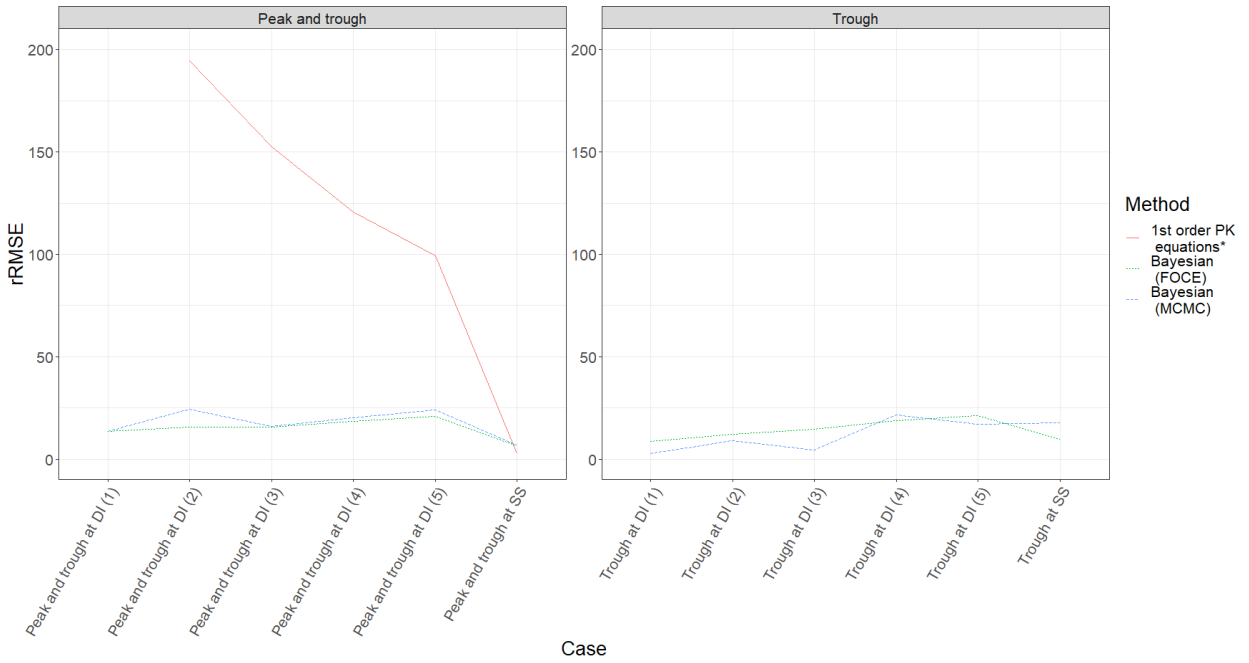


Figure S4.13. Line plot of RMSE result of MIPD Trial B. Each subplot represents the case of a peak and a trough or a trough. Each color represents using the case of a peak and a trough or a trough. Each color represents using the full-Bayesian, the conventional Bayesian approach, or first-order PK equations. Pre-steady state dosing interval violates PK equation underlying assumptions.

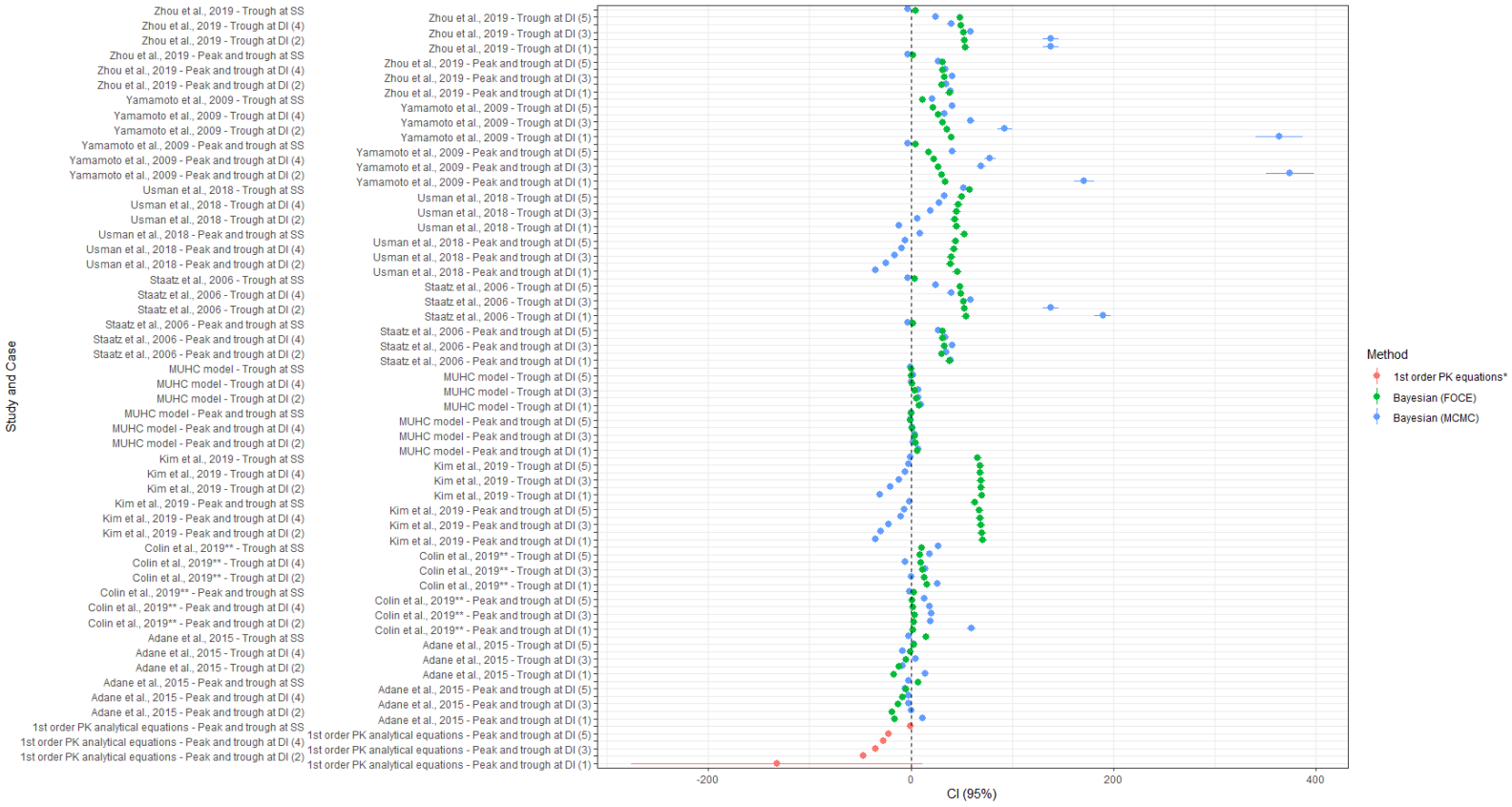


Figure S4.14. A plot of rMPE 95% CIs from clinical trial simulation A and B. A 95% CI that included zero (plotted as a dashed line) was considered to be associated with an acceptable combination, *i.e.,* model/case. The simulation model is our MUHC model. *Pre-steady state dosing interval violates its underlying assumptions. **Model was modified for MCMC algorithm requirements.

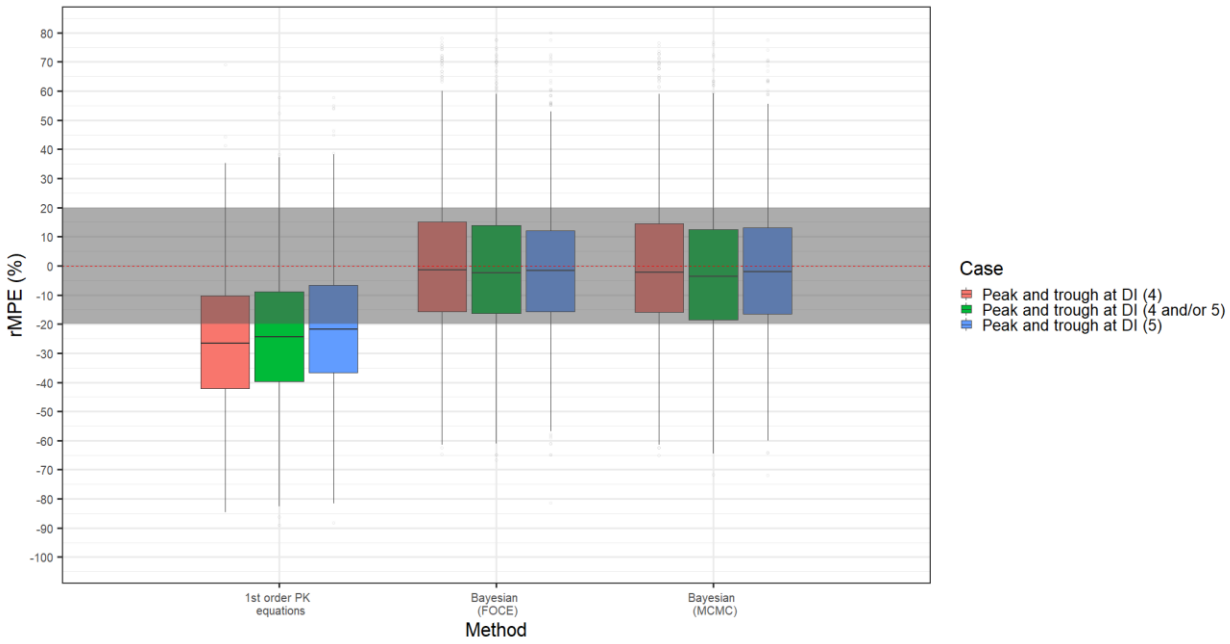


Figure S4.15. Box plot representing rMPE results of MIPD clinical trial simulation C. Using a peak and a trough with the full-Bayesian, the conventional Bayesian, and 1st order PK equations. Each color represents a single or combined 4th and 5th dosing intervals. The shaded area represents ± 20% rMPE, and the red dashed line is at y=0. Pre-steady state dosing interval violates PK equation underlying assumptions.

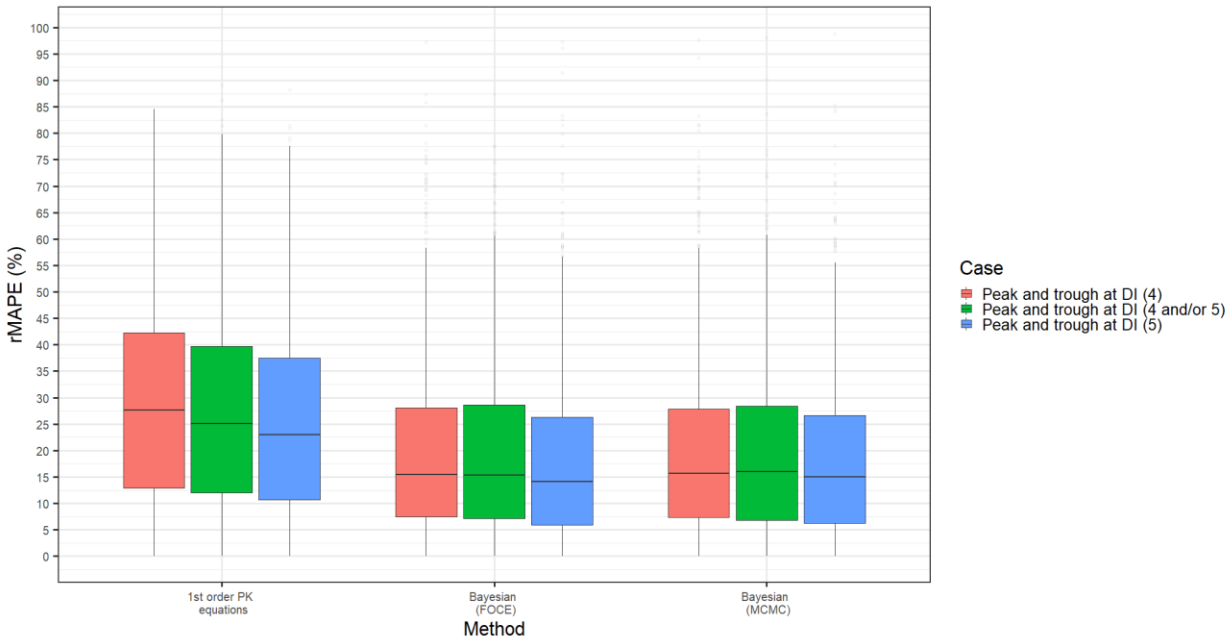


Figure S4.16. Box plot representing rMAPE results of MIPD clinical trial simulation C, representing cases of a peak and a trough or a trough only at varying doing intervals with the

full-Bayesian and the conventional Bayesian approaches. As well as estimating AUC using 1st order PK equations using a peak and a trough were plotted. Pre-steady state dosing interval violates PK equation underlying assumptions.

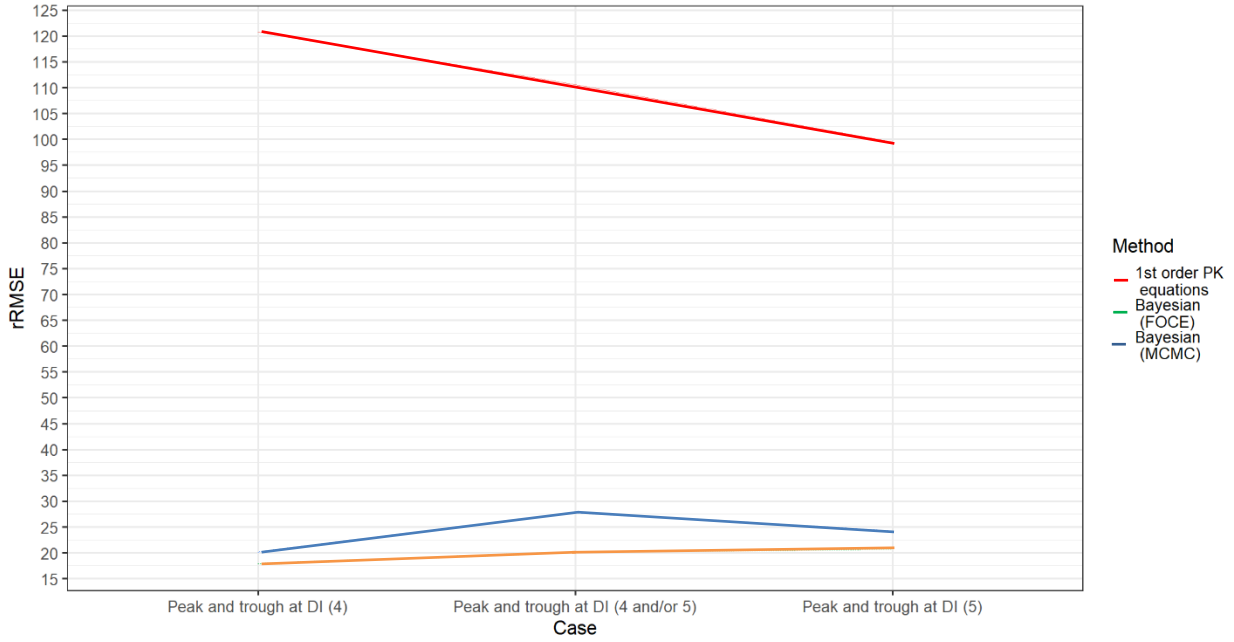


Figure S4.17. A plot of rRMSE result of MIPD Trial C. Each color represents using the Full-Bayesian, the conventional Bayesian approach, or 1st order PK equations. Pre-steady state dosing interval violates PK equation underlying assumptions.

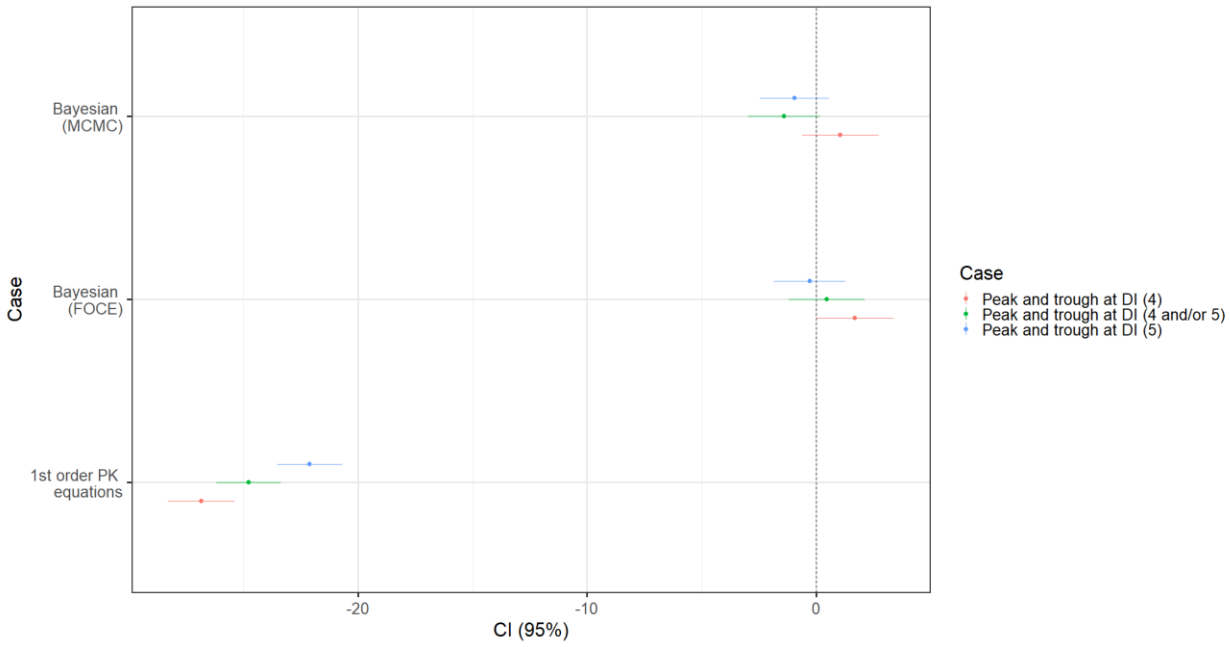


Figure S4.18. A plot of rMPE 95% CIs from clinical trial simulation C. A 95% CI that included zero (plotted as a dashed line) was considered to be associated with an acceptable combination model/case.

Supplement References

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Chapter 5.

Critical Assessment of Vancomycin Monitoring Methods of the Revised Guidelines

In light of the revised vancomycin monitoring guidelines, we aimed at exploring key concepts of vancomycin monitoring. This chapter might help clinicians optimize vancomycin therapeutic monitoring.

5 Article IV Critical Assessment of Vancomycin Monitoring Methods of the Revised Guidelines

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Abstract

Background

The revised vancomycin guidelines recommend replacing trough-only with troughs or peak/trough Bayesian and peak/trough first-order equations monitoring, citing their better AUC predictions and poor AUC-trough correlation. Yet, evidence suggesting good AUC-trough correlations has been overlooked, and the optimality of peak/trough samples has been doubted. The guidelines recommend Bayesian programs implementing richly sampled PopPK priors despite their scarcity. Therefore, whether complex Bayesian and sample-demanding first-order equations can bring significant advantages to the practice over simple trough-only monitoring is worth weighing.

Objectives

The primary aim is to comprehensively re-evaluate AUC predictions methods. Then, the impact of nonadherence to peak/trough sampling is investigated. Moreover, we report the nature of PopPK priors used in Bayesian programs to assess the applicability of guideline recommendations.

Methods

Using a well-established PopPK model combined with real data, we compared AUC monitoring methods. This also served to assess the impact of sampling protocol nonadherence. A thorough exploration of Bayesian programs in terms of their priors is performed.

Results

Bayesian, first-order, and trough-only AUC predictions resulted in 43% to 83%, 3% to 70%, and 3 to 70% patients within acceptable accuracy, respectively. Random or trough samples with Bayesian monitoring resulted in similar performance. Contrary to the recommendation, very few programs implemented richly sampled priors.

Conclusion

Bayesian monitoring is fast and reliable, but its prerequisites are rarely met. First-order equations are reliable only near steady-state. Simple trough-only can, sometimes, be as effective. Constraints regarding peak/trough sampling times could be relaxed. The scarcity of richly sampled Bayesian priors questions the applicability of the revised guidelines recommendation.

5.1 Introduction

The published revised vancomycin therapeutic monitoring guidelines for the management of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections have recently introduced a major shift in vancomycin therapeutic monitoring (1). The revised guideline no longer advocates for the use of trough concentrations of 15-20 mg/L as surrogates of the therapeutic target area-under-the concentration-time-curve over minimum inhibitory concentrations (AUC/MIC) of ≥ 400 for serious MRSA infections, arguing that variations around the AUCs mean was reported to be poorly explained by a regression model (i.e. poor coefficient of determination R^2) and the availability of better approaches (1). Alternatively, Bayesian-based AUC monitoring using two samples (i.e., troughs or peaks) or just one sample (i.e., trough) is recommended, as well as the option of using first-order pharmacokinetic (PK) analytic equations with peak and trough samples.

Advantages of Bayesian-based AUC monitoring include rapid and reliable AUC predictions leading to, potentially, shorter duration of therapy, lower nephrotoxicity, and fewer blood samples (1, 2). Yet, Bayesian-based AUC monitoring might be complex to the average clinician, and its implementation requires specialized programs, expertise, and an additional sample compared to trough-only monitoring (3). It might seem intuitive to assume better AUC predictions using Bayesian methods compared to those based on trough-only or first-order PK equations. The Bayesian approach in its essence incorporates prior knowledge, patients' specific characteristics, administered doses, and drug levels to produce the posterior parameter likelihood distribution (1, 4).

Numerous studies reported moderate to strong AUC-trough R^2 in both adult (5-8) and pediatric (9-11) populations, some of which used actual clinical data as reviewed in detail by Jorgensen et al. (12). These studies suggest that AUC can be reliably approximated by trough-only monitoring (3, 12), contrasting, overwhelmingly, the revised guideline argument of weak AUC to trough R^2 based on a single study (4). Considering the potential variety of AUC-trough R^2 strengths, a contextual comparison of Bayesian monitoring with the other monitoring methods is worth pursuing.

Multiple variables and scenarios that can limit the proper implementation of the revised guideline recommendations and potentially affect optimal vancomycin therapeutic drug monitoring (TDM) are worth investigating. First, collecting a trough or, preferably, peak and trough samples to use with the Bayesian-based AUC monitoring was recommended as the preferred AUC monitoring method in adults(1) (primary recommendation number 8 with A-II grade (1, 13)). However, evidence exists suggesting that peaks and/or troughs might not necessarily be associated with the optimal Bayesian-guided AUC predictions (2, 4, 14). Further,

Neely et al. in (2) and (15) reported that sampling trough levels, recommended in the original vancomycin guideline, were poorly adhered to in practice. Second, the revised guidelines stated the monitoring preference for using Bayesian software programs, specifically, programs that incorporated a Bayesian population pharmacokinetic (PopPK) prior constructed with rich data (1). Therefore, the status of such programs that satisfy this rich data condition is worth investigating in order to evaluate the feasibility of this recommendation. Finally, another variable that might affect optimal vancomycin TDM is the wide variability reported in the higher range of AUC values corresponding to a single trough value (1, 4). Although this was mentioned in the revised guideline (1), its potential biological source or mathematical explanation, as well as its clinical relevance, seem to be lacking.

In the quest for optimal vancomycin TDM, the main objective of the current study is to compare AUC prediction using Bayesian-, first-order equations-, and trough-only-guided AUC monitoring. We also aim to investigate the potential impact of the nonadherence to the recommended sampling protocol consisting of troughs or peaks and troughs. In order to assess the applicability of the new guideline recommendation, we report the current status of Bayesian programs in terms of the sampling density of their priors.

5.2 Methods

5.2.1 Virtual Population

The goal of this step was to make a reference dataset with a known steady-state AUC (i.e., individual reference AUC) in order to use it as a benchmark value for method comparison. For this, we conducted a literature survey to identify a potential PopPK model candidate that is well-established and relevant to large clinical populations. The identified PopPK model was then used to generate a virtual population of 1000 adult subjects. NONMEM (Version 7.4; GloboMax LLC,

Hanover, MD, USA) and PsN interface (16) were used for this simulation. For every individual, the reference individual AUC (AUC_i) was calculated according to:

$$AUC_i = DOSE_i/CL_i$$

To serve the objectives of this study, this reference dataset was split into three subsets containing: A) only trough vancomycin levels; B) random vancomycin levels (neither peak nor trough), and C) peak and trough vancomycin. These levels were simulated at the first, second, third, fourth, and fifth dosing interval, as well as at a confirmed steady-state (i.e., SS=1 in NONMEM).

5.2.2 AUC Prediction

The goal of this step was to calculate AUC_i using different monitoring methods suggested by the original and the revised guidelines (1, 17). The old method was using trough-only samples as surrogates for AUC, while the new considered methods were the Bayesian approach and the first-order PK equations, as detailed below in every subsection.

5.2.2.1 Trough-only AUC Prediction

To quantitively evaluate the trough-only predictive performance, we used linear regression equations that described the relationship between AUC and trough. We screened the literature to identify linear regression equations that described the relation between vancomycin AUCs and troughs in adults. In case a study reported the AUC-trough plot only, without the linear regression model, we extracted the data using an open-source tool WebPlotDigitizer (18), and calculated the linear regression model in R (www.r-project.org). Further, we obtained and used the linear regression models for our McGill University Health Center (MUHC) data (described in section 5.2.2.2) as well as the reference model used in section 2.1 above to simulate the reference

dataset. These linear regression formulae were coded in R and were used to estimate individual reference AUC in subset A.

5.2.2.2 Bayesian-Based AUC Prediction

We used here a Bayesian-based approach to predict the AUC_i. The PopPK model that served as a Bayesian prior for this estimation was a model that we developed earlier for renal function stable patients (Chapter 4). These excluded patients with renal replacement therapy, extracorporeal support membrane oxygenation, acute kidney failure, or end-stage renal disease, admitted to MUHC who had at least four intravenous vancomycin administrations for suspected or confirmed MRSA infections. Concentration-time profiles were best described using a one-compartment model with linear elimination, exponential interindividual variability (IIV), and combined proportional and additive error model. Creatinine clearance and weight were involved as covariates in the description of vancomycin clearance and volume of distribution, respectively. This PopPK model was evaluated for compatibility with the simulated dataset (Methods 2.1 and Results 3.1), based on model diagnostic criteria, namely the visual overlap between individual distribution densities η_i with the theoretical η-distribution $N(0, \omega^2)$, the visual predictive check (VPC), and normalized prediction distribution errors (NPDE). Using the obtained model parameters, we estimated individual reference AUC for subsets A, B, and C described above. The estimation was conducted in NONMEM using the first-order conditional estimation (FOCE) algorithm with MAXEVAL=0.

5.2.2.3 First-order PK Analytic Equations AUC Prediction

First-order PK equations, suggested in the revised guideline (1), were coded in R and were used to estimate individual reference AUC of subset C (peak and trough samples), as this method requires at least two samples.

5.2.3 The Impact of Adherence to the Timing of Samples Collection

The impact of non-adhering to the proper sampling time of trough with the Bayesian-based AUC predictions was evaluated using subsets A and B, and the Bayesian approach that was described in section 5.2.2.2.

5.2.4 Review of PopPK Models Used as Priors in Bayesian Software Programs

The use of Bayesian software programs, specifically programs using richly sampled PopPK model-fitted priors, is the preferred AUC monitoring approach (1). We searched the internet and the literature for all Bayesian programs that are used for vancomycin TDM. We identified the PopPK models included as the Bayesian prior in each software program through the program's official website, complemented by personal communications with their developers when needed, and information available from the literature.

5.2.5 Predictive Performance

We estimated the predictive performance of the new AUC estimation methods, i.e., Bayesian-based and first-order PK equation, versus linear regression equations. As described in detail in Chapter 4, the respective method accuracy was evaluated using relative mean percentage prediction error (rMPE) and relative mean absolute percentage prediction error (rMAPE), while the relative root mean squared error (rRMSE) was used for precision evaluation. The performance of each method was also evaluated using the percentage of patients who achieved rMPE within ± 20%.

5.3 Results

5.3.1 Virtual Populations

The model developed by Colin et al. (19) was identified as the best PopPK candidate model for the generation of a virtual population. This model was built on data pooled from 14 studies

across different countries and composed of a large sample size of 8300 concentrations, collected from 2554 patients (19). It also includes diverse age and clinical subgroups, such as adults, elderly, trauma, and obese patients. Therefore, this model was used to generate the reference dataset, containing individual reference AUC (AUC_i), which was further divided into subsets A, B, and C described in Section 5.2.1. Model diagnostics suggested proper compatibility between the Colin et al. and our prior, as depicted in VPC and NPDE plots in Supplementary Figures 5.S1 and S5.2.

5.3.2 Bayesian-, First-order order PK Equation-, or Linear Regression Equation-Based AUC Estimation

Our results, shown in Figure 5.1 and Figures S5.3, S5.4, and S5.5, suggest that the Bayesian-based AUC approach might perform better than the other methods. Indeed, as depicted in Figure 5.1, using Bayesian-based AUC predictions resulted in 43% to 72% and 45% to 83% of patients falling within the desired rMPE ±20% range when trough-only, and peak and trough samples were used for monitoring, respectively. Also, using the first-order PK equations-based AUC prediction with 2 samples (peak and trough) gave rise to 3% to 70% of patients within the desired rMPE ±20% range. On the other hand, results of monitoring using regression model based on a single trough varied depending on the regression models used and dosing interval (4-8, 19-22), as the percentage of patients within the rMPE ±20% range varied from 3% to 70 % (Figure 5.2). An incremental gain in predictive performance as we move towards steady-state was observed with the Bayesian approach, the first-order PK equations, and most of the regression models, except for Pai et al. and Smit et al (4, 22). It should be noted that first-order PK equations and the regression models (if the regression models were derived at steady-state) should only be clinically applicable with samples collected near a steady state. Further, the

reported R^2 did not seem to be a strong generalizable indicator of predictive performance. For example, Bel Kamel et al. (20) had the second weakest reported R^2 of 0.51 but showed a better predictive performance than many other studies that reported a much stronger R^2, such as Abulfathi et al., Turner et al., and Smit et al.(5, 8, 22). Six of the ten regression models achieved > 60% of the patients within the rMPE ±20% at a steady-state. Overall, the predictive performance of most of the regression equations was relatively similar to that of the first-order PK equations at steady-state but much better at pre-steady-state dosing intervals, despite requiring only one sample

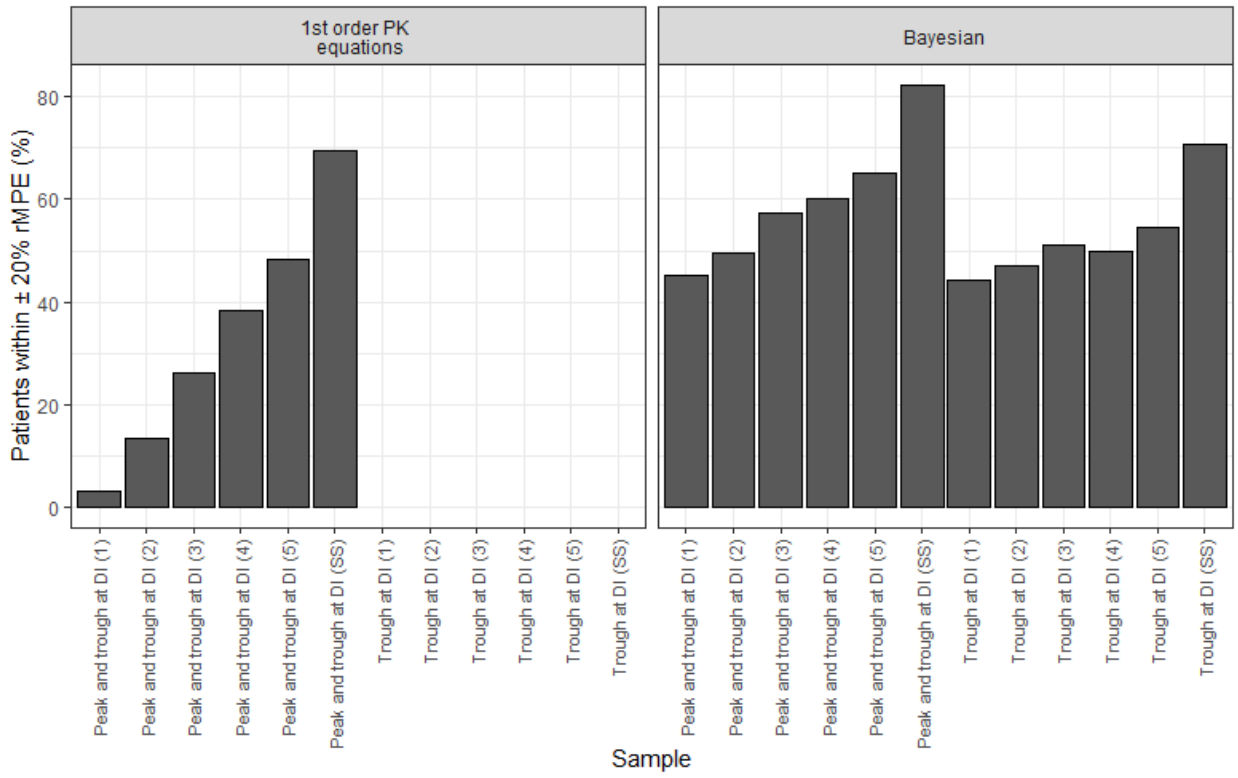

Figure 5. 1 The percentage of patients with acceptable perceived accuracy (i.e., within ± 20% rMPE) at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS) with two samples (peak and trough) or one sample (trough). Two methods were used, first-order PK equations (left) and the Bayesian approach (right). Note that first-order PK equations can only be used with at least two samples obtained near steady-state.

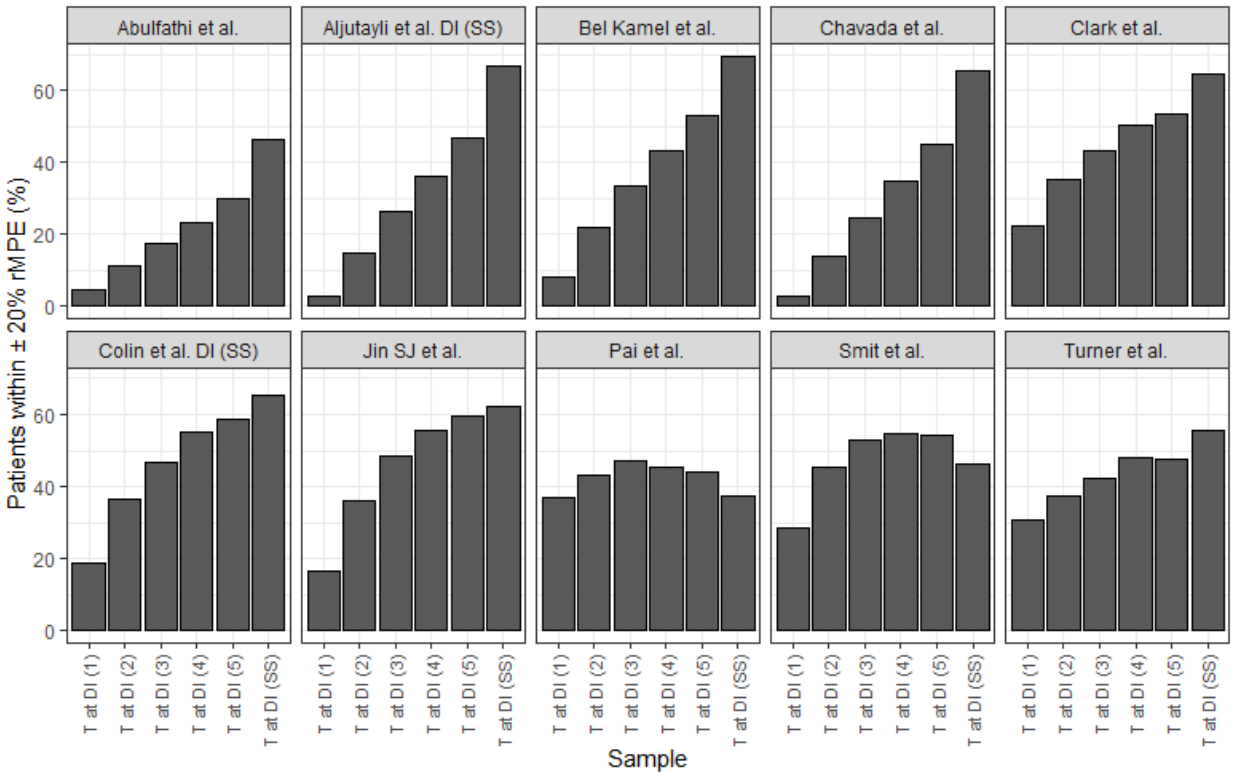

Figure 5. 2 The percentage of patients with acceptable perceived accuracy (i.e., within ± 20% rMPE) at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS), using one sample (trough). Each subplot represents a linear regression formula (4-8, 19-22).

5.3.3 Trough-only Versus Random-only Bayesian-Based AUC Predictions

Results depicted in Figure 5.3 and Figure S5.6, S5.7, S5.8 suggest that there could be a small difference between Bayesian-based AUC estimation using a single trough versus using a single random (not a peak or a trough level). Bayesian methods showed a good performance with either a single trough or a single random level. This suggests that nonadherence to time sampling (trough in general), reported to be frequent in clinical settings (2, 15), could not significantly alter the Bayesian-based prediction performance.

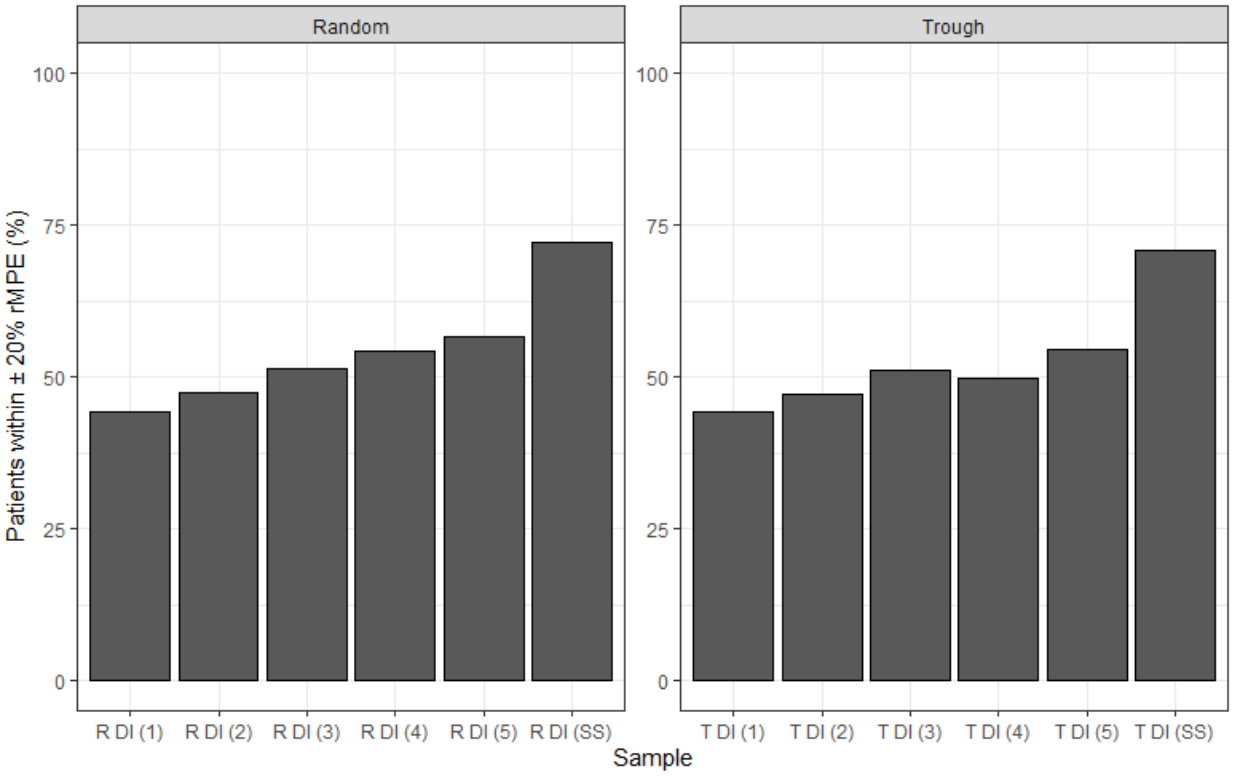

Figure 5. 3 The percentage of patients with acceptable perceived accuracy (i.e., within ± 20% rMPE) at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS), using one random (R) or trough (T) level with Bayesian-based approach.

5.3.4 Review of PopPK Models Used as the Priors by Bayesian Software Programs

To assess the compliance with rich sampling conditions mandated by the revised guideline, we reported information, including population, study type, and the number of samples of PopPK models that were implemented as Bayesian prior in different Bayesian TDM software programs. Most reviewed models in Tables 5.1 and 5.2 were collected as part of TDM and were sparsely sampled, questioning the applicability of requiring the rich sampling condition when using Bayesian TDM software programs.

Table 5. 1 Reported PopPK models (or data) used as the Bayesian priors in varying Bayesian TDM software programs

Bayesian TDM Program	Reported Model (or data) Implemented as the PopPK Bayesian Prior (Note: models might have been or can be modified for specific sites)
AutoKinetics (23, 24)	Roberts et al. (25) AutoKinetics tested different priors including, Garcia et al. (26), Llopis-Salvia et al. (27), Mangin et al. (28), Medellin-Garibay et al. (29), Revilla et al. (30), Udy et al. (31)
BestDose (formerly RightDose)	Standalone windows version: Based on data from Hurst et al. (32) Web-version: The model/models are based on data from Neely et al. (including Hurst et al.) and unpublished 231 neonates and 62 pediatric TDM data with varying degrees of renal function. The mean (range) of samples per subject was 4.4 (1-30).
DoseMeRx (33)	Buelga et al. (34)
	Frymoyer et al.(35)
	Goti et al. (36)
	Lamarre et al. (37)
	Sabourenkov et al.(38)
DosOpt (39)	Allegaert et al. (40)
	Anderson et al. (41)
	Bhongsatiern et al. (42)
	De Cock et al. (43)
	Frymoyer et al. (35)
	Grimsley et al. (44)
	Kimura et al. (45)
	Lo et al. (46)
	Marques-Minana et al. (47)
	Oudin et al. (48)
	Seay et al. (49)
	Zhao et al. (50)
ID-ODS (51)	Goti et al. (36)
	Matzke et al. (52)
InsightRx	Adane et al. (53)
	Anderson et al. (41)
	Buelga et al. (34)
	Capparelli et al. (54)
	Carreno et al.(55)
	Colin et al. (19)
	Crass et al.(56)
	Dolton et al.(57)
	Frymoyer et al. (35)
	Germovsek et al. (58)
	Goti et al. (36)
	Kloprogge et al. (59)
	Lamarre et al. (37)
	Le et al. (60)
	Le et al. (61)
	Revilla et al.(30)
	Rodvold et al.(62)
	Thomson et al.(63)
	Oda et al.(64)
	Zhao et al. (50)

MwPharm++	NA
NextDose	Multicentre published and unpublished TDM data from premature neonates, neonates, infants, children, and adult patients
PrecisePK (formerly T.D.M.S. 2000™ before 2015)*	Capparelli et al (54)
	Frymoyer et al. (35)
	Le et al. (60)
	Le et al. (61)
Tucuxi	Colin et al. (19)
	Dao et al. (65)
	Goti et al. (36)
	Liu et al. (66)
	Llopis-Salvia et al.(27)
	Staatz et al. (67)
	Thomson et al. (63)
	Yamamoto et al. (68)
Rxkinetics APK©	Derived from Winter et al. (69)
	Derived from Matzke et al. (52)

TDM: therapeutic drug monitoring, NA: not available.

*PopPK models mentioned here are based on another review. Many other children and adult PopPK models are potentially implemented (70).

Table 5. 2 Description of PopPK models used by the TDM Software programs reported in Table 5.1

Study	Population	Study type	No. of Individuals	No. of reported samples		Sampling frequency
				Per patient	Total	
Adane et al. (1)	Adults (obese)	Prospective	29	NR	93	Peak, random, and trough
Allegaert et al. (2)	Preterm neonates	Retrospective (TDM)	249	2 (1-9)[b] as reported by Colin et al. (3)	648	Peak and trough
Anderson et al. (4)	Preterm neonates	Retrospective (TDM)	214	NR	604	Peak and trough
Bhongsatiern et al. (5)	Neonates (late-onset sepsis)	Retrospective (TDM)	152	NR	528	Peak and trough
Buegla et al.(6)	Adults (hematological malignancies)	Retrospective (TDM)	Model:215	3.5 ± 1.9[a]	1004	Peak (34.3%), trough (48.4%), and other (17.3%)
			Validation:59	2	124	Peak (10.5%), trough (81.4%), and other (8.1%)

Capparelli et al (7).	Neonates and infants	Multi-center retrospective (TDM)	Model: 374	At least one sample and Included intensive PK data of Kildoo et al.(8) from 15 infants (mostly 5 samples per patient)	1103	Peak, random, and trough
			Validation:67	NR	160	
Carreno et al. (9)	Adults (obese)	Prospective	12	5	71	At 1, 2, 4, 6 h, and a trough
Crass et al. (10)	Adults (obese)	Retrospective (TDM)	346	NR	NR	Peak and trough
Colin et al. (3)	Included: premature neonates, adults, burn-injured adults, obese, critically ill, trauma patients, and healthy volunteers. Excluded: CRRT, ECMO, hemodialysis, and hemodiafiltration patients	Pooled from 14 previously published studies, including 9 studies from this table (2, 6, 11-17)	2254	(1-32)[a]	8300	Varies per component study
Dao et al.(18)	Neonates	Retrospective (TDM)	Model: 405	4.5 (1-19)[b]	1821	Time after dose: 8.8 h (0.02-64) [b]
			Validation: 78	1.4 (1-4)[b]	112	Time after dose: 60 h (17.8-455) [b]
De Cock et al.(19)	Same data as Allegaert et al.(2)					
Dolton et al. (20)	Adults (sever burn injuries)	Retrospective (TDM)	Model: 37	4 (1-32)[a]	NR	Trough = 76 samples
			Control: 33	2 (1-20)[a]		Trough = 21 samples
Frymoyer et al. (21)	Neonates (NICU level 3)	Retrospective (TDM)	249	NR	1702	Peak and trough

Garcia et al. (22)	Critically ill adult patients	Retrospective (TDM)	46	≥3	233	Trough (80%)
Germovsek et al. (23)	Neonates and infant (intermittent and continuous infusion)	TDM	Model: 54 Validation: 34	NR	Intermittent:81 continuous:102 Intermittent:23 continuous: 84	Peak and trough
Goti et al.(24)	Adults (18.5% Hemodialysis)	Retrospective (TDM)	1812	NR	2765	Single level (in 67% of patients)
Grimsley et al.(25)	Neonates (NICU)	TDM	59	NR	347	Peak (44%), mid (3%), and trough (53%)
Hurst et al. (26)	Cardiac outpatients (endocarditis prophylaxis for dental procedure)	Prospective	Group A: 11	See the article for more details (26)		0.5 h into and at the end of infusion, just before and after the dental procedure, and 24 h after the start of infusion
	Acutely ill cardiac patients	Prospective	Group B:7			Just before and at the end of infusion, 1 h, 2 h, at 2/3, and end of the dosing interval every 4 days
	Patients admitted to internal medicine wards	Retrospective (TDM)	Group C: 20			Peak and trough

Kimura et al. (27)	Neonates (NICU)	Prospective (TDM)	19	NR	88	Peak and trough (6 h after the end of infusion or just before the next dose) at days 1, 3, and 6
Kloprogge et al. (28)	Pediatrics	Retrospective (TDM)	616	7 (2-50)	4137	NR
Le et al.(29)	Children	Retrospective (TDM) from two centers	138	NR	712	0-1 h (3%), 1.1-2 h (29%), 2.1-3 h (9%), 3.1-4 h (4%), 4.1-5 h (5%), and >5 h (49%) post infusion.
Le et al. (30)	Pediatric	Retrospective (TDM)	702	454 patients with ≥ 2 concentrations	1660	0-1 h (3%), 1.1–2 h, (20%), 2.1–5 h (32%), and >5 h (45%) post infusion.
Lamarre et al. (31)	Children	Retrospective (TDM)	Model: 78	NR	256	Peak and trough
		Prospective (TDM)	Validation:19	NR	84	Two peaks and two troughs
Liu et al.(32)	Adults (note: vancomycin CL is a function of GFR calculated using Cystatin C according to Hoek's equation)	Prospective	Model: 200	NR	514	Trough then a non-trough level at 1, 2, 5, or 7 h on the following dosing interval
			Validation: 74	NR	216	
Llopis-Salvia et al. (33)	Critically ill adult patients	Retrospective (TDM)	Model: 30	7.8 ± 4.1[a]	234	At least one concentration
			Validation: 20	5.1 ± 3.2[a]	103	Peak and trough
Lo et al. (15)	Neonates	Retrospective (TDM)	116	6 (2-27)[b] as reported in Colin et al. (3)	835	At least two

Mangin et al. (34)	Critically ill (post-sternotomy mediastinitis)	Retrospective (TDM)	30	14 (1-34)[b]	359	Trough
Matzke et al. (35)	Various degrees of renal function Group 1: CLcr > 60 ml/min) Group 2 (CLcr 10-60 ml/min) Group 3 (Clcr< 10 ml/min)	Retrospective (TDM)	Group 1: 7 patients Group 2: 13 patients Group 3: 36 patients	3.4 ± 0.5[a] 3.9 ± 0.9[a] 4.87 ± 2.60[a]	37 66 204	Trough then 3, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 h after infusion during the 24 h, 96 h, and 168 h after infusion for groups 1, 2, and 3, respectively
Marques-Minana et al.(36)	Neonates (NICU)	TDM	Model: 70 Validation:41	NR	NR	Peak and trough
Medellín-Garibay et al. (16)	Critically ill adult patients	Retrospective (TDM)	Model: 54 Validation: 18	8 (1-36)[a] NR	874 233	At least one sample NR
Neely et al. (37)	Dataset A: 9 patients from group A and 6 from group B of Hurst et al.(26)					
	Dataset B: Varying degrees of renal function from Rodvold et al.(38)	Prospective (TDM)	22 of the 37 patients included in the original study	NR	NR	Just before and after infusion, then at 0.25, 0.5, 0.75, 1, 1.5, 3, 5, 7, and 11 h ± 17 and 23 h serum samples (in addition to vancomycin urine concentrations from two 0-12 h and 12-24 h urine collections)
	Dataset C: Healthy adult volunteers	Prospective	10	7	NR	NR
Oda et al. (39)	Adults (CRRT)	Retrospective (TDM)	Model: 17 Control: 13 Validation: 23	NR	80 NR NR	NR

Oudin et al. (17)	Neonates NICU	Prospective (TDM)	68	2 (1-6)[b] as reported in Colin et al. (3)	151	At least two samples Sample 1: at least once within 24-28 h and Sample 2: after 48 h of initiating the therapy
Revilla et al. (14)	Critically ill adult patients	Retrospective (TDM)	Model 191	3 ± 2.5 (1-19)[a]	569	Trough (79.8%)
			Validation 46	NR	73	NR
Roberts 2011 et al. (13)	Critically ill adult patients	Retrospective (TDM)	206	2 to 3	579	Daily
Sabourenkov et al. (40)	Obese adults	Multi-center retrospective (TDM)	NR	NR	NR	NR
Seay et al. (41)	Neonates	Retrospective (TDM)	192	NR	520	Peak, random, and trough
		Prospective	30	NR	NR	
Staatz et al. (42)	Cardiothoracic surgery patients with unstable renal function	Retrospective (TDM)	Model: 102	3 (1-19)[b]	408	16 h (3-135) post-dose (Mostly random or trough with 76% sampled at least 10 h post-infusion)
			Validation:37	4 (1-13)[b]	151	14.5 h (2.7-67.5)[b] post-dose
Thomson et al. (11)	Adults	Retrospective (TDM)	398 (including 102 patients from Staatz et al.(42))	3 (1-19)[b]	1557	11.9 h (1.1–92.3)[b] (62% sampled at least 10 h after the start of infusion)
			Validation :100	2 (1-5)[b]	171	12.4 h (0.3–57.3)[b] (62% sampled at least 10 h after

						the start of infusion)
Udy et al. (43)	Adults (CRRT)	Retrospective (TDM)	81	2 to 3	199	24, 48, 72 h and daily
Yamamoto et al. (12)	Adult patients	Retrospective (TDM)	100	2.5 (1-16)[b] as reported in Colin et al.(3)	311	Per standards of care at the study hospital
	Healthy volunteers	Prospective	6	NR	45	0, 1, 1.5, 2, 3, 5, 7, 12, 24 h
Zhao et al. (44)	Neonates (continues infusion)	Multicentre TDM	Model: 116	NR	207	26.8 h (9.8-137.8 h)[b] from the start of treatments
			Validation: 58	NR	NR	Within 6–12 h from the start of treatments

Study	**Population**	**Study type**	**No. of Individuals**	**No. of reported samples**		**Designed sampling frequency**
				Per patient	Total	
Allegaert et al. (2)	Preterm neonates	Retrospective (TDM)	249	2 (1-9)[b] as reported by Colin et al. (3)	648	Peak and trough
Anderson et al. (4)	Preterm neonates	Retrospective (TDM)	214	NR	604	Peak and trough

Bhongsatiern et al. (5)	Neonates (late-onset sepsis)	Retrospective TDM	152	NR	528	peak and trough
Buegla et al.(6)	Adults (hematological malignancies)	Retrospective (TDM)	Model:215	3.5 ± 1.9[a]	1004	Peak (34.3%), trough (48.4%), and other (17.3%)
			Validation:59	2	124	Peak (10.5%), trough (81.4%), and other (8.1%)
Colin et al. (3)	Included: premature neonates, adults, burn-injured adults, obese, critically ill, trauma patients, and healthy volunteers. Excluded: CRRT, ECMO, hemodialysis, and hemodiafiltration patients	Pooled from 14 previously published studies, including 9 studies from this table (2, 6, 11-17)	2254	(1-32)[a]	8300	Varies per component study
Dao et al.(18)	Neonates	Retrospective (TDM)	Model: 405	4.5 (1-19)[b]	1821	Time after dose: 8.8 h (0.02-64) [b]
			Validation:78	1.4 (1-4) [b]	112	Time after dose: 60 h (17.8-455) [b]
De Cock et al.(19)	Same data as Allegaert et al.(2)					
Frymoyer et al. (21)	Neonates (NICU level 3)	Retrospective (TDM)	249	NR	1702	Peak and trough
Garcia et al. (22)	Critically ill adult patients	Retrospective (TDM)	46	≥3	233	Trough (80%)
Goti et al.(24)	Adults (18.5% Hemodialysis)	Retrospective (TDM)	1812	NR	2765	Single level (in 67% of patients)
Grimsley et al.(25)	Neonates (NICU)	TDM	59	NR	347	Peak (44%), mid (3%), and trough (53%)
Hurst et al. (26)	Cardiac outpatients (endocarditis prophylaxis for dental procedure)	Prospective	Group A: 11	See the article for more details (26)		0.5 h into and at the end of infusion, just before and after the

						dental procured, and 24 h after the start of infusion
	Acutely ill cardiac patients	Prospective	Group B:7			Just before and at the end of infusion, 1 h, 2 h, at 2/3, and end of the dosing interval every 4 days
	Patients admitted to internal medicine wards	Retrospective (TDM)	Group C: 20			Peak and trough
Kimura et al. (27)	Neonates (NICU)	Prospective (TDM)	19	NR	88	Peak and trough (6 h after the end of infusion or just before the next dose) at days 1, 3, and 6
Le et al.(29)	Children	Retrospective (TDM) from two-centers	138	NR	712	0-1 h (3%), 1-2 h (29%), 2-3 h (9%), 3-4 h (4%), 4-5 h (5%), and >5 h (49%)
Lamarre et al. (31)	Children	Retrospective (TDM)	Model: 78	NR	256	Peak and trough
		Prospective (TDM)	Validation:19	NR	84	Two peaks and two troughs
Liu et al.(32)	Adults (note: vancomycin CL is a function of GFR calculated using Cystatin C according to Hoek's equation)	Prospective	Model: 200	NR	514	Trough then a non-trough level at 1, 2, 5,
			Validation: 74	NR	216	or 7 h on the following dosing interval
Llopis-Salvia et al. (33)	Critically ill adult patients	Retrospective (TDM)	Model: 30	7.8 ± 4.1[a]	234	At least one concentration
			Validation: 20	5.1 ± 3.2[a]	103	Peak and trough
Lo et al. (15)	Neonates	Retrospective (TDM)	116	6 (2-27)[b] as reported in Colin et al. (3)	835	At least two
Mangin et al. (34)	Critically ill (post-sternotomy mediastinitis)	Retrospective (TDM)	30	14 (1-34)[b]	359	Trough
Matzke et al. (35)	Various degrees of renal function Group 1: CLcr > 60 ml/min)	Retrospective (TDM)	Group 1: 7 patients	3.4 ± 0.5[a]	37	Trough then 3, 6, 9, 12, 24, 48, 72, 96,
	Group 2 (CLcr 10-60 ml/min)		Group 2: 13 patients	3.9 ± 0.9[a]	66	120, 144, and 168 h after infusion during
	Group 3 (Clcr< 10 ml/min)		Group 3: 36 patients	4.87 ± 2.60[a]	204	the 24 h, 95 h, and 168 post-infusion for

						groups 1, 2, and 3, respectively
Marques-Minana et al.(36)	Neonates (NICU)	TDM	Model: 70	NR	NR	Peak and trough
			Validation:41			
Medellín-Garibay et al. (16)	Critically ill adult patients	Retrospective (TDM)	Model: 54	8 (1-36)[a]	874	At least one sample
			Validation: 18	NR	233	NR
Neely et al. (37)	Dataset A: 9 patients from group A and 6 from group B of Hurst et al.(26)					
	Dataset B: Varying degrees of renal function from Rodvold et al.	Prospective (TDM)	22 of the 37 patients included in the original study	NR	NR	Just before and after infusion, then at 0.25, 0.5, 0.75, 1, 1.5, 3, 5, 7, and 11 h ± 17 and 23 h serum samples (in addition to vancomycin sampling from two 12 h urine collection)
	Dataset C: Healthy adult volunteers	Prospective	10	7	NR	NR
Oudin et al. (17)	Neonates NICU	Prospective (TDM)	68	2 (1-6)[b] as reported in Colin et al. (3)	151	At least two samples sample1: at least once within 24-28 h and Sample 2: after 48 h after initiating therapy
Revilla et al. (14)	Critically ill adult patients	Retrospective (TDM)	Model 191	3 ± 2.5 (1-19)[a]	569	Trough (79.8%)
			Validation 46	NR	73	NR
Roberts 2011 et al. (13)	Critically ill adult patients	Retrospective (TDM)	206	2 to 3	579	Daily
Sabourenkov et al. (40)	Obese adults	Multi-center retrospective (TDM)	NR	NR	NR	NR
Seay et al. (41)	Neonates	Retrospective (TDM)	192	NR	520	Peak, random, and trough
		Prospective	30	NR	NR	
Staatz et al. (42)	Cardiothoracic surgery patients with unstable renal function	Retrospective (TDM)	Model: 102	3 (1-19)[b]	408	Mostly random or trough; 76% sampled at least 10 h post-infusion 16 h (3-135) post-dose

			Validation:37	4 (1-13)[b]	151	14.5 h meidan (2.7-67.5) post-dose
Thomson et al. (11)	Adults	Retrospective (TDM)	398 (including 102 patients from Staatz et al.)	3 (1-19)[b]	1557	64% sampled at least 10 h post-infusion 11.9 h (1.1–92.3)[b]
			Validation :100	2 (1-5)[b]	171	62% sampled at least 10 h after start of infusion 12.4 h (0.3–57.3)[b]
Udy et al. (43)	CRRT	Retrospective (TDM)	81	2 to 3	199	24, 48, 72 h. and daily
Yamamoto et al. (12)	Adult patients	Retrospective (TDM)	100	2.5 (1-16)[b] as reported in Colin et al.(3)	311	Per standards of care at the study hospital
	Healthy volunteers	Prospective	6	NR	45	0, 1, 1.5, 2, 3, 5, 7, 12, 24 h
Zhao et al. (44)	Neonates (note: continues infusion)	Multicentre TDM	Model: 116	NR	207	26.8 h (9.8-137.8 h)[b] from the start of treatment
			Validation: 58	NR	NR	Within 6–12 h from the start of treatment

CRRT: continuous renal replacement therapy, ECMO: extracorporeal membrane oxygenation, NICU: neonates intensive care unit, NR: not reported, TDM: therapeutic drug monitoring.
[a] Mean ± SD (range)
[b] Median (range)

5.4 Discussion

In this study, we compared the AUC-guided monitoring methods recommended in the revised guideline (i.e., Bayesian and first-order PK equations) to trough-only monitoring using different regression models. Overall, Bayesian-based AUC monitoring might yield the best predictive performance compared to the other methods even with a single sample across any dosing interval. Bayesian monitoring allows for rapid and reliable therapeutic target achievement, which is crucial for certain patients. An example is vancomycin administration on a wide dosing interval (e.g., every 24 h) to renal unstable patients. Once the steady-state can be assumed and additional blood samples are not burdensome, first-order PK equations can be applied while expecting a relatively acceptable predictive performance. In practice, the administration of a loading dose might help achieve the therapeutic target fast, bringing concentrations to near steady-state concentrations. Finally, trough-only monitoring using regression models (i.e., not a trough range) seems to be the most practical method because of its simplicity, with no significant clinical difference between its predictive performance and that of the other methods.

One reason for abandoning trough-only monitoring was the poor R^2 reported for the AUC-trough relation [1, 2]. We aimed to assess if trough measurement is, indeed, a poor predictor of AUC as well as whether the R^2 is a generalizable metric to assess the predictive performance. Yet, there was a challenge as the original guidelines recommended a range of steady-state troughs (15-20 mg/L) and not a specific model. Also, this range of troughs appears to have been derived from (3-5), and only received a level III and grade B recommendation (6). Thus, instead of using this assumed range, we used ten regression models to assess the predictive performance of the trough-only monitoring approach and its generalizability. Our analysis suggests that a trough

level is a reasonable predictor of AUC and that R^2, although informative, has, non surprisingly, some limitations in describing the predictive performance (7). Another possible reason was that Bayesian-guided AUC monitoring could reduce vancomycin-induced nephrotoxicity compared to trough-only monitoring (8, 9). However, comparing a model-based approach (i.e., Bayesian models) to a non-model-based approach (15-20 mg/L generalized trough range) should be expected to intuitively favor the model-based approach. It is worth mentioning that just like with the Bayesian approach as discussed below, a regression model might be subject to transferability assessment and a trough can be subject to a limited sampling strategy. While there seems to be a common inaccurate belief that trough samples can carry the most information regarding clearance and consequently AUC, other sampling times can be as much, or, more informative.

Concerning the variability observed only in the larger AUC values per trough value (10), it seems that this is specific to the simulation and plot generation conditions used in a particular study (1). Further, there is overwhelming evidence not supporting this observation in clinical settings (11-30). We conducted a series of simulation-based investigations of the potential source of this observation (results not presented here), which seems to suggest that this variability is multifactorial and depends on a combination of factors such as the type and size of inter-individual variability, the error model used, and the distribution of covariates [e.g., normal, uniform, truncated normal for example for CL_{cr} with lower and upper limits of 30 and 150 mL/min, respectively]. While such discussion is beyond the scope of this article, the described variability does not seem to be a piece of substantial evidence against trough-only monitoring and it is clinical relevance and practical application seem limited.

While the revised guideline no longer recommends trough-only monitoring citing that troughs are likely not an optimal surrogate for AUCs (10), it is unclear why it still advocates collecting

trough samples for the Bayesian approach despite evidence not supporting Bayesian trough sampling (9, 31). For example, using an optimal sampling times algorithm in a prospective trial determined 21.5% and 43.5% of the optimally timed samples as trough and random (not peak or trough) measurements, respectively (9).

One advantage of the PopPK approach is its ability to handle sparse data. The revised guideline advocated the use of software programs that implemented richly sampled PopPK models (1). Yet, the existence of such programs (and models) seems to be scarce, as reviewed here (Table 5.2) and as it can be seen in the literature (32, 33). The recommendation for the use of a richly sampled PopPK model as a Bayesian prior seems to have originated from (1, 34), which stated that non-richly sampled PopPK models, such as those built with peak and trough levels only, might be suboptimal in predicting the true AUC (1, 34). It was unclear however how these suboptimal predictions compare to those of other AUC prediction methods, especially in the case Bayesian prior models had a large sample size, intensive samples across a wide range of post-infusion times, and were validated.

In our analysis, it can be observed that the Bayesian-based approach, while much better than the other methods, resulted in a modest accuracy and precision in pre-steady state dosing intervals. This can be attributed to the TDM nature of data used to construct the Bayesian prior component and the high level of the random variability. The Bayesian approach has the capacity for a significant improvement in accuracy and precision given better conditions, such as more informative priors.

The current study might be limited by the underlying simulation conditions described above; it rests also on the assumption that the generated AUC_i reflects the true AUC value. Considering that no monitoring approach is currently supported by randomized clinical trials (35), our study

can help guide vancomycin monitoring. We aimed here at evaluating each method's predictive performance, assuming the difference can translate into significantly improved clinical outcomes. It is important to state that this manuscript does not attempt to identify another trough range as it is known to be a poor approach (34).

In conclusion, motivated by the existing controversy around the new vancomycin therapeutic monitoring guidelines and the lack of a thorough investigation of the recommended methods, we collected hospital data and built a modeling framework that allowed us to assess the guideline recommendations of the monitoring methods. We showed that the Bayesian approach should not be taken for granted, and alternative methods can be equally viable. We showed that Bayesian monitoring does not necessarily require trough or peak concentration levels and can in fact be performed using a random level. Until randomized clinical trials are conducted, our study can help guide vancomycin TDM.

Conflict of interest statement

All authors declared no conflicting interests.

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5.5 Supplementary Material

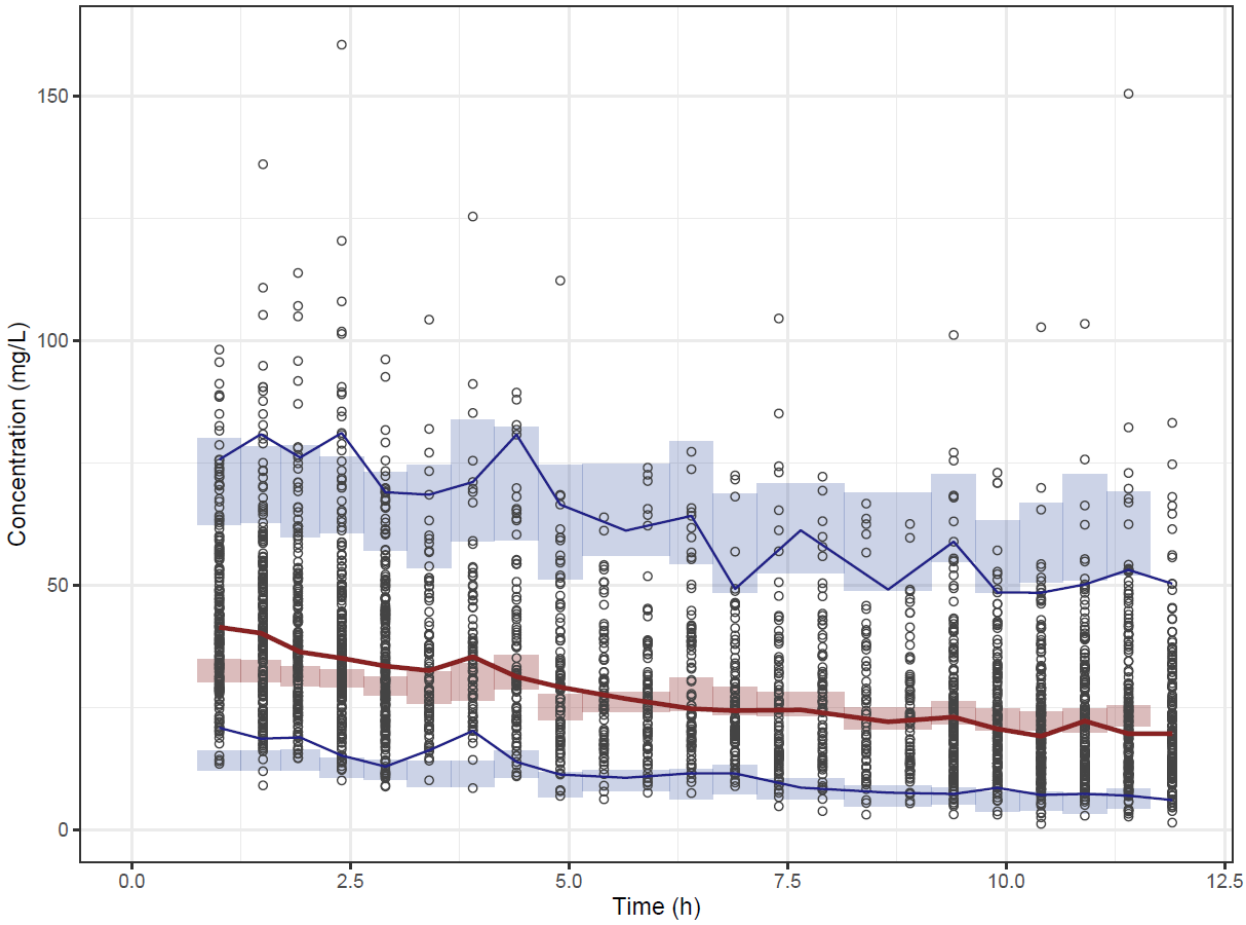

Figure S5.1. Prediction corrected visual predictive check (pcVPC) for vancomycin concentration observations generated from Colin et al. model versus time. This simulation-based model diagnostic plot might indicate a proper model fit as the 50th percentile (solid red line) and the 10th and 90th percentile of the observed data (solid blue lines) of observations (black circles simulated from Colin et al. model) are contained within the corresponding shaded areas.

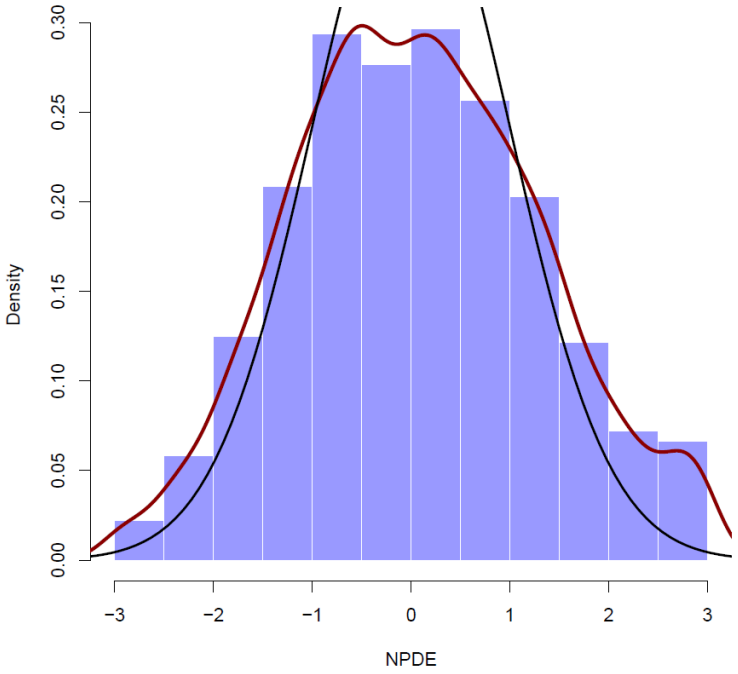

Figure S5.2. Normalized prediction distribution error density plot (NPDE) of predicted and observed concentrations simulated from Colin et al. model.

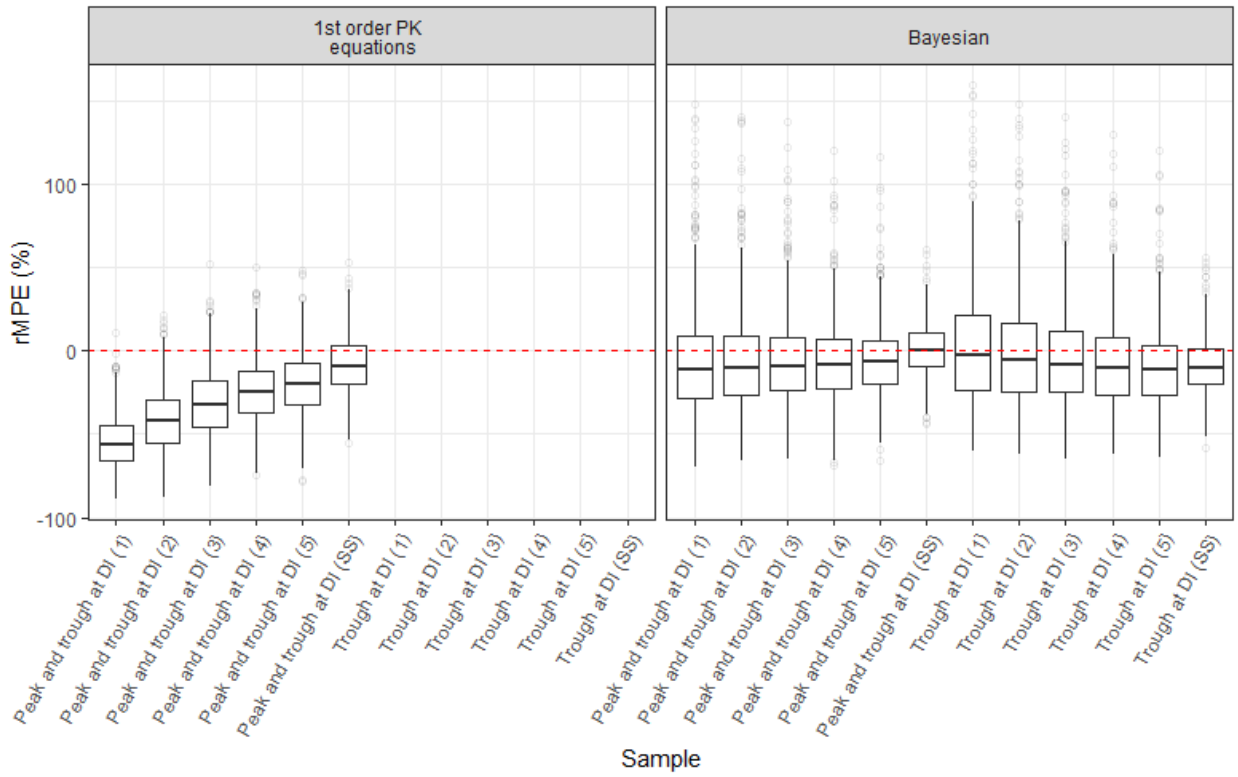

Figure S5.3. Box plot of rMPE (%) results at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS) with two samples (peak and trough) or one sample (trough). Two methods were used, 1st first-order PK equations (left) and the Bayesian approach (right). Note that 1st first-order PK equations can only be used with at least two samples and using them pre-steady-state is improper. The red dashed line is at y=0.

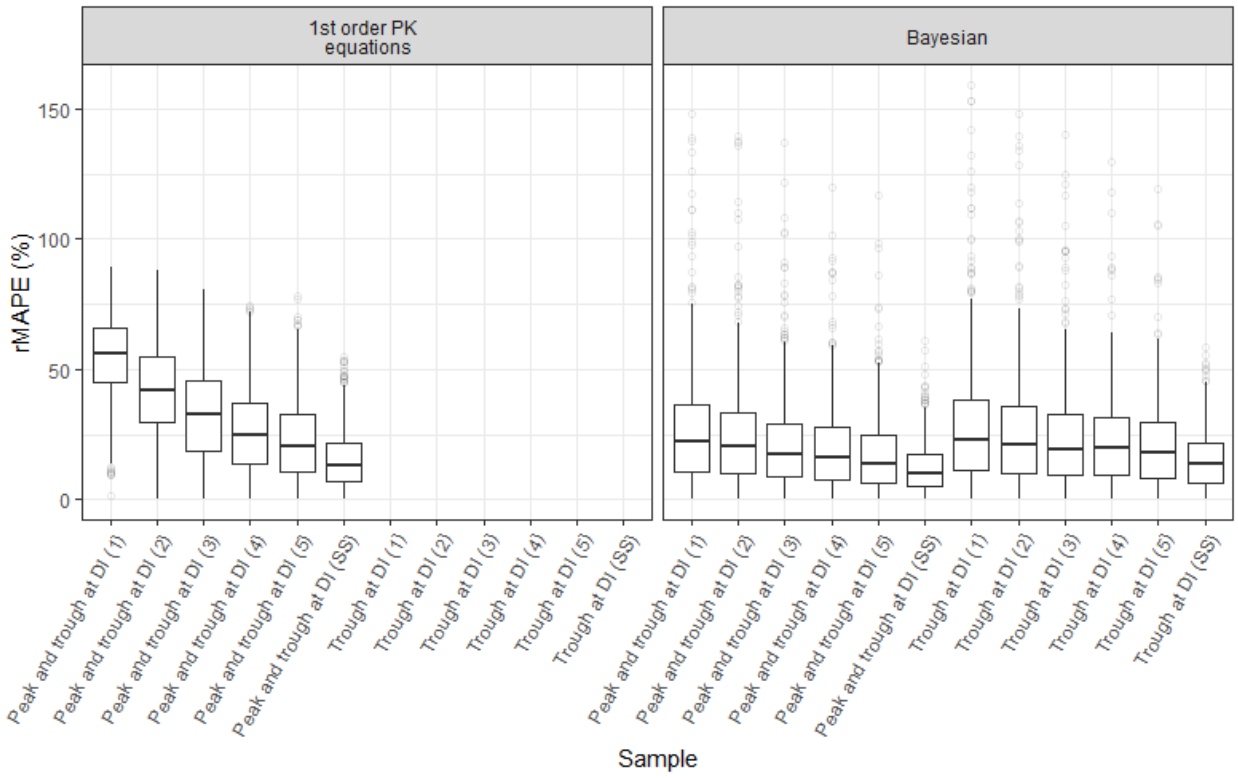

Figure S5.4. Box plot of rMAPE (%) results at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS) with two samples (peak and trough) or one sample (trough). Two methods were used, 1stfirst -order PK equations (left) and the Bayesian approach (right). Note that first-order 1st order PK equations can only be used with at least two samples and using them pre-steady-state is improper.

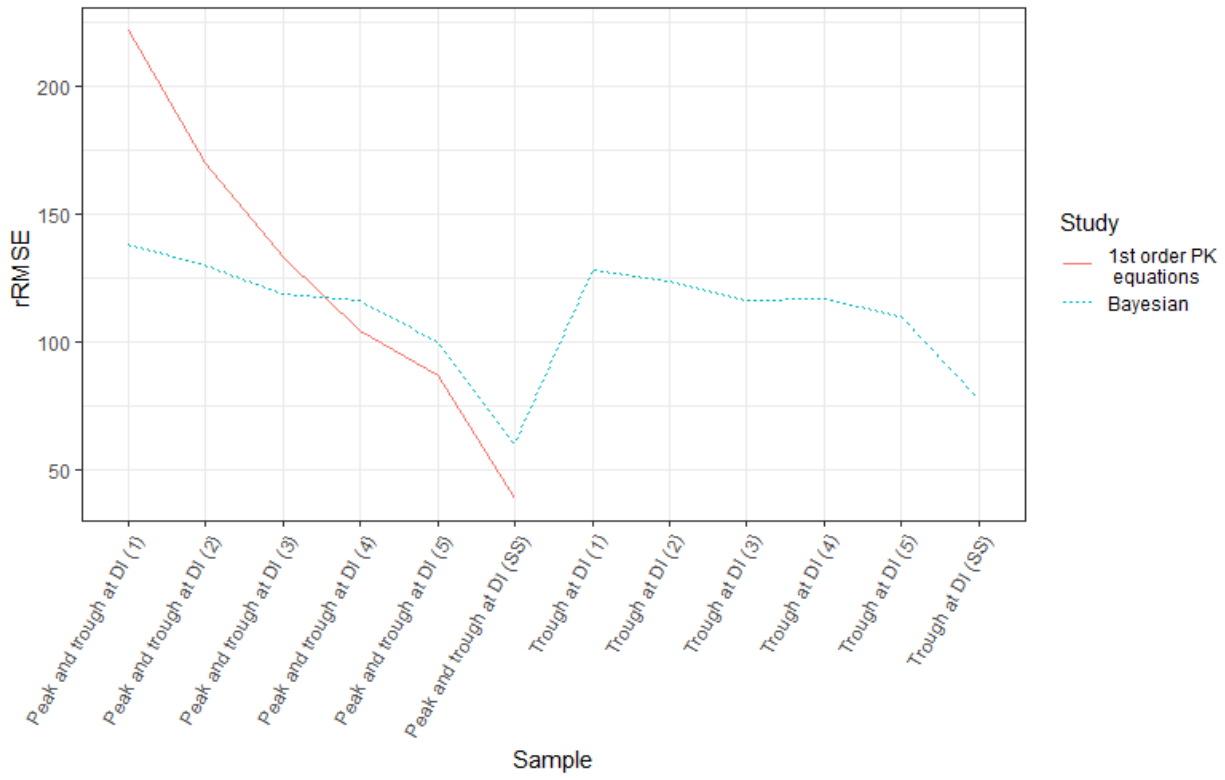

Figure S5.5. plot of rRMSE results at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS) with two samples (peak and trough) or one sample (trough). Two methods were used, first-order 1st order PK equations (red line) and Bayesian approach (blue dashed line). Note that first-order 1st order PK equations can only be used with at least two samples and using them pre-steady-state is improper.

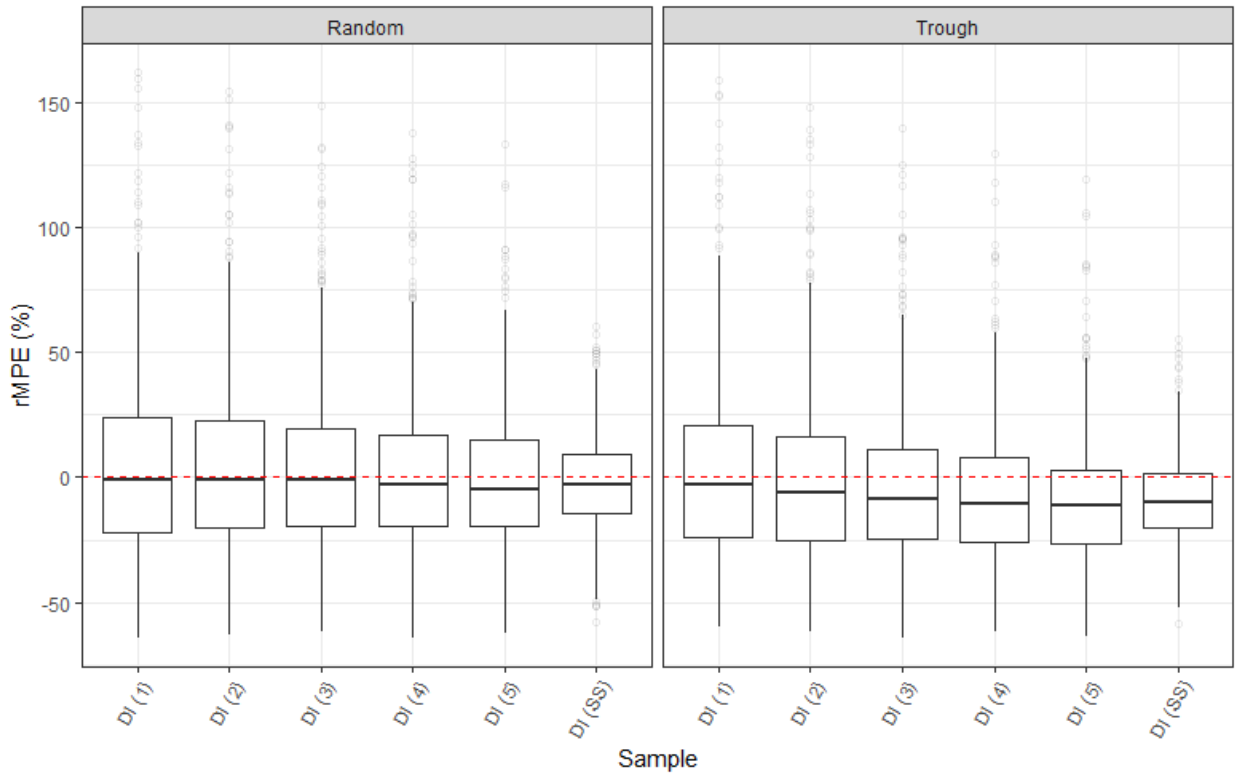

Figure S5.6. Box plot of rMPE at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS), using one random (R) or trough (T) level with Bayesian-based approach.

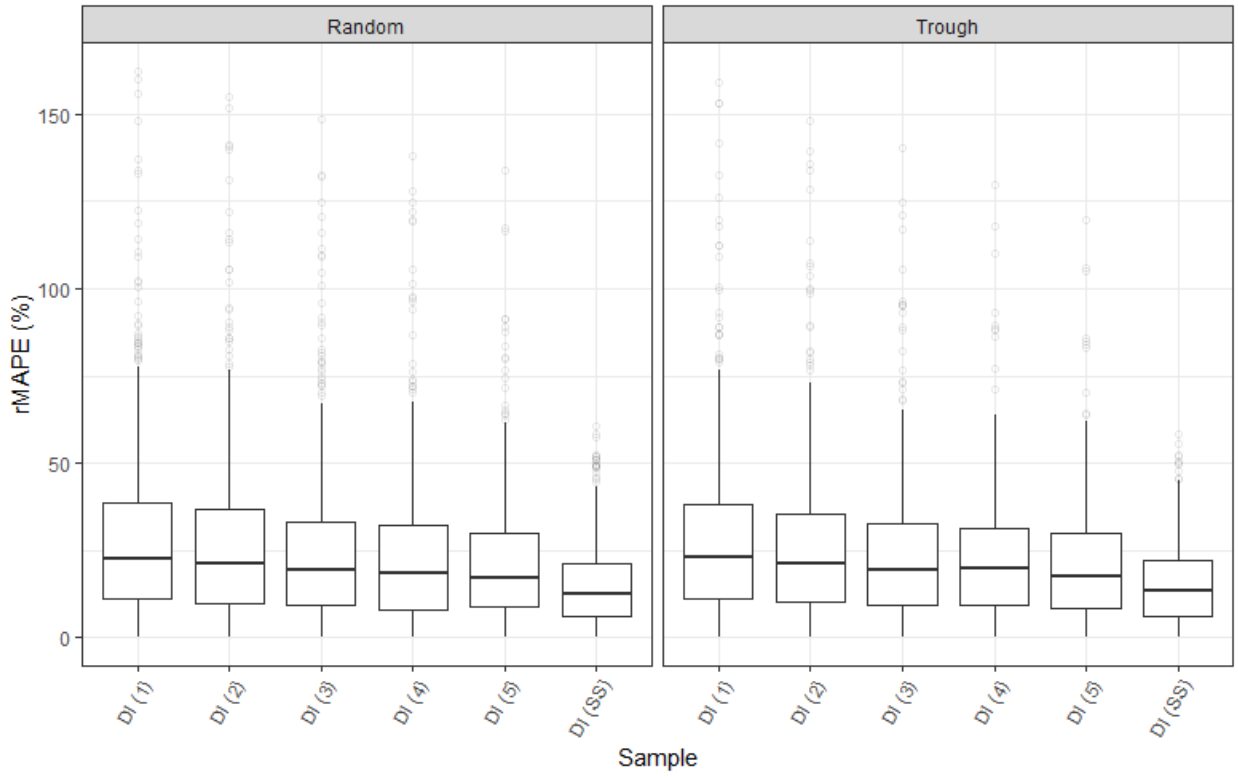

Figure S5.7. Box plot of rMAPE at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS), using one random (R) or trough (T) level with Bayesian-based approach.

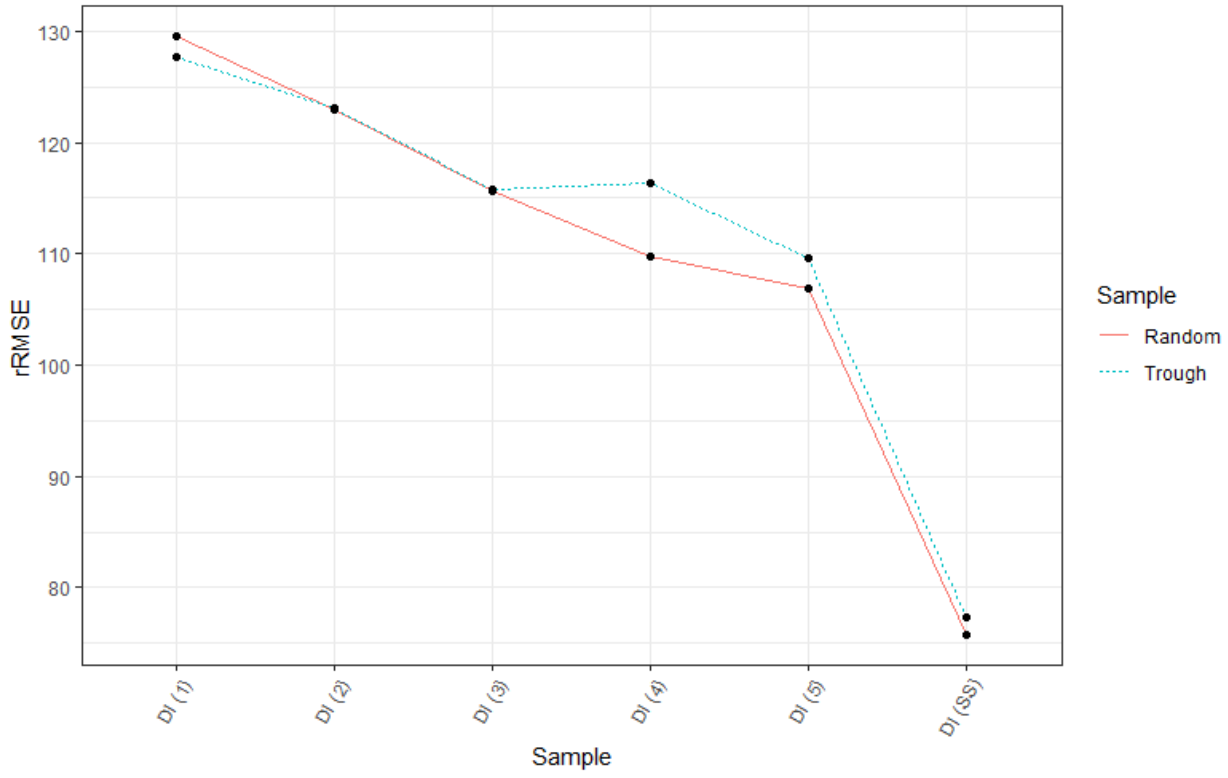

Figure S5.8. A plot of rRMSE at varying dosing intervals (DI) from the 1st to the 5th DI, as well as at steady state (SS), using one random (red) or trough (blue) level with a Bayesian-based approach.

Chapter 6.

6 Discussion and Conclusion

Vancomycin dose optimization is, still, a controversial topic despite six decades in use. The revisions to the original vancomycin therapeutic monitoring guidelines only 11 years following the release of the original guidelines, the controversy these guidelines generated (1-9), and the volume of publications between 2010 and 2020 approaching vancomycin PopPK (as reviewed in this dissertation), all indicate the volume of interest in vancomycin TDM. Factors that have contributed to such controversy include the large inter- and intra-subject variability, the lack of high-quality evidence or the evolving evidence regarding the therapeutic targets, the development of nephrotoxicity, and the emergence of resistance. It can be inferred, as well, that the population pharmacokinetic approach (nonlinear mixed-effects modeling) appeared to have spiked in its popularity being the crux of Bayesian-guided AUC monitoring and model-informed precision dosing. In fact, from 2010 to 2020, exclusive, the number of PopPK vancomycin analyses using the population approach was 63; a drastic increase during the period from inception to 2010 compared to the 25 publications before. This trend can be expected to continue growing, and older vancomycin dose optimization publications could be re-examined to reflect the shift in the therapeutic target.

This dissertation reviewed sixty-three (63) vancomycin population pharmacokinetic analyses on adult and pediatric populations. Most of the included studies aimed at the optimization of

vancomycin dosage regimens by developing PopPK models and identifying potential sources of variability that can alter the PK in adults and pediatric subpopulations. These models, and their parameters' estimates, were, mostly, then used to conduct Monte Carlo simulations to determine optimal dosage regimens. The impact of more than 60 and 56 predictors on vancomycin PK parameters for adults and pediatric patients, respectively, were evaluated for their influence on many special subpopulations such as patients with critical illness, obesity, neutropenia, trauma, cystic fibrosis, renal impairment, hematological malignancy, solid malignancy, hemodialysis, hemofiltration, renal replacement therapy, and extracorporeal membrane oxygenation, as well as preterm neonates and patients who underwent surgery, therapeutic hypothermia or normothermia. While we reported important observations and tried to relatively compare various patients' subpopulations to identify subpopulations at higher risks of potential PK alterations, such comparison might be limited by the variation in study settings, such as differences in the sample sizes (number of patients and sampling frequency), study design, covariate modeling approach, and different parametrization.

While parts of this dissertation were being prepared, a major shift in vancomycin therapeutic monitoring was introduced. The use of trough measurements as a surrogate of AUC is no longer recommended. Instead, AUC should be directly estimated using Bayesian or first-order PK approaches. This shift, initially, was instigated by the release of reports showing weak AUC-trough predictability as well as a better AUC prediction that can be achieved with a Bayesian software program, namely BestDose (10-12). It is worth mentioning that (11) showed no improvement in efficacy using Bayesian-guided AUC monitoring compared to trough-only monitoring. However, it showed a significant improvement in the nephrotoxicity profile when using BestDose compared to targeting a trough range of 10-20 mg/L. This might be the result of

an elevated trough range that overexpose patients to vancomycin, as evidenced by the fact that 31% and 68% of AUCs above ≥400 mg in this study (11) were associated with a trough of <10 and <15 mg/L, respectively (11). Considering such evidence, it might be reasonable to assume that improvements in the predictive performance would consequently yield improved outcomes, an assumption used throughout this work.

There seems to be momentum in the literature advocating for the implementation of MIPD at the bedside (13, 14). The usefulness of MIPD can be immense, especially for drugs having wide variability extending beyond the desired therapeutic window. Despite many attempts to develop user-friendly software to facilitate implementations of MIPD and aid decision-making, MIPD potentials are yet to be fully exploited and adopted in clinics (15-18). In practice, however, such implementation still lacks high-quality clinical evidence (19). Additionally, technical concerns come with the implementation of MIPD. Many PopPK models that are available for vancomycin in the literature that can be adopted as Bayesian priors were built using TDM data (sparse and without optimal sampling times). Although some models used external or internal validation methods, it is not clear how such suboptimality in PopPK model priors can influence the AUC prediction, especially when the gold standard AUC is unknown. Population modeling inherently can indeed overcome such limitations, and some of the Bayesian software programs provide systematic model evaluation and validation (20, 21). Yet, it might not be well established how predictive performance be ranked based on systematic model evaluation, many of which are graphical. Model validation, such as external model validation, assesses how well model predictions compare to the observations. Considering the case that both model and observations are likely from TDM settings, and the true target (gold standard AUC) is unknown, it is unclear

if such result is a clear indication of model inappropriateness rather than a carryover of the inherited bias. Therefore, MIPD can be a useful complementary TDM tool in the management of vancomycin therapy, only in tandem with evidence-based clinical judgment.

Model validation and evaluation require large data, high-quality priors, and expertise (21-23). In theory, multiple alternative approaches can be used. Using such data to construct a local PopPK model can be more efficient and less assumption-demanding in comparison to adopting and validating varying vancomycin PopPK models. Other potential approaches include meta-analysis combining all different models, automated model selection, or model averaging algorithms [4, 17]. Such an automation process could help find the best model or models for each patient. In our work, we did not attempt to use such approaches, i.e., meta-analysis or model averaging considering that we implemented Colin *et al.* [19] model who pooled data from 14 studies design.

Simulations conducted in this dissertation are valid within the simulation scenarios. Simulations can explore different scenarios and provide relevant insights into future research interests. Usually, simulations are performed in a large number of replicates. In our analyses, conducting such replicates for the size of our study is very computationally intensive, especially in the case of the MCMC algorithm. Our simulation-based analysis requires at least 100 MCMC runs of thousands of iterations on multiple independent Markov chains to predict individual parameters for a big dataset containing 1000 virtual subjects. This is not computationally feasible and probably does not provide a significant added value for the purpose of comparing a single point estimate (*maximum a posteriori*) between different methods. Despite this, the observations described in our simulation-based analysis appeared to be consistent regardless of methods, scenarios, or data sources.

The predictive performance of population PK modeling is correlated with levels of random effects (inter-individual variability and residual error). In the fourth and fifth chapters, the sparsity nature and the non-optimal sampling times can yield a relatively higher shrinkage (24), which explains the limited predictive performance of our model. While our decision to proceed with such TDM data did not result in the most desirable results, we believe that our approach is highly relevant as it is meant to resemble the status in literature and signify the paramount importance of the well-constructed study as well as the limitations that can arise from using TDM data. The guideline has specified the use of rich constructed PK models as priors. Such models are limited for most special populations in the literature (25, 26).

We seem to be at a critical juncture following the release of the revised guidelines. As Keith Rodvold said in his editorial commentary ” 60 plus Years Later and We Are Still Trying to Learn How to Dose Vancomycin” (27). This dissertation attempted to clarify and explore key vancomycin monitoring concerns aiding the transition to a more optimized vancomycin monitoring. Many practitioners trying to transit to the revised guidelines monitoring approaches are likely to benefit from this dissertation.

Future Perspectives

Although the recommendations of the revised vancomycin therapeutic monitoring guidelines were based on the best available evidence, no level I (defined as evidence from at least one properly randomized controlled trial) recommendations were made. The revised guidelines underscored the need for prospective, multicenter, large, randomized, and dose-optimized clinical trials to evaluate outcomes in all patients populations such as renal insufficiency. Likewise, our conclusion was based on the best available evidence generated with the data in hand, yet it might require further intensive-sampled data to confirm the potential impact of the

vancomycin monitoring approaches on outcomes, and whether AUC or trough can be reasonably approximated by each other.

The revised vancomycin monitoring recommendations demand intensive financial and personal resources, such as the use of proprietary Bayesian software programs, an additional serum sample, and expertise. This shifts the finite human and financial available resources on vancomycin monitoring approaches instead of dedicating resources to other, probably, valuable interventions and higher priority patient care. Thus, the adaptability of such recommendations, especially in developing countries, might warrant a careful cost-benefit analysis.

We here adopted a pharmacometrics and statistical approach tackling the problem of vancomycin TDM. This was mainly to question the appropriateness of the proposed therapeutic surrogates, such as AUC/MIC or trough values. However, once the utility of these surrogates is well established, other approaches can be envisioned. One of the most promising ones is to recourse to optimal control theory, a purely mathematical approach, to optimize vancomycin use. For this, a PopPK model, with its associated parameters, as well as the therapeutic target must be defined. In this perspective, the optimal control of colistin, another antibiotic drug of 60 years old, resulted in relatively more optimized loading and maintenance doses, and consequently faster and safer target attainment (28).

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