

REVIEW

Bayesian method application: Integrating mathematical modeling into clinical pharmacy through vancomycin therapeutic monitoring

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Abstract

The most recent consensus guidelines for dosing and monitoring vancomycin recommended the use of area-under-the-curve with Bayesian estimation for therapeutic monitoring. As this is a modern concept in the practice of clinical pharmacy, the main objective of this review is to introduce the fundamentals of Bayesian estimation and its mathematical application as it relates to vancomycin therapeutic drug monitoring. In addition, we aim to identify pharmacokinetic (PK) software programs that incorporate Bayesian estimation for vancomycin dosing and to describe the PK models utilized in those software programs for the adult population. Twelve software programs that utilize Bayesian estimation were identified, which included: Adult and Pediatric Kinetics, Best Dose, ClinCalc, DoseMeRx, ID-ODS, InsightRx, MwPharm++, NextDose, PrecisePK, TDMx, Tucuxi, and VancoCalc. The software programs varied in the population PK models used as the Bayesian a priori. With the presence of various vancomycin Bayesian software programs, it is important to choose those that utilize PK models reflective of the specific patient population.

KEYWORDS

Bayes theorem, pharmacokinetics, therapeutic drug monitoring, vancomycin

1 | INTRODUCTION

The concept of Bayesian estimation originated in 1763 when Thomas Bayes, an English statistician, and philosopher, published his idea of inverse probability. Originally, Bayes strived to determine the probability of a future event occurring based on how many times it had occurred in the past. A prominent French mathematician, Pierre-Simon Laplace, further developed the theory and published the formal equation.^{1,2}

Bayesian estimation has been used in many diverse fields. Historically, Bayes analysis was used in World War II by Alan Turing

to decipher the Enigma code.³ In healthcare, Bayes analysis has been studied in the diagnosis and prognosis of clinical conditions, drug development and discovery, as well as therapeutic drug monitoring (TDM) and pharmacokinetics (PK).⁴⁻⁷

In 2020, the American Society of Health-Systems Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists published the vancomycin consensus guidelines for dosing and monitoring vancomycin, which was an update to the 2009 vancomycin guidelines.⁸ The revised guidelines recommended the use of

Abbreviations: AUC, Area under the curve; MIC, Minimum inhibitory concentration; TDM, Therapeutic drug monitoring; PK, Pharmacokinetics.

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area-under-the-curve over 24h to minimum inhibitory concentration (AUC/MIC) and the Bayesian approach for vancomycin TDM.⁸ The AUC/MIC is considered the most appropriate pharmacokinetic/pharmacodynamic target for vancomycin.⁸ In addition, studies demonstrated less vancomycin-associated nephrotoxicity with the AUC-based dosing.⁹⁻¹³ However, in a survey of 364 critical care pharmacists, over 80% of the pharmacists reported using vancomycin trough concentrations rather than the AUC to assess exposure and to determine further dosing.¹⁴ Other studies reported similar findings demonstrating that the majority of institutions have not yet implemented the AUC-guided monitoring utilizing the Bayesian approach, as recommended by the guidelines.^{15,16} The most common barriers to implementation have mainly been the pharmacist and provider's unfamiliarity with AUC-based monitoring, training requirements, the unclear benefit of AUC-based monitoring, time allocation, and cost.^{15,16}

Since the Bayesian theory is a modern concept in the practice of clinical pharmacy, the main objective of this review is to introduce the fundamentals of Bayesian estimation and its mathematical application as it relates to vancomycin. Integration of Bayesian estimation with AUC therapeutic drug monitoring in clinical practice is available through various software tools. Therefore, we also aim to identify PK software programs that incorporate Bayesian estimation for vancomycin dosing and to describe the PK models utilized in those software programs for the adult population.

2 | FUNDAMENTALS OF BAYESIAN ANALYSIS

In the traditional probability (frequentist) approach, the parameter of interest is assumed to be unknown but fixed. For example, in flipping heads or tails, the probability of flipping onto one face is one-half. In contrast, the Bayesian method approaches the coin flip using all observed and unobserved parameters in a statistical model and gives each parameter a joint probability distribution, a probability that is dependent on several factors. The knowledge about the factors impacting the model is further updated with newly observed data.^{2,17}

Bayesian estimation involves three main elements: (1) prior distribution, (2) likelihood function, and (3) posterior inference.^{2,17} Each component is described below, along with its implication in PK calculations and TDM. For the purposes of this article, the following definitions are used: observed or measured concentrations are those obtained from the patient receiving vancomycin; the predicted or estimated concentrations are those determined by utilizing the Bayesian or non-Bayesian methods for calculating the concentrations; the prior PK model concentrations refer to those derived from the population PK models.

2.1 | Prior distribution

The prior (termed a priori) refers to the knowledge known before experimentation and reflects the expected observation(s) for a

specific population.^{2,17} For dose calculations, the Bayesian prior is the population-based probability distribution from available, and preferably published, population PK models. A prior distribution PK model that accurately represents the population through rich sampling is an important component of Bayesian dosing.

2.2 | Likelihood function

For drug dosing, the likelihood function is determined by observed evidence such as the patient's clearance, the volume of distribution, weight, and real-time measured levels. The function is used to determine how the observed data works in tandem with the prior distribution to predict individual parameter estimates.^{2,17}

2.3 | Posterior inference

The posterior estimates the patient's optimal PK values and AUC by combining the prior and likelihood probabilities. Through balancing prior knowledge with observed data, the distribution is updated to the final dosing estimation.^{2,17} Available Bayesian dosing software programs are continuously personalized with patient details by minimizing an objective function to reach the optimized posterior probability for individualized treatment.

3 | BAYESIAN MATHEMATICAL APPLICATION FOR VANCOMYCIN

To explain how vancomycin concentrations and doses are predicted using the Bayes theorem, we will review a simple one-compartment model. Using the following equation for first-order kinetics,¹⁸ the concentration can be extracted in an exponential function based on dose, volume of distribution (Vd), clearance (CL), and time (t):

$$\text{Predicted Concentration}(t) = \frac{\text{Dose}}{\text{Vd}} e^{-kt} = \frac{\text{Dose}}{\text{Vd}} e^{-\frac{\text{CL}}{\text{Vd}}(t)}$$

According to this equation, the concentration depends on two PK parameters, the Vd and CL, which vary greatly between individuals. The between-subject variability can be reduced by using population PK models which incorporate patient-specific clinical factors such as weight, height, and serum creatinine. However, there are other patient and non-patient parameters that may affect the individual PK values, which are not incorporated in the population PK models but may be addressed through Bayesian modeling.¹⁹ Such parameters may include patient-related characteristics and random variance in one's observed concentrations.

The goal of Bayesian modeling is to enhance the precision of "individual" patient-specific PK parameters, compared to what population PK models predict. In PK models, the relationship between the patient's creatinine clearance and the computed clearance shows significant variability, which can be addressed by Bayesian dosing.¹⁹

To achieve this, an error function, which is the sum of the squared difference between the observed PK concentrations and Bayesian predicted concentrations, is determined. To do so, Bayesian estimation aims to maintain PK parameters that reflect the actually observed concentrations of the patient, an element that is not considered if using population PK models alone for predictions.¹⁹ In addition, while minimizing the error function, Bayes theorem considers outliers and possible errors with patient observed concentrations, such as timing or lab errors. The Bayesian method also ensures that the fitted Bayesian predictions do not deviate greatly from what a population PK model would predict. These two factors are accounted for in the following equation²⁰:

$$\sum_{i=1}^n \frac{(\text{Predicted Levels}_i - \text{Observed Levels}_i)^2}{\text{Expected Errors in Measuring Observation}} + \sum_{j=1}^k \frac{(\text{Prior PK}_j - \text{Fitted PK}_j)^2}{\text{Standard Deviation of PK parameters}_j}$$

In patients with suspected or documented serious infections due to methicillin-resistant *Staphylococcus aureus*, the guidelines for vancomycin dosing and monitoring recommend the use of AUC/MIC for vancomycin therapeutic monitoring, with a target of 400–600, assuming a vancomycin MIC of 1 mg/L.⁸ In addition, the guidelines recommend estimating the AUC using first-order pharmacokinetic equations or Bayesian software programs, with the latter being the preferred approach. The main limitations of using the pharmacokinetic equations include: (1) It assumes steady-state after the 3 doses, which may not always be the case; (2) It assumes a linear elimination by estimating the slope of the line connecting the two concentrations over 24 h; (3) It requires two measured concentrations; (4) It does not account for concentration measurement errors related to the time of measurement or standard assay errors.^{2,17,19} In contrast, with Bayesian estimation these issues are addressed and, to a large degree, mitigated. Bayesian starts with a population PK assumption model and integrates a non-steady-state serum graph as a prior dataset. This eliminates the need for concentrations to be obtained at steady state and can rely on one concentration instead of two.^{2,17,19} However, an important aspect of the Bayesian-guided AUC monitoring is the quality of data that is used to build the prior, which, in the case of vancomycin, are the PK models. The vancomycin guidelines recommend the use of PK models that are based on richly sampled vancomycin data as the prior, but the availability of such models is limited.²¹ In such cases, two levels rather than one are recommended to estimate the AUC using the Bayesian approach.⁸

In a large study by Neely et al,²² when a model based on richly sampled vancomycin samples was used as the Bayesian prior, trough-only data produced accurate and reliable AUC estimates that deviated from the actual AUC by an average of about 3%. However, when the PK model was based on limited samples, it did not perform well in predicting AUC from a single level. However, when two concentrations were used, the predictive performance of the model improved.

Aljutayli et al²³ demonstrated similar findings in a study that aimed to compare the AUC derived from non-Bayesian first-order

PK equations versus AUC estimated using the Bayesian approach. The accuracy and precision of the Bayesian and non-Bayesian approaches were similar when using two levels near or at steady state. A major advantage of the Bayesian estimation was demonstrated when using a single trough level at pre-steady state, as early as after the first dose; the AUC estimates were comparable to those obtained with two levels at steady state. Such advantage with the Bayesian approach would allow clinicians to optimize the vancomycin therapeutic regimen of patients early on in treatment rather than wait until steady state. However, it should be noted that the findings of the study by Aljutayli et al²³ was in the absence of a loading dose. Therefore, in the case of administering a loading dose, at which the therapeutic concentrations can be achieved faster, it is unclear if the Bayesian approach would continue to be favorable to AUC-based monitoring.

4 | BAYESIAN PHARMACOKINETIC SOFTWARE PROGRAMS

In patients with suspected or documented serious infections due to methicillin-resistant *Staphylococcus aureus*, the guidelines for vancomycin dosing and monitoring recommend Bayesian-derived AUC monitoring.⁸ This recommendation is based on the advantages of the Bayesian-based approach, compared to the non-Bayesian, that were discussed earlier in the paper. Given that estimating the AUC using the Bayesian approach is difficult to perform manually, the guidelines recommend the use of Bayesian pharmacokinetic software programs for Bayesian-based dosing and monitoring of vancomycin.⁸

Several pharmacokinetic software programs are available to calculate AUC calculations with Bayesian prediction and to compute individually personalized AUC. To identify the available software programs, we conducted a literature search using PubMed as well as a web search with the following search terms: Vancomycin, Bayesian, software programs, therapeutic drug monitoring, and precision dosing. In addition, we searched the references of relevant citations. The population PK models included in those software programs were reviewed. The search and assessment were primarily focused on the adult population as an earlier publication by Han et al²⁴ had already evaluated the software programs and PK models available for neonatal and pediatric patients.

Based on the search, we identified 12 software programs that utilize Bayesian estimation for vancomycin therapeutic monitoring in adult patients, which included: Adult and Pediatric Kinetics, Best Dose, ClinCalc, DoseMeRx, ID-ODS, InsightRx, MwPharm++, NextDose, PrecisePK, TDMx, Tucuxi, and VancoCalc. We also identified Autokinetics, and TDM for R as Bayesian software programs for vancomycin but they were not included in this paper since we were unable to retrieve sufficient information about the programs. Both ClinCalc and VancoCalc are free online dosing software while all others require subscription fees.

The performance of the vancomycin Bayesian software programs depends largely on the PK models that are used as the prior in accurately

TABLE 1 Summary of population pharmacokinetic models of vancomycin used in PK software for adult patients

Adult model	Population (n)	PK samples (n)	Type of population	Age (years) (median/range)	Weight (kg) (median/range)	Creatinine clearance (median/range)	Adopted software
Adane 2015 ²⁵	31	93	Extremely obese BMI > 40 mg/m ²	43 (38.5–53)	147.9 (142.8–178.3)	124.8 ml/min/1.73 m ² (106.0–133.9)	PrecisePK ClinCalc TDMx VancoCalc ³²
Buelga 2005 ²⁶	Training set 215 Validation set 59	1004 124	Hematological malignancies Hematological malignancies	Mean ± SD 51.5 ± 15.9 Mean ± SD 51.4 ± 16.9	Mean ± SD 64.7 ± 11.3 Mean ± SD 67.1 ± 12.1	Mean ± SD 89.4 ± 39.2 ml/min Mean ± SD 89.6 ± 42.5 ml/min	ClinCalc DoseMeRx InsightRX VancoCalc
Carreno 2017 ²⁷	12	60	Obese	61 (39–71)	BMI 45 (40–52)	86 ml/min (75–120)	InsightRX
Claisse 2019 ²⁸	NR	NR	Critically ill receiving RRT	NR	NR	NR	PrecisePK
Colin 2019 ²⁹	2554	8300	Adults Newborns Elderly Obese adults Very elderly Underweight adults Children/adolescents	Varying	Range of averages 120–148	Varying	InsightRX Tucuxi
Crass 2018 ³⁰	346	NR	Obese	Mean ± SD 57 ± 14	Mean ± SD 132.5 ± 32.6	Mean ± SD 119 ± 29 ml/min	PrecisePK
Dolton 2009 ³¹	Burn 37	Median/Range 4 (1–32)	Burn	34 (15–88)	69 (42.5–116)	Mean ± SD 124.0 ± 55.5 ml/min	InsightRX
Goti 2018 ³²	Control 33 1812	2 (1–20) 2765	Control ICU 33% Ward 67% Hemodialysis 18.5%	72 (38–95) 57 (17–101)	67 (48.9–111) 79 (33–255)	75.0 ± 47.8 ml/min 62 ml/min (4–150)	DoseMeRx InsightRX TDMx Tucuxi
Liu 2019 ³³	74	216	Adult Hospitalized	Mean ± SD 51.84 ± 14.53	Mean ± SD 59.59 ± 9.63	Mean ± SD 98.88 ± 33.36 ml/min	Tucuxi
Llopis-Salvia 2006 ³⁴	20	40	Critically ill	Mean ± SD 60 ± 14	Mean ± SD 71.15 ± 12.27	Mean ± SD 72.80 ± 34.16	Tucuxi
Mangin 2014 ³⁵	30	359	Survived Post-sternotomy Mediastinitis	63 (35–81)	82 (62–104)	NR	TDMx
Masich 2020 ³⁶	16	64	Obese with sepsis or septic shock	62 (30–78)	112.7 (72.6–129.1)	46 ml/min (14–123)	ClinCalc VancoCalc
Matzke 1984 ^{37,38}	56	616	Group I, ClCr >60; Group II, ClCr 10–60; Group III ClCr <10 ml/min	Mean ± SD Group I: 46.5 ± 16.6 Group II: 66.8 ± 17.0 Group III: 62.6 ± 11.8	Mean ± SD Group I: 67.8 ± 5.2 Group II: 69.7 ± 8.9 Group III: 59.6 ± 12.2	Mean ± SD Group I: 87.6 ± 22.3 Group II: 37.4 ± 17.1 Group III: <10 ml/min	APK

TABLE 1 (Continued)

Adult model	Population (n)	PK samples (n)	Type of population	Age (years) (median/range)	Weight (kg) (median/range)	Creatinine clearance (median/range)	Adopted software
Medellin-Garibay 2016 ³⁹	40	511	Trauma	Mean ± SD 73.4 ± 15.0	Mean ± SD 70.9 ± 13.0	Mean ± SD 76.5 ± 43.3 ml/min	TDMx
Neely 2014 ¹³	47	569	Group I, Prosthetic cardiac valves (outpatient) and Cardiac ICU Group II, various levels of renal function; Group III, healthy volunteers	NR	NR	Group I: 78.0 (6.4–112.8) Group II: 56.8 (29.8–174.7) Group III: NR ml/min	InsightRX
Revilla 2010 ⁴⁰	46	73	ICU	Mean ± SD 61.1 ± 16.3	Mean ± SD 73.0 ± 13.3	Mean ± SD 74.7 ± 58.0 ml/min	TDMx
Roberts 2011 ⁴¹	206	579	Critically ill with sepsis	Mean ± SD 58.1 ± 14.8	Mean ± SD 74.8 ± 15.8	Mean ± SD 90.7 ± 60.4 ml/min/1.73 m ²	ClinCalc MwPharm++ TDMx VancoCalc
Rodvold 1988 ⁴²	37	NR	Group I, >70 Group II, 40–70 Group III, 10–39 ml/min/1.73 m ²	Mean ± SD Group I: 46.3 ± 11.6 Group II: 49.5 ± 14.3 Group III: 61.6 ± 18.4	Mean ± SD Group I: 86.4 ± 19.7 Group II: 73.7 ± 24.2 Group III: 68.8 ± 15.5	Mean ± SD Group I: 93.4 ± 28.3 Group II: 51.0 ± 8.3 Group III: 23.9 ± 8.2 ml/min/1.73 m ²	PrecisePK
Sabourenkov 2019 ⁴³	1717	NR	Group I, Class 1 obesity Group II, Class 2 obesity Group III, Class 3 obesity	Mean ± SD Group I: 62.2 ± 15.0 Group II: 59.6 ± 14.5 Group III: 58.3 ± 13.7	Mean ± SD Group I: 95.1 ± 13.1 Group II: 109.5 ± 14.6 Group III: 135.0 ± 25.1	NR	DoseMeRx
	1276	NR	Group I, Class 1 obesity Group II, Class 2 obesity Group III, Class 3 obesity	Mean ± SD Group I: 62.7 ± 15.5 Group II: 60.6 ± 15.5 Group III: 57.8 ± 13.9	Mean ± SD Group I: 94.8 ± 13.5 Group II: 108.6 ± 15.0 Group III: 140.3 ± 30.3	NR	
Thomson 2009 ⁴⁴	Model building 398 Model evaluation 100	1557 171	Adult hospitalized Adult hospitalized	66 (16–97) 71 (22–91)	72 (40–159) 65 (35–130)	64 ml/min (12–216) 50 ml/min (12–148)	InsightRX TDMx Tucuxi

(Continues)

TABLE 1 (Continued)

Adult model	Population (n)	PK samples (n)	Type of population	Age (years) (median/ range)	Weight (kg) (median/ range)	Creatinine clearance (median/ range)	Adopted software
Tong 2021 ^{45a}	2853	6251	Elderly	75 (65–104)	79.4 (26.3–225.2)	NR	InsightRX
Westra 2019 ⁴⁶	Model development 17	159	Hemodiafiltration	63 (46–85)	72.9 (53–95.7)	2.9 ml/min (0.4–16.5)	PrecisePK
Yamamoto 2009 ⁴⁷	Validation 21 100	132 311	Low-flux hemodialysis Adult hospitalized	66 (39–78) Mean ± SD 61.4 ± 15.1	70 (38–133) Mean ± SD 52.6 ± 12.7	3.3 ml/min (0.07–9.6) NR	Tucuxi

Note: A model by Winter et al is a model in APK but was not included here due to lack of access.

Abbreviations: BMI, body mass index; NR, not reported; SD, standard deviation; RRT, Renal replacement therapy.

^aOriginal model based on Goti (2018).³²

representing the population as well as the patient-related co-variables that are incorporated in the analysis, such as age, body weight, and kidney function. The software programs utilize various PK vancomycin models, some of which are published PK models while others may be internally developed by the software company. Table 1 provides a summary of the published PK models included in the software programs that we identified for vancomycin therapeutic monitoring.^{13,25–47}

Though the vancomycin guidelines recommend Bayesian software programs that utilize PK models based on richly sampled vancomycin data as the prior, the availability of richly sampled models in the literature is limited. Most of the available models included a limited number of vancomycin samples that were routinely taken as part of therapeutic drug monitoring (e.g., peak, trough, random levels) and included relatively small number of patients, which raises the concern about the accuracy, precision and generalizability of the models.²¹ In addition, PK models may not be available for all patient populations encountered. To address this issue, most of the software programs allow institutions to incorporate local PK models or PK parameters that reflect their patient population and some may use the local data that is entered in the software program to further enhance the performance of its Bayesian estimations. Such features may not be clearly stated on the website of the software company but it would be important to address when deciding on which software program to purchase and/or use.

Most Bayesian software programs include more than one PK model, offering flexibility for clinical pharmacists to select the optimal model for their patients, based on the setting and patient characteristics, as outlined in Table 1. Though most of the PK models have had some kind of validation, the most appropriate model remains difficult to determine due to the limitations of the available PK models and the limited studies that have compared the performance of the various PK models. Broeker et al⁴⁸ evaluated the predictive performance of 31 published population PK models when used in Bayesian-based estimation of AUC. Data from 292 patients from two hospitals were used to evaluate the predictive performance of the models to estimate vancomycin concentrations and AUC by solely relying on patient characteristics (e.g., weight, renal function), as well when including vancomycin concentrations from the previous dosing using Bayesian-based approach. The model published by Goti et al³² had the highest predictive performance when used for vancomycin dosing and therapeutic drug monitoring before and after vancomycin concentrations are available and was therefore recommended for use in hospitalized patients. The Goti model is listed as one of the models that can be used in DoseMeRx, InsightRx, TDMx, and Tucuxi.

Due to the limitations, we discussed earlier for the available vancomycin PK models, the choice of the most appropriate PK model may not be a straightforward step. For example, one may consider the Gotti model³² as appropriate for critically ill patients since it included patients in intensive care units or may consider the Thomson model⁴⁴ based on a study that showed this model to be the most suitable for critically ill patients.⁴⁹ However, when these two models were more closely evaluated, they were found to have low precision in the critically ill.⁵⁰

Another important element in Bayesian dosing is the co-variables that are included in the models and the software programs. While

age, weight, and renal function are commonly included co-variables in most PK models, additional co-variables are also seen, such as race, diabetes, critical illness, and furosemide administration. Furthermore, some software programs have included co-variables other than those that are included in the selected PK model to further enhance the Bayesian estimation.

5 | CONCLUSIONS

Bayesian estimation has wide use in biological and medicinal sciences. From the PK side, the Bayesian method aims to enhance the precision of vancomycin dosing and monitoring to support decision making in clinical pharmacy practice. Several Bayesian PK software programs are available and vary in their features and the PK models they utilize. It is important to choose those that utilize PK models reflective of the specific patient population. However, further research is necessary to determine the most appropriate PK models and software programs based on the patient population and setting.

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AUTHOR CONTRIBUTION

AC and LN: devised the main conceptual ideas. AC and DO did the literature and database search as well as the data extraction; AC, AG, and LN wrote various parts of the article; LN reviewed the manuscript and edited it critically for important intellectual content. All authors read and approved the final manuscript.

ETHICS STATEMENT

No ethical review needed, given that this is a review article.

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All other authors have no financial relationships or conflicts of interest relevant to this article.

DISCLOSURE

Dr. Gupta is the Chief Executive Officer at PreciseRx Inc, which has one of the vancomycin Bayesian software programs discussed in this paper. To mitigate any bias, the process of obtaining and synthesizing information regarding the available software for the Bayesian analysis of vancomycin therapeutic monitoring was performed consistently by the first and corresponding authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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