Discrepancies Between Bayesian Vancomycin Models Can Affect Clinical Decisions in the Critically Ill

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1.Introduction

International clinical practice guidelines and position statements suggest that the therapeutic drug monitoring of vancomycin should be guided by area under the curve (AUC) values [1–3]. This is because AUC-guided dosing is associated with less treatment failure and improved safety compared to trough-guided monitoring in patients with methicillin-resistant Staphylococcus aureus infection [4]. The ratio of the 24-hour AUC to the minimum inhibitory concentration (AUC_{24}/MIC) is the pharmacokinetic (PK) parameter used to guide dosing decisions [1]. An AUC_{24}/MIC target of 400–600 mg·h/L is considered to be optimal when MIC is determined by broth microdilution [1, 5]. In clinical practice actual MIC is often not available, and an MIC of 1 mg/L is assumed. Thus, an AUC_{24} <400 mg·h/L would prompt a dose increase to avoid treatment failure, and an AUC_{24} >600 mg·h/L would suggest a dose decrease is required to avoid acute kidney injury or other toxicity.
AUC$_{24}$ can be estimated by first-order linear PK equations using two concentrations within a dose interval. This can be calculated manually or via readily available online calculators [6]. Alternatively, AUC$_{24}$ can be estimated via population PK models using Bayesian software platforms [7]. The logistical advantage of the latter approach is that the AUC$_{24}$ value estimate can be obtained using only one vancomycin concentration [6]. However, previous studies have shown a low precision of an AUC$_{24}$ estimation using Bayesian software and a single concentration [8, 9]. In a cohort study of hospitalized patients ($n = 978$), clinical agreement was 76.8% between AUC$_{24}$ values predicted by linear and Bayesian one-concentration [9]. The study was not specifically conducted among the critically ill. However, the investigators evaluated one Bayesian model [10] in the critically ill subset of the cohort.

Some of the Bayesian software platforms available offer multiple population PK models for the same medication, and end-users are required to select the most appropriate model. Thus, studies are needed to compare the clinical agreement between population PK models in the critically ill to inform this decision. It is possible that depending on the population PK model selected, it could lead to different dosing decisions. The objective of this study was to assess the agreement in AUC$_{24}$ value estimates between commonly used vancomycin population PK models in the critically ill.

2. Methods

2.1. Ethics/Institutional Review Board. The study was approved by the Human Research Ethics committee of the Sydney Local Health District-Royal Prince Alfred Hospital zone (Approval number: 2019/ETH12033).

2.2. Study Design and Setting. This was a retrospective cohort study using data obtained from the intensive care unit (ICU) of a quaternary care hospital in Sydney, Australia. This is a substudy of a previously reported investigation evaluating the predictive performance of three vancomycin population PK models [8]. The hospital uses trough-based vancomycin monitoring to guide dosing decisions. Usually only one vancomycin concentration is obtained per dosing interval. Bayesian software is not used for clinical care, and AUC$_{24}$ based monitoring has not been implemented. The ICU has a fully electronic medical record that includes all medications and pathology values used for the study (Philips IntelliSpace Critical Care and Anesthesia). Vancomycin concentrations are determined using an immunoassay, as has been previously described [8].

2.3. Participants and Data Acquisition. The study included adults (>18 years old) who were admitted to the ICU between 1 January 2019 and 31 May 2020, had received intravenous vancomycin via intermittent infusion, and had at least one vancomycin serum concentration available. Patients were excluded if they received continuous renal replacement therapy (CRRT) or a continuous infusion of vancomycin. Patients were also excluded if they were administered vancomycin doses on a non-ICU ward and subsequently transferred to the ICU, as dosing data were not available. All data were obtained from the electronic medical record. Vancomycin concentrations were categorized independently by two investigators as true trough concentrations or true troughs at steady state. A true trough concentration was defined as a concentration taken within 60 minutes before administration of an anticipated dose. A true trough at steady state was defined as a concentration taken within 60 minutes of the anticipated 4$^{th}$ dose in treatment courses with <60-minute deviations from scheduled times for all prior doses.

2.4. Estimation of Vancomycin AUC$_{24}$ Values. An AUC$_{24}$ value was estimated for each dosing interval for which a vancomycin concentration was available using Tucuxi via a command line interface (revision cd7bd7a8 joint development by HEIG-VD, Yverdon-les-Bains, Switzerland and CHUV, Lausanne, Switzerland). All AUC$_{24}$ value estimates were determined using a single vancomycin concentration. AUC$_{24}$ values were estimated using three previously published vancomycin population PK models: (1) Goti [10], (2) Colin [11], and (3) Thomson [12]. Thus, each vancomycin concentration had three corresponding AUC$_{24}$ value estimates.

2.5. Data Analysis. AUC$_{24}$ values were categorized as subtherapeutic (<400 mg·h/L), therapeutic (400–600 mg·h/L), or toxic (>600 mg·h/L) for each model, assuming a minimum inhibitory concentration of 1 mg/L. These categorizations were defined and based on cut-off values from international guidelines [1, 3]. AUC$_{24}$ value categorization was compared across the three models and reported descriptively as percent agreement. In other words, if an AUC$_{24}$ value with one model was nontherapeutic and another model was therapeutic, then the two models would be discrepant and could result in different vancomycin dosing decisions. The concordance between AUC$_{24}$ values from models was reported as scatter plots with the concordance correlation coefficient ($r_c$) [13]. Other parameters calculated were Pearson’s $r$, the average difference, the standard deviation of the difference, and Bland and Altman’s 95% limits of agreement [14].

Two sensitivity analyses were conducted. First, the discrepancy between models was evaluated in the subset of concentrations that were considered as true troughs. Second, the discrepancy between models was evaluated in the subset of concentrations that were considered as true troughs at steady state. This was done as trough levels are commonly used in clinical practice, and it is possible that predictive performance is different in this subset [15]. All analyses were conducted in STATA 15 (College Station, Texas), and scatter plots were created using the R software (version 4.0.3, Vienna, Austria).
The two sensitivity analyses using the subset of concentrations that were true troughs or true troughs at steady state showed similar or lower agreement than the overall sample (Supplementary Appendix (available here)). Overall, agreement for true trough subset was 48% between all models ($n = 121/250$), and true trough at steady state subset was 42% between all models ($n = 47/113$). Parameters for concordance between models and scatterplots for the sensitivity analysis subsets are in the Supplementary Appendix (available here). There were 37 concentrations that were therapeutic (15–20 mg/L) and considered true troughs at steady state. Of these, 28 (75%) in the Goti model, 8 (22%) in the Colin model, and 20 (54%) in the Thomson model had estimates of a therapeutic AUC$_{24}$ value.

4. Discussion

The key finding of this investigation was that agreement between vancomycin PK models occurred approximately two-thirds of the time. In other words, clinicians may come to different dosing decisions based on standard cut-off values for AUC$_{24}$ in 1 of 3 ICU patients, depending on the PK model used. The Goti model had lower AUC$_{24}$ estimates than Colin and Thomson. Thus, using Goti-based AUC$_{24}$ estimates, clinicians would be prompted to use higher doses than the other two models.

The question regarding the most appropriate PK model for the critically ill has not been settled. Some commonly used Bayesian software platforms have recommended the Goti model for ICU patients [9]. Although the three models used in our investigation were not derived using critically ill patients exclusively, they have been subsequently evaluated in ICU cohorts [8,16,17]. In a retrospective study, data from 82 ICU patients was used to evaluate 12 vancomycin PK models [16]. The investigators considered a model to be clinically acceptable if the relative bias was ±20% and the 95% CI included zero. The Goti model was the only one considered to be clinically acceptable based on both $a$ priori and $a$ posteriori approaches. However, the definition for acceptability did not include parameters for precision. In a larger study ($n = 188$ patients) of the same cohort as our current investigation [8], it appeared that the Goti model may be slightly more suitable based on precision, but the extent of the differences between PK models were too small to be clinically meaningful. Another smaller investigation with data from 50 patients and using simulation techniques considered the model by Thomson to have the best predictive performance [17]. However, precision appeared to be low based on the relative root mean squared error reported by the authors. In addition, the model by Goti was not evaluated in the aforementioned study. Vancomycin PK models need to be improved for suitable precision of AUC$_{24}$ estimated from one concentration. It is possible that sparse sampling has been a contributor to models with poor precision.

The AUC$_{24}$ can also be estimated by taking two concentrations within a dose interval (e.g., peak and trough levels). The estimation is based on first-order PK equations. A detailed approach to these calculations has been described.
Although this can be done manually, readily available software programs can be used to conduct these calculations with relatively little training [6]. AUC24 estimation via first order PK calculations using two levels is the reference standard to which Bayesian estimates have been compared [9]. Such a comparison has been described in a retrospective cohort study [9] (n = 978 patients) where clinical agreement was assessed between first-order PK equation-calculated AUC24 vs Bayesian two- (i.e., peak and trough) and one-concentration AUC24 (i.e., trough only). Clinical agreement was defined similarly to the cut-off values in our study. The PK model used for Bayesian estimation depended on the patient (noncritically ill, critically ill, and obese). The Goti model was used in the critically ill subset and 69% of the patients were critically ill. Clinical agreement was higher with two-concentration estimates (87.4%) than one-concentration (76.8%) estimates. In clinical practice, the advantage of the Bayesian AUC24 is that it can be estimated using just one concentration. Thus, the results pertaining to the one-concentration estimate are more relevant. If two concentrations are taken, then clinicians could use the reference standard first-order PK equations, and Bayesian estimates are not needed. The clinical agreement using one-concentration Bayesian AUC24 was still higher than the agreement we found between PK models in our study. This may be because there was less variability in the noncritically ill patients in the aforementioned study that made up approximately one-third of the patient subset.

| Demographics | Full sample | True trough | True trough at steady state |
|---------------|-------------|-------------|-----------------------------|
|               | np = 188   | np = 136    | np = 71                     |
|               | nC = 466   | nC = 250    | nC = 113                    |
| Age (years), mean (SD) | 58 (17) | 59 (17) | 59 (17) |
| Sex (male), n (%) | 119 (63) | 89 (65) | 48 (68) |
| APACHE III score, mean (SD) | 62 (22) | 62 (21) | 64 (22) |
| Mechanical ventilation, n (%) | 74 (39) | 60 (44) | 34 (45) |
| Vasopressors, n (%) | 66 (35) | 48 (35) | 33 (46) |

np = number of patients; nC = number of concentrations; SD = standard deviation; APACHE = acute physiology and chronic health evaluation.

**Table 1: Patient demographics.**

| AUC<sub>24</sub> mg·h/L | <400 n (%) | 400–600 n (%) | >600 n (%) | Total |
|-------------------------|------------|---------------|------------|-------|
| Goti                    |            |               |            |       |
| <400                    | 75 (16)    | 5 (1)         | 0 (0)      | 80    |
| 400–600                 | 63 (14)    | 122 (26)      | 10 (2)     | 195   |
| >600                    | 2 (<1)     | 113 (24)      | 76 (16)    | 191   |
| Total                   | 140        | 240           | 86         | 466   |

**Table 2: Agreement between models at decision cut-offs.**

| Agreement | 59% (273/466) | 68% (318/466) | 67% (314/466) |
|-----------|---------------|---------------|---------------|
| Goti-Colin|               |               |               |
| Thomson   |               |               |               |
| Colin     |               |               |               |
| Thomson   |               |               |               |
| Colin     |               |               |               |
| Thomson   |               |               |               |
|<400       | 67 (14)       | 34 (7)        | 2 (<1)       | 103   |
| 400–600   | 13 (3)        | 133 (29)      | 75 (16)      | 221   |
| >600      | 0 (0)         | 28 (6)        | 114 (24)     | 191   |
| Total     | 80            | 195           | 191          | 466   |

**Table 3: Concordance between models.**

|          | Goti-Colin | Goti-Thomson | Colin-Thomson |
|----------|------------|--------------|---------------|
| ρ<sub>c</sub> | 0.75       | 0.77         | 0.81          |
| Pearson’s r | 0.88       | 0.81         | 0.84          |
| Difference |            |              |               |
| Average (mg·h/L) | −93       | −48          | 45            |
| Standard deviation (mg·h/L) | 82       | 98           | 97            |
| 95% LOA (mg·h/L) | −253–68  | −239–144     | −145–235      |

ρ<sub>c</sub> = concordance correlation coefficient; LOA = Bland and Altman’s limits of agreement.
Sensitivity analyses were conducted to evaluate subsets of patients with true troughs and true troughs at steady state. We considered that some PK models are developed using routine clinical data rather than richly sampled data with multiple concentrations taken during a dosing interval. This is true for the Goti model, where most patients had only one sample taken [10]. These are usually trough concentrations (or similar). Thus, prediction using such a PK model may be different for troughs. In addition, trough concentrations are more likely to reflect what is done in clinical practice. However, we did not show that agreement between PK models changed in the subsets with true troughs.

Given the uncertainty of the evidence, the availability of different PK models within Bayesian software platforms, and the possible lack of agreement between PK models, we suggest that if clinicians use a one-concentration Bayesian estimation using currently available PK models, it may be useful to verify the estimation using two different PK models available within the software program (e.g., Goti and Thomson). This can be done relatively quickly and does not require the re-entry of patient data into the software platforms we are aware of. A mid-interval concentration may also improve estimates [15]. The discrepancies in the estimate and direction of the discrepancy could help guide dosing decisions, which must be made in the context of the clinical situation. For example, a subtherapeutic AUC$_{24}$ with the Goti model but a therapeutic AUC$_{24}$ with the Thomson model would still support a dose increase if an infection was severe or the patient was deteriorating. Based on the uncertainty and lack of precision, our institution has not implemented the use of Bayesian software platforms. Instead, there are ongoing efforts to transition to AUC$_{24}$ estimation using two concentrations calculated from first-order PK equations in the ICU.

Figure 2: Scatter plot of AUC$_{24}$ comparisons between models. Blue dots = agreement; black dots = no agreement; (a) Goti vs Colin models; (b) Goti vs Thomson models; and (c) Thomson vs Colin models.
Our study has some limitations. First, we have only compared AUC_{24} estimates between PK models. From the data available we were unable to determine the “true” AUC value as a reference. As such, we are unable to comment on the accuracy of AUC value estimates derived from each of the population PK models. Second, we did not assess the implication of drug exposure on clinical outcomes. However, that was not the intent of this study. An evaluation of clinical outcomes would require a comprehensive clinical dataset to adjust for any potential confounders as well as an appropriate assessment of the drug concentration and pathogen susceptibility [19]. Third, ICU patients are a heterogenous population and it is possible that clinical agreement would be improved in some subsets or phenotypes of patients. However, we do not have the data to meaningfully delineate this.

5. Conclusion

In critically ill patients, vancomycin AUC_{24} values estimated from different PK models are often discordant, potentially contributing to differences in dosing decisions. This highlights the importance of selecting the optimal model. Given the lack of agreement between PK models currently used in Bayesian software, it may be useful to use more than one model to guide decisions that are supported by clinical context, especially when estimates are close to decision cutoff values for AUC_{24}.

Data Availability

Data are available upon reasonable request to the corresponding author.

Additional Points

What is already known about this subject: Monitoring of vancomycin should be guided by 24-hour area under the curve (AUC_{24}). AUC_{24} can be estimated via population pharmacokinetic (PK) models using Bayesian software platforms. Different vancomycin population PK models are available for AUC_{24} estimation. What this study adds: Vancomycin AUC_{24} values obtained from different PK models were often discordant at decision thresholds. Clinical dosing decisions of vancomycin may be dependent on the PK model used.

Ethical Approval

The study was approved by the Human Research Ethics committee of the Sydney Local Health District-Royal Prince Alfred Hospital zone (Approval number: 2019/ETH12033).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Supplementary Materials

Table S1: Cross-tabulation of agreement between models at decision cut-offs in the subset with true troughs. Table S2: Cross-tabulation of agreement between models at decision cut-offs in the subset with true troughs at steady state. Table S3: Concordance parameters between models in the sensitivity analysis subsets. Figure S1: Scatterplot of AUC24 between models in subset of concentrations that were true troughs. Figure S2: Scatterplot of AUC24 between models in subset of concentrations that were true troughs at steady state. (Supplementary Materials)

References

[1] K. Matsumoto, K. Oda, K. Shoji et al., “Clinical practice guidelines for therapeutic drug monitoring of vancomycin in the framework of model-informed precision dosing: a consensus review by the Japanese society of chemotherapy and the Japanese society of therapeutic drug monitoring,” *Pharmaceutics*, vol. 14, no. 3, p. 489, 2022.
[2] S. E. Reuter, S. L. Stocker, J. W. C. Alfenaar et al., “Optimal practice for vancomycin therapeutic drug monitoring: position statement from the anti-infectives committee of the international association of therapeutic drug monitoring and clinical toxicology,” *Therapeutic Drug Monitoring*, vol. 44, no. 1, pp. 121–132, 2022.
[3] M. J. Rybak, J. Le, T. P. Lodise et al., “Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American society of health-system pharmacists, the infectious diseases society of America, the pediatric infectious diseases society, and the society of infectious diseases pharmacists,” *American Journal of Health-System Pharmacy*, vol. 77, no. 11, pp. 835–864, 2020.
[4] M. Tsutsuura, H. Moriyama, N. Kojima et al., “The monitoring of vancomycin: a systematic review and meta-analyses of area under the concentration-time curve-guided dosing and trough-guided dosing,” *BMC Infectious Diseases*, vol. 21, no. 1, p. 153, 2021.
[5] M. J. Rybak, “The pharmacokinetic and pharmacodynamic properties of vancomycin,” *Clinical Infectious Diseases*, vol. 42, no. 1, pp. S35–S39, 2006.
[6] G. Sanford, “Vancomycin Calculator,” 2022, https://www.sanfordguide.com/vancomycin-dosing/.
[7] P. G. Drennan, M. Doogue, S. J. van Hal, and P. Chin, “Bayesian therapeutic drug monitoring software: past, present and future,” *International Journal of Pharmacokinetics*, vol. 3, no. 4, pp. 109–114, 2018.
[8] S. W. Narayan, Y. Thoma, P. G. Drennan et al., “Predictive performance of Bayesian vancomycin monitoring in the critically ill,” *Critical Care Medicine*, vol. 49, no. 10, pp. e952–e960, 2021.
[9] K. B. Olney, K. L. Wallace, R. P. Mynatt et al., “Comparison of bayesian-derived and first-order analytic equations for calculation of vancomycin area under the curve,” *Pharmaco-therapy: The Journal of Human Pharmacology and Drug Therapy*, vol. 42, no. 4, pp. 284–291, 2022.
[10] V. Gotti, A. Chaturvedula, M. J. Fossler, S. Mok, and J. T. Jacob, “Hospitalized patients with and without hemodialysis have markedly different vancomycin pharmacokinetics: a population pharmacokinetic model-based analysis,” *Therapeutic Drug Monitoring*, vol. 40, no. 2, pp. 212–221, 2018.
[11] P. J. Colín, K. Allegaert, A. H. Thomson et al., “Vancomycin pharmacokinetics throughout life: results from a pooled population analysis and evaluation of current dosing recommendations,” *Clinical Pharmacokinetics*, vol. 58, no. 6, pp. 767–780, 2019.
[12] A. H. Thomson, C. E. Staatz, C. M. Tobin, M. Gall, and A. M. Lovering, "Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations," *Journal of Antimicrobial Chemotherapy*, vol. 63, no. 5, pp. 1050–1057, 2009.

[13] L. I. K. Lin, "A concordance correlation coefficient to evaluate reproducibility," *Biometrics*, vol. 45, no. 1, pp. 255–268, 1989.

[14] J. Martin Bland and D. G. Altman, "Statistical methods for assessing agreement between two methods of clinical measurement," *The Lancet*, vol. 327, no. 8476, pp. 307–310, 1986.

[15] R. V. Shingde, S. E. Reuter, G. G. Graham et al., "Assessing the accuracy of two Bayesian forecasting programs in estimating vancomycin drug exposure," *Journal of Antimicrobial Chemotherapy*, vol. 75, no. 11, pp. 3293–3302, 2020.

[16] C. B. Cunio, D. W. Uster, J. E. Carland et al., "Towards precision dosing of vancomycin in critically ill patients: an evaluation of the predictive performance of pharmacometric models in ICU patients," *Clinical Microbiology and Infections*, vol. 27, no. 5, pp. 783.e7–783.e14, 2021.

[17] R. Heine, R. J. Keizer, K. Steeg et al., "Prospective validation of a model-informed precision dosing tool for vancomycin in intensive care patients," *British Journal of Clinical Pharmacology*, vol. 86, no. 12, pp. 2497–2506, 2020.

[18] C. A. DeRyke and D. P. Alexander, "Optimizing vancomycin dosing through pharmacodynamic assessment targeting area under the concentration-time curve/minimum inhibitory concentration," *Hospital Pharmacy*, vol. 44, no. 9, pp. 751–765, 2009.

[19] A. G. Martson, M. G. G. Sturkenboom, J. Stojanova et al., "How to design a study to evaluate therapeutic drug monitoring in infectious diseases?" *Clinical Microbiology and Infections*, vol. 26, no. 8, pp. 1008–1016, 2020.