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# Pharmacokinetic/pharmacodynamic evaluation of tobramycin dosing in critically ill patients: the Hartford nomogram does not fit

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**Objectives:** Extended-interval dosing of tobramycin is widely applied in patients with the Hartford nomogram as a representative, while this dosing approach has not been extensively evaluated in critically ill patients. The goal of this study was to characterize the pharmacokinetics of tobramycin and to evaluate the appropriateness of the Hartford nomogram in critically ill patients.

**Methods:** A retrospective analysis was performed based on a medical critical care database. The extracted concentration data of tobramycin were used for the construction of the population pharmacokinetic model using a non-linear mixed-effects modelling approach. Real-world data-based simulations were conducted to evaluate the pharmacodynamic target attainment ($C_{max}$/MIC $\geq$10) and safety (concentration <0.5 mg/L for at least 4 h) of the Hartford nomogram.

**Results:** A population pharmacokinetic model was built based on 307 measurements in 140 unique patients and externally validated by an independent study dataset. A two-compartment model was optimal for the structure model and creatinine clearance remained as the only covariate in the final model correlating to the clearance of tobramycin. Simulations indicated that the Hartford nomogram is effective for infections due to pathogens with an MIC of $\leq$1 mg/L, but not with an MIC of 2 mg/L. The percentage of patients who reached the non-toxicity target was quite low under the Hartford nomogram and a further extension of the dosing interval was necessary to minimize the toxicity.

**Conclusions:** The Hartford nomogram was not suitable for critically ill patients with pathogen MICs of 2 mg/L and drug monitoring is required to manage efficacy and toxicity.

## Introduction

Tobramycin is an aminoglycoside antibiotic that is used primarily in patients with severe infections due to Gram-negative bacteria.[1] Clinically, tobramycin is frequently used to treat the most important cystic fibrosis pathogen, *Pseudomonas aeruginosa*.[2]

Tobramycin is mainly eliminated unchanged via the kidney (76%–92%) and is characterized by a narrow therapeutic index.[1] The volume of distribution of tobramycin is equivalent to about 30% of the total body weight and the half-life of tobramycin is about 2 h.[1] The bactericidal actions of tobramycin are directly linked to its pharmacokinetics (PK) in a concentration-dependent manner.[3] Tobramycin $C_{max}$/MIC $\geq$10 (which is measured at the end of the infusion) and AUC/MIC $\geq$100 are the commonly used pharmacodynamic (PD) indices for characterizing its bactericidal effect.[4] It is not totally clear which PD index is more appropriate for predicting the bactericidal activity of tobramycin.[5] Nevertheless, *in vitro* studies have shown that a $C_{max}$/MIC $\geq$10 is associated with optimal bacterial killing and the validity of this target has been demonstrated in several clinical studies for patients with Gram-negative bacteraemia and pneumonia.[3,6,7] Tobramycin also exhibits a post-antibiotic effect (PAE) with a short *in vitro* PAE (1–3 h) and a long *in vivo* PAE (5–10 h).[8–10] The presence of a PAE provides the ability to suppress bacterial growth after the drug levels fall below the MIC for the bacterium. Along with its needed effects, tobramycin may cause unwanted effects. Trough concentrations above 1–2 mg/L increase the risk of two severe side effects of tobramycin (reversible nephrotoxicity and irreversible ototoxicity).[11]

Traditionally, tobramycin was administered by intermittent infusions three or four times daily (usually 1–3 mg/kg/dose) and this dosing regimen raised serious toxicity concerns.[2] In 1995, Nicolau *et al.*[12] proposed a fixed 7 mg/kg dose by 1 h infusion with a drug administration interval based on estimated creatinine clearance ($CL_{CR}$; 20–39 mL/min q48h, 40–59 mL/min q36h and

≥60 mL/min q24h) to optimize the treatment (termed the Hartford nomogram) by producing a $C_{max}$/MIC ≥10 and a drug-free period (concentration <0.5 mg/L) of at least 4 h. Theoretically, the use of a high dose increases the $C_{max}$/MIC ratio for the infecting organism(s), an extended-interval dosing reduces the trough concentrations and the PAE exhibited by aminoglycosides permits trough concentrations to drop below the MIC for a short period of time, thereby maximizing bacterial killing and minimizing toxicity. Data from both animal studies and clinical trials have demonstrated that the extended-interval aminoglycoside dosing regimens are at least as effective as conventional regimens and can reduce the risk of ototoxicity and nephrotoxicity associated with aminoglycoside therapy.[13–15]

Although the Hartford nomogram has been applied widely, this dosing approach has not been extensively evaluated in critically ill patients[16–19] and the PK of tobramycin in this patient population is poorly understood.[19] It is well known that the PK of tobramycin in patients is quite different from that in healthy volunteers and also varies between different patient populations.[20] Critical illness involves a range of pathophysiological alterations, usually leading to increased volume of distribution and diminished clearance for the drug.[21,22] The increased volume of distribution may lower the peak concentration, while decreased kidney function can prolong the half-life time. These altered physiological conditions produce considerable PK variability and lead to an uncertain efficacy and toxicity profile for tobramycin in critically ill patients.[23] Currently, there is little data on the efficacy and toxicity of the Hartford nomogram in critically ill patients and little information is available for the optimal dosing of tobramycin to ensure adequate therapy and to minimize the risk of toxicity.[16–19]

The purpose of this study was 2-fold: (i) to characterize the PK and covariates of tobramycin in critically ill patients using a non-linear mixed-effects modelling approach; and (ii) to evaluate the PK/PD target attainment and risk of toxicity of the Hartford nomogram of tobramycin in this patient population.

## Patients and methods

### Data source

We performed a longitudinal, retrospective and single-centre study of tobramycin by extracting electronic records from a Medical Information Mart for Intensive Care III (MIMIC-III) database,[24] which is developed by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (MIT). The MIMIC-III is publicly available and comprises de-identified health-related data associated with over 40 000 patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012.

### Ethics

The use of the MIMIC-III database has been approved by Institutional Review Boards of Beth Israel Deaconess Medical Center and MIT, and a waiver of informed consent was granted.

### Study population

The study cohort was characterized by the IV administration of tobramycin either with traditional dosing or extended-interval dosing for patients admitted to the ICU. The inclusion criteria for the patients were available documentation of complete dosing records (such as dose, administration time and duration of infusion) and concentration measurements of tobramycin as well as body weight (used for the calculation of the exact amount of administrated tobramycin). We excluded the patients if they had any missing information for the required records mentioned above.

Baseline patient-level characteristics prior to ICU admission were collected, including demographics (sex, age, ethnicity, body weight and height), laboratory measurements (serum creatinine, blood urea nitrogen, serum albumin, ALT, AST and total bilirubin) and derived covariates (BMI, fat-free mass and $CL_{CR}$ based on the Cockcroft and Gault[25] formula). The infecting pathogen and associated MIC of tobramycin were also extracted if the microbiology information was recorded.

All data extraction and aggregation were conducted using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

### Population PK modelling

We developed the population PK model of tobramycin using non-linear mixed-effects modelling program NONMEM® (version 7.3; Icon Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation with interaction ('FOCEI') method was used for the parameter estimation. The Perl-speaks-NONMEM ('PsN') program (version 4.9.0; Uppsala University, Uppsala, Sweden) was utilized to aid the model development and validation[26] and Pirana software (version 2.9.9; Pirana Software & Consulting BV) was adopted as the graphical user interface.[27] Dataset preparation, plotting and simulations were all carried out in R version 3.6.1.

One- and two-compartment models with first-order elimination were tested during model development. The inter-individual variability (IIV) of the population PK parameters was assumed to be log-normally distributed with a mean of zero and a variance of $\omega^2$. Residual unexplained variability was examined using additive, proportional and combined (additive + proportional) residual error models.

The aforementioned patient characteristics were investigated for an influence on the PK of tobramycin. The potential covariates were initially explored through graphic inspection and were individually tested in univariate analysis. The linear, exponential and power models were tested for continuous covariates and a different fixed-effect parameter for each category was estimated for categorical covariates. A $P$ value <0.05 was considered significant, corresponding to an objective function value (OFV) drop of 3.84. The significant covariates were further screened by a stepwise forward inclusion ($P < 0.05$) and backward elimination ($P < 0.01$; corresponding to an OFV rise of 6.63) manner.

Model selection was based on the assessment of OFV and goodness-of-fit (GOF) plots (observations versus population and individual predictions, conditional weighted residuals versus population predictions and time after dosing). Internal model validation for the final PK model consisted of the prediction-corrected visual predictive check (pcVPC) ($n = 1000$)[28] and the parameter uncertainty check using the sampling importance resampling (SIR) procedure ($n = 1000$).[29] External validation of the PK model was performed by assessing the predictive performance of the model for new individuals (validation dataset) treated with tobramycin under conditions similar to those for the study population. Also, the predictive performance of our final PK model was compared with that of a published population PK model in ICU patients by Conil *et al.*[19] Available data of routine monitoring of tobramycin concentrations from 97 hospitalized patients following multiple dosing regimens were used as the validation dataset.[23] The predictive performance of the PK models was assessed by the comparison of the observed concentrations ($C_{obs}$) and the individual predicted concentrations ($C_{ipred}$) obtained using *post hoc* Bayesian estimation with the models. The mean relative error (MRE; in %; Equation 1) was calculated as a measure of bias and the relative root mean squared error (RMSE; in %; Equation 2) was calculated as a measure of precision, where $n$ shown in the equations denotes the number of observations.[30]

$$\mathrm{MRE} = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{C_{\mathrm{ipred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}}\right) \quad (1)$$

$$\mathrm{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\frac{C_{\mathrm{ipred}} - C_{\mathrm{obs}}}{C_{\mathrm{obs}}}\right)^2} \quad (2)$$

### *Simulation-based efficacy and toxicity analysis*

The final part of this study was to assess the benefits and risks of the Hartford nomogram of tobramycin in ICU patients in relation to different categories of $CL_{CR}$ (20–39 mL/min q48h, 40–59 mL/min q36h, 60–139 mL/min q24h and 140–314 mL/min q24h) and to investigate the rational regimens. The 60–139 mL/min group was designed to mimic the non-ICU patients with $CL_{CR}$ >60 mL/min in the Hartford study[12] and the 140–314 mL/min group represented the ICU patients with augmented renal clearance. Virtual ICU patients ($n$ = 10 000) were created by randomly sampling the $CL_{CR}$-matched subjects from the MIMIC-III database. A 7 mg/kg dose of tobramycin by 1 h infusion was proposed for each patient and these patients were then randomly allocated PK parameters through the final PK model. A $C_{max}$/MIC ≥10 and a drug-free period (concentration <0.5 mg/L) of at least 4 h were set as the main targets of the Hartford nomogram. The PD target AUC/MIC ≥100 and non-toxicity target (trough concentration <1 or 2 mg/L) were also evaluated. The PTA against pathogens with MICs of 1 or 2 mg/L and cumulative fraction of response (CFR) against *P. aeruginosa* from the EUCAST database were calculated.

## Results

### *Patients*

Of the over 40 000 patients in the MIMIC-III database, we identified 334 unique patients who received IV tobramycin treatment. Of these, we included 140 patients in our study cohort, after careful screening with the inclusion criteria. The characteristics of the cohort are summarized in Table 1. Forty-one patients (29.3%) received the traditional dosing (1–3 mg/kg IV q8h) and 99 patients (70.7%) received the extended-interval dosing (3–8 mg/kg IV q24h). The most frequently applied dose regimens were 5, 6 and 7 mg/kg IV q24h, accounting for 14.3% (20 patients), 18.6% (26 patients) and 26.4% (37 patients) of the patient cohort, respectively.

### *Model development*

The PK modelling included 307 tobramycin measurements from 140 ICU patients. Figure 1 shows the tobramycin concentrations plotted against time after dose with different dosing and sampling regimens (peak, trough and random sampling). The dataset was well described by a two-compartment model, providing an OFV drop of 57.2 points compared with a one-compartment model. The unexplained residual variability was well described by a proportional error model.

During the univariate analysis of the clinical variables, age, serum creatinine, blood urea nitrogen and $CL_{CR}$ were identified as the significant covariates ($P$ < 0.05) on the PK of tobramycin (Table S1, available as Supplementary data at *JAC* Online). After the stepwise covariate screening, we only retained $CL_{CR}$ as the statistically significant covariate ($P$ < 0.01) with a power model function on the clearance (CL) of tobramycin, resulting in a reduction of the variability of CL from 75.8% to 49.5%. The final covariate $CL_{CR}$ included on CL is shown in Equation 3.

$$\mathrm{CL} = \theta_{\mathrm{CL}} \cdot \left(\frac{\mathrm{CL_{CR}}}{81}\right)^{\theta_{\mathrm{CLCR}}} \cdot e^{\eta_{\mathrm{CL}}} \quad (3)$$

where $\theta_{CLCR}$ is the exponent of the power model describing the $CL_{CR}$ effect on CL, $\theta_{CL}$ is the population estimate of CL and $\eta_{CL}$ is the IIV of CL.

The estimates of the final model are presented in Table 2. As can be seen, the unexplained residual variability associated

**Table 1.** Demographics and clinical characteristics of study patients ($N$ = 140)

| Demographics and clinical characteristics | $n$ (%) or median (IQR) |
|---|---|
| Male/female | 87 (62)/53 (38) |
| Ethnicity (white/others) | 109 (78)/31 (22) |
| Age (years) | 62.0 (52–70) |
| Body weight (kg) | 79 (68–94) |
| Height (m) | 1.70 (1.63–1.78) |
| BMI (kg/m$^2$) | 27.1 (23.5–31.4) |
| Fat-free mass (kg) | 57.3 (47.8–64.1) |
| Serum creatinine (mg/dL) | 0.95 (0.67–1.35) |
| $CL_{CR}$ (Cockcroft and Gault; mL/min) | 81 (57–119) |
| Blood urea nitrogen (mg/dL) | 22.7 (16.4–34.0) |
| Serum albumin (g/dL) | 2.9 (2.5–3.3) |
| ALT (IU/L) | 34.0 (19.2–76.4) |
| AST (IU/L) | 44.0 (27.7–81.4) |
| Total bilirubin (mg/dL) | 0.60 (0.33–1.12) |
| Pathogens (*Escherichia coli*/ *P. aeruginosa*/*Klebsiella pneumoniae* /others)[a] | 27 (29)/25 (27)/17 (18)/24 (26) |
| MIC (≤1/≥4 mg/L) | 75 (81)/18 (19) |

[a]The isolated pathogens and related MICs of tobramycin were available for 93 patients.

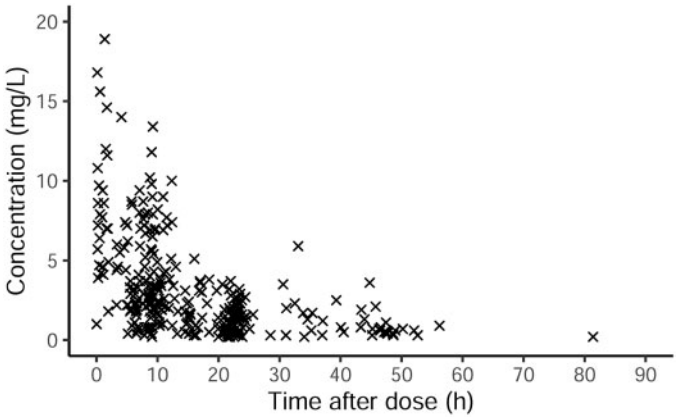


**Figure 1.** Tobramycin concentrations versus time after dose in 140 ICU patients with different dosing and sampling regimens.

**Table 2.** Parameter estimates of the final population PK model of tobramycin and the results of the SIR approach

| Parameter | Final PK model, estimate (RSE%) [shrinkage%] | SIR results | |
|---|---|---|---|
| | | median | 95% CI |
| Fixed effects | | | |
| CL (L/h) | $\theta_{CL} \times (CL_{CR}/81)^{\theta_{CLCR}}$ | | |
| $\theta_{CL}$ (L/h) | 3.27 (5.0) | 3.27 | 2.95–3.63 |
| $\theta_{CLCR}$ | 0.76 (10.2) | 0.77 | 0.62–0.92 |
| $V_1$ (L) | 21.3 (11.4) | 21.9 | 17.5–26.4 |
| Q (L/h) | 2.40 (19.8) | 2.52 | 1.70–3.57 |
| $V_2$ (L) | 16.3 (13.6) | 16.9 | 12.4–21.7 |
| IIV | | | |
| CL (CV%) | 49.5 (18.2) [12.1] | 50.7 | 42.9–60.2 |
| $V_1$ (CV%) | 35.7 (46.7) [65.3] | 38.3 | 20.7–55.4 |
| $V_2$ (CV%) | 77.6 (35.8) [49.5] | 79.8 | 51.9–117 |
| Residual variability | | | |
| proportional error (%) | 28.5 (16.3) [24.7] | 28.8 | 25.0–32.7 |

RSE, relative standard error; CL, clearance; $CL_{CR}$, creatinine clearance; $\theta_{CL}$, population estimate of CL; $\theta_{CLCR}$, exponent of the power model describing the $CL_{CR}$ effect on CL, $V_1$, volume of distribution of the central compartment; Q, inter-compartmental clearance between the central and peripheral compartments; $V_2$, volume of distribution of the peripheral compartment.

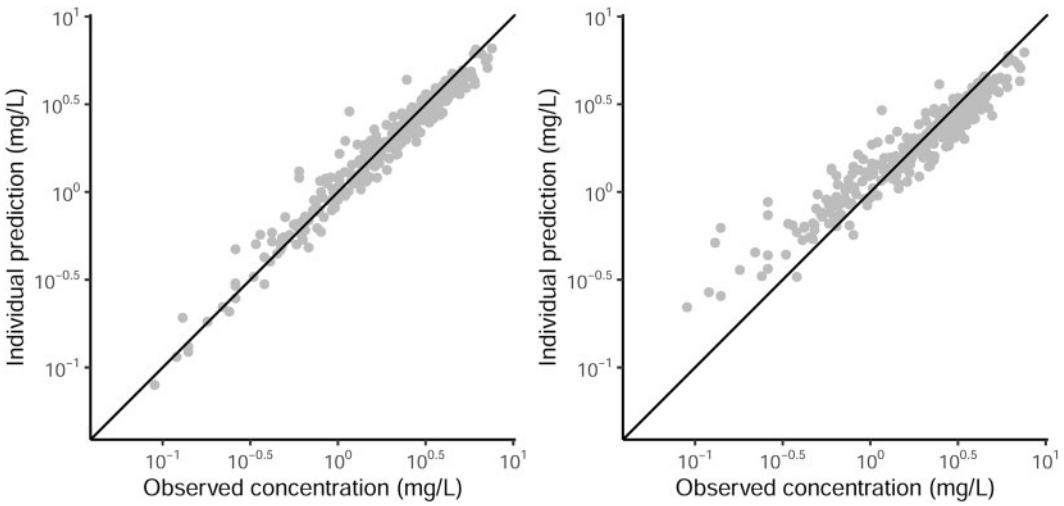


**Figure 2.** Individual predicted versus observed tobramycin concentrations for the validation dataset by our PK model and the published model by Conil *et al.*[19]

with the final model was good (28.5%). The Eta-shrinkage on CL was low (12.1%), while the values on central volume of distribution ($V_1$) and peripheral volume of distribution ($V_2$) were high (65.3% and 49.5%, respectively). The high shrinkage indicates the limited value of GOF plots, although the GOF plots (Figure S1) suggest no apparent model mis-specification. The pcVPC shown in Figure S2 demonstrates a reasonable agreement between the simulated and observed tobramycin concentrations. The SIR results shown in Table 2 confirm the robustness of the final model parameters.

The patients' age and $CL_{CR}$ from the validation dataset ranged from 16 to 85 years (median = 51 years) and from 10 to 166 mL/min (median = 65 mL/min), respectively. The characteristics of these patients were generally comparable to our study cohort (median age of 62 years and median $CL_{CR}$ of 81 mL/min), while the $CL_{CR}$ of these patients differed to some extent from those in the Conil *et al.*[19] study (median age of 61 years and median $CL_{CR}$ of 108 mL/min). Figure 2 displays the individual predicted versus observed concentrations for the validation population based on the Bayesian estimation from our final PK model and the published model by Conil *et al.*[19] The graphic comparison indicates that our PK model produced a smaller bias and imprecision. This is in good agreement with the numerical estimates for the model predictive performance. The MRE and RMSE from our PK model were 0.0084% and 21.1%, respectively, which were much more desirable than those obtained by Conil *et al.*[19] (MRE of 8.1% and RMSE of 44.9%).

### *Simulation-based dose evaluations*

Table 3 summarizes the percentages of virtual ICU patients with various degrees of renal function achieving the efficacy and non-toxicity targets given a 7 mg/kg tobramycin dose for the treatment of *P. aeruginosa*. The Hartford nomogram achieved a desirable $C_{max}$/MIC ≥10 target rate (>96%) for pathogens with MICs of 1 mg/L, while at an MIC of 2 mg/L the fraction of patients attaining the $C_{max}$/MIC ≥10 target was low (<61% for patients with $CL_{CR}$s <140 mL/min). For the target AUC/MIC ≥100, the attainment rate at an MIC of 1 mg/L was high (>90%) for patients with $CL_{CR}$s <60 mL/min, but the target rate was unacceptably low (7.9%–70.6%) in patients with pathogen MICs of 2 mg/L. The CFR for target $C_{max}$/MIC ≥10 was similar in different patient groups (86.8%–89.4%) and the CFR for target AUC/MIC ≥100 decreased with $CL_{CR}$ (from 88.6% to 68.1%). Regarding the non-toxicity targets, the percentages of patients with a drug concentration <0.5 mg/L for at least 4 h were quite low (11.3%–36.1%) and the percentages were still not high enough for the non-toxicity concentration target of 1 or 2 mg/L.

## Discussion

The population PK model described here is the first model (to the best of our knowledge) with systematic external validation for tobramycin PK in a relatively large sample size of critically ill patients. The benefits and risks of the Hartford nomogram of tobramycin in this patient population were comprehensively investigated.

To the best of our knowledge, the PK of tobramycin in critically ill patients is poorly described in the literature. Population PK models of tobramycin for critically ill patients in early studies were often on the basis of a one-compartment model[16–18,31] and no external validation was performed. Recently, Conil *et al.*[19] reported an externally validated population PK model of tobramycin in 49 ICU patients using a two-compartment model. Likewise, in this study we developed a population PK model for tobramycin based on the two-compartment model as well and our model displayed a better predictive performance during the systematic external validation.

Altered PK of aminoglycosides in critically ill patients is well known.[19,31] The central volume of distribution in critically ill patients from our study ($V_1$ of 21.3 L) was much higher than that of normal adult patients ($V_1$ of 15.1 L),[32] indicating an increased volume of distribution in critically ill patients. In the meantime, the CL of tobramycin in our patients (3.27 L/h) was near 50% lower than the reported value in normal adult patients (6.03 L/h).[32] From another perspective, the $V_1$ and CL found in our study cohort were in good agreement with the reported values in the ICU patients reported by Conil *et al.*[19] ($V_1$ of 25.5 L and CL of 3.83 L/h).

$CL_{CR}$ is a frequently reported covariate for the CL of tobramycin. Our results demonstrated that $CL_{CR}$ alone explains near 50% of the variability in CL of tobramycin by using a power model function. Further addition of other covariates did not significantly reduce the variability, indicating that $CL_{CR}$ is the most predictive marker for the CL of tobramycin. The correlation between $CL_{CR}$ and the CL of tobramycin was previously often described by a linear model either in ICU patients or normal hospitalized patients.[19,20,23] In some studies, no correlation between the $CL_{CR}$ and CL of tobramycin was also reported.[16,33] The different $CL_{CR}$ characteristics of the study patients may explain these different findings. Depending on the $CL_{CR}$ range of the study patients, different correlation models may be identified or even no relationship may be observed. For the first time, to the best of our knowledge, our population PK model quantified the relationship between $CL_{CR}$ and CL of tobramycin in the widest range of ICU patients. Consequently, a better predictive performance was observed for our model compared with the Conil *et al.*[19] model for an independent patient cohort.

Body weight, including actual body weight and fat-free mass, is also a common covariate for the volume of distribution and CL of tobramycin.[33] However, these relationships were not seen in our study patients and the ICU patient cohort in Conil *et al.*[19] The body weight of an ICU patient may not be an informative predictor due to the marked and varied oedema in this population.[19]

Extended-interval dosing of aminoglycosides has become a popular treatment strategy since the report of the Hartford nomogram in 1995.[12] The Hartford study excluded patients with highly variable or altered aminoglycoside PK, such as ICU patients. The data evaluating the extended-interval dosing in ICU patients are limited and uninformative, and there are still concerns in extrapolating the Hartford nomogram to ICU patients. Most of the previous studies in ICU patients either simply evaluated whether the mean

**Table 3.** Percentages of virtual ICU patients with different $CL_{CR}$s achieving the efficacy and non-toxicity targets given a 7 mg/kg tobramycin dose for the treatment of *P. aeruginosa*

| Different efficacy and non-toxicity targets | $CL_{CR}$ 20–39 mL/min, 7 mg/kg q48h | $CL_{CR}$ 40–59 mL/min, 7 mg/kg q36h | $CL_{CR}$ 60–139 mL/min, 7 mg/kg q24h | $CL_{CR}$ 140–314 mL/min, 7 mg/kg q24h |
|---|---|---|---|---|
| $C_{max}$/MIC ≥10 (MIC = 1 mg/L) | 96.8% | 96.4% | 98.2% | 99.2% |
| $C_{max}$/MIC ≥10 (MIC = 2 mg/L) | 55.2% | 55.3% | 60.1% | 74.3% |
| CFR of $C_{max}$/MIC ≥10 | 86.9% | 86.8% | 87.8% | 89.4% |
| AUC/MIC ≥100 (MIC = 1 mg/L) | 97.6% | 90.6% | 70.2% | 54.1% |
| AUC/MIC ≥100 (MIC = 2 mg/L) | 70.6% | 40.9% | 13.7% | 7.9% |
| CFR of AUC/MIC ≥100 | 88.6% | 83.8% | 74.9% | 68.1% |
| Drug-free period (concentration <0.5 mg/L for at least 4 h) | 11.3% | 13.0% | 13.9% | 36.1% |
| $C_{min}$ <1 mg/L | 30.2% | 37.7% | 42.1% | 71.3% |
| $C_{min}$ <2 mg/L | 58.0% | 66.4% | 70.1% | 89.4% |

**Table 4.** Attainment rate for the PD targets of $C_{max}$/MIC ≥10 and AUC/MIC ≥100 in ICU patients who received different tobramycin doses against pathogens with MICs of 2 mg/L

| | $C_{max}$/MIC ≥10 | | | | AUC/MIC ≥100 | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg) | $CL_{CR}$ 20–39 mL/min | $CL_{CR}$ 40–59 mL/min | $CL_{CR}$ 60–139 mL/min | $CL_{CR}$ 140–314 mL/min | $CL_{CR}$ 20–39 mL/min | $CL_{CR}$ 40–59 mL/min | $CL_{CR}$ 60–139 mL/min | $CL_{CR}$ 140–314 mL/min |
| 8 | 67.8% | 68.0% | 73.5% | 83.7% | 79.4% | 53.1% | 22.6% | 13.2% |
| 9 | 77.3% | 77.7% | 82.8% | 90.3% | 85.9% | 63.5% | 31.3% | 20.3% |
| 10 | 84.5% | 84.7% | 88.9% | 94.2% | 90.2% | 72.0% | 40.6% | 26.9% |
| 11 | 89.3% | 89.5% | 92.8% | 96.4% | 93.3% | 78.5% | 49.2% | 34.0% |
| 12 | 92.7% | 93.1% | 95.3% | 97.9% | 95.3% | 83.8% | 57.4% | 41.2% |

$C_{max}$/MIC ratio was adequate or considered the non-weight-based dosing regimens (e.g. mg per dose rather than mg/kg per dose) instead.[17–19] The Rea *et al.*[31] study predicted that the majority of critically ill patients would not achieve the $C_{max}$/MIC ≥10 target under the 7 mg/kg aminoglycoside dose in the general ICU patient population by stochastic simulation.

In the present study, we utilized a real-world data-based simulation approach to evaluate the benefits and risks of the Hartford nomogram in critically ill patients. The use of real patient characteristics for simulation could achieve a more realistic representation of clinical outcomes and thus are more generalizable in clinical-practice settings.[34] Our simulation predicted that the Hartford nomogram was adequate for ICU patients (independent of renal function) infected with pathogens with an MIC ≤1 mg/L, but was insufficient to achieve the PD target for pathogens with an MIC of 2 mg/L. To achieve a desirable $C_{max}$/MIC ≥10 attainment rate (>90%) for pathogens with MICs of 2 mg/L, a higher dose should be considered (Table 4), and the minimal required dose varied for different patient groups (12 mg/kg for the 20–39 mL/min and 40–59 mL/min $CL_{CR}$ groups, 11 mg/kg for the 60–139 mL/min $CL_{CR}$ group and 9 mg/kg for the 140–314 mL/min $CL_{CR}$ group). The AUC/MIC target for an MIC of 2 mg/L was hard to attain even at a dose of 12 mg/kg. From a safety perspective, the extended dosing interval based on the Hartford nomogram was not suitable for ICU patients and a further extension of the dosing interval is needed to minimize the risk of toxicity. We advocate the combination of Bayesian forecasting and a two-point drug monitoring approach (such as peak and 24 h after dosing) to advance the determination of the suitable infusion time and/or dosage for the subsequent administration after the initial dose.

Our study has some limitations. First, the key pathophysiological conditions (e.g. oedema and sepsis) of the ICU patients may significantly influence tobramycin PK and the impact of these factors on tobramycin PK was not determined. Second, we did not consider the potential impact of the dynamic physiological alterations on the PK/PD of tobramycin. The ICU patients generally showed stable renal function during the tobramycin treatment, thus at least the clearance of the tobramycin was not significantly changed.

In conclusion, we developed a predictive population PK model for tobramycin in critically ill patients and highlighted the altered PK in this special patient population. The Hartford nomogram was not appropriate for all the critically ill patients and therapeutic drug monitoring is warranted for individual dosing to achieve the PD target, while minimizing the risk of toxicity.

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## Transparency declarations

None to declare.

### *Author contributions*

F.X. developed the population PK model and prepared the first draft of the manuscript. Y.W., Y.P. and Z.C. collected the data and reviewed the manuscript. S.L. conceived the idea, reviewed the manuscript and approved the final version of the manuscript.

## Supplementary data

Table S1 and Figures S1 and S2 are available as Supplementary data at *JAC* Online

## References

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