**Tools for the Individualized Therapy of Teicoplanin for Neonates and Children**

**Individualized Therapy of Teicoplanin for Children**

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**ABSTRACT**

 The aim of the study was to develop a population PK model for teicoplanin across childhood age ranges to be used as Bayesian prior information in the constructed software for individualized therapy. We developed a non-parametric population model fitted to PK data from neonates, infants and older children. We then implemented it in the BestDose multiple-model Bayesian adaptive control algorithm to show its clinical utility. It was used to predict the required dosages to achieve teicoplanin optimal pre-dose targets (15 mg/L) from day 3 of therapy. We performed individual simulations in an infant and a child from the original population, who provided early first dosing interval concentration time-data. An allometric model that linked weight to clearance and volume of distribution (Ke and V) and incorporating renal function as a power function of estimated glomerular filtration rate (eGFR) or Post-natal age (PNA)/ serum creatinine(SCr) for infants < 3 months, best described the data. The median population PK parameters were as follows: Ke= 0.03\*(wt/70)-0.25 \* Renal (h-1); V=19.5\*(wt/70) (L), being Renal= eGFR0.07 (ml/min/1.73m2) or PNA/SCr (μmol/L). Increased teicoplanin dosages and alternative administration techniques (extended infusions and fractionated multiple dosing) were required in order to achieve the targets safely by day 3 in simulated cases. The software was able to predict individual measured concentrations and the required dosages and administration techniques to achieve the desired target concentrations early in therapy. Prospective evaluation is now needed in order to ensure that this teicoplanin individualized therapy approach is applicable in the clinical setting.

**INTRODUCTION**

The pharmacokinetics (PK) of teicoplanin are highly variable in children and neonates (1, 2). Weight-based dosing is advocated (3). Weight affects estimates of clearance and has been incorporated into structural PK models using linear and allometric scaling functions (2, 4–7). Different levels of renal function (quantified in terms of serum creatinine and eGFR) also explain a portion of PK variability in adults and children (7, 8). However, most of the inter-patient variability in PK remains unexplained (7, 9). Consequently, nomograms based on simple covariates cannot be used to adjust dosages to achieve therapeutic targets that are deemed safe and maximally effective.

The area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) is the pharmacodynamic index that best links teicoplanin drug exposure with the observed effect against methicillin-resistant *Staphylococcus aureus* (MRSA) (V. Ramos-Martín, A. Johnson, L. McEntee, N. Farrington, K. Padmore, P. Cojutti, F. Pea, M. Neely, W. Hope, submitted for publication). Nevertheless, the pre-dose concentration (Cmin (mg/L)) is the most widely used measure of drug exposure to guide therapeutic drug monitoring (TDM) (10). A Cmin target ≥ 15 mg/L by days 3-5 of therapy is recommended for most indications (11). These targets have recently increased to 20 and 30-40 mg/L in the Summary of Product Characteristics (SPC) for the treatment of deep-seated infections (bone and joint infections) and infective endocarditis, respectively (11). Currently recommended targets are based on small retrospective studies in adults that have explored the relationship between teicoplanin trough exposure and clinical outcomes (12, 13). More recently, daily AUCs >750-800 mg\*h/L by day three of therapy have been linked to microbiological cure of adults with MRSA infection (14, 15).

In this study, we report the development of a non-parametric population PK model of teicoplanin in hospitalized neonates, infants and older children (up to 16 years old). We then describe the application of this model for the construction of software that provides decision support for dose individualization of teicoplanin. Such an approach enables the achievement of desired drug exposure targets in an optimally precise manner and at anytime during the therapeutic course. This approach constitutes a further extension of our broad goal of developing the tools and knowledge to deliver optimized antimicrobial therapy in neonates and children.

**RESULTS**

**Demographics**

The demographics and clinical characteristics of the 57 patients used in the population PK model are summarized in **Table 1.** The total population (n=57) was comprised of neonates (n=18), infants and toddlers 1-23 months old (n=16), children 2-11 years old (n=20), and children 11-16 years old (n=3). The majority of patients (n=23, 40.35%) were recruited from the ICU, in most cases after cardiac surgery. Other subjects included oncologic patients with febrile neutropenia (n=17, 29.8%), general medical (n=8, 28.1%) and cardiac medical conditions (n=1, 1.75%). A total of 394 PK samples were available for analysis with each patient contributing a mean of 5.3 and 7.6 observations in the neonates and older children, respectively.

**Population PK of Teicoplanin in Neonates and Children**

 **Fig. 1** shows the relationships between the posterior median estimates from the PK parameters for each patient from the base model and potentially relevant covariates. Allometric relationships were apparent between both clearance (Figure 1 A and B) and volume (Figure 1 C and D) and weight. A linear relationship between Cl and age (E) and volume and age (F) was also apparent. There was an exponential relationship between eGFR and clearance (Fig 1 G) with progresively higher estimates of clearance as eGFR increased. There were two distinct periods of change in eGFR as a function of age, which formed the basis for using separate functions that described the effect of changes in renal function on the elimination of teicoplanin (Fig 1 H, I). For neonates and young infants <3 months PNA/creatinine was used as an alternative measure of renal function in this age-group. For infants >3 months and children, eGFRpw was used. There was no relationship between serum albumin and the Bayesian estimates of clearance and volume; thus, albumin was not included as a covariate in the final model.

A model comparison and diagnostics between the standard model without covariates and the final model is shown in **Table 2.** A number of candidate models that examined the impact of age on Ke and V using both linear scaling functions and sigmoidal functions were developed, but did not describe the data better than the use of allometric scaling using weight.

The parameter values (means, medians and standard deviation) for the final model are summarized in **Table 3**. For the final model, the linear regression of observed versus Bayesian-predicted values had a coefficient of determination of r2 = 0.92 with measures of bias and precision of -0.15 mg/L and 0.9 mg2/L2, respectively. The population and individual observed versus predicted plots of the final model are shown in **Fig. 2.** Normalized distribution predition error (NPDE) results (Q-Q plot and histogram) are summarized graphically in **Fig. 3.** The weighted residual error distributions are shown in **Fig. 4.** The NDPE and weighted residual error distributions both suggest that the fit of the model to the data was acceptable.

**Performance and simulations to demonstrate the clinical utility of the teicoplanin dose optimization software**

The dose optimization software predicted the PK profile of the individual patients and achieved a target with minimal bias and imprecision. The **Table 4** shows the bias, % bias, imprecision, % imprecision and the coefficient of determination (r2) of the linear regression of the observed *vs* predicted measured concentrations. Individual weighted mean PK parameter values were obtained. The median (range) average daily AUC0-24 for each patient is shown.

**Fig. 5 and 6** show representative plots from the dose controller for the infant and the older child, respectively. They represent the software predicted PK profiles with their respective measured concentrations (circles) and the target concentration (squares). In the case of the infant, all required optimized doses by day 2 of therapy and a day 3 pre-dose target of 15 mg/L were 1.8 to 2.2 times higher than currently recommended maintenance dose (10 mg/kg) for 12-h extended infusions and a 24-hourly bolus administration, respectively (**Fig. 5**). The regimen with daily 24-hour infusions required similar and subsequent slightly decreased dosages. Increased dosages and differing infusion times did not reach peak concentrations >60 mg/L, except for the first case (bolus administration by day 2 of therapy)(**Fig. 5A**). In the case of the 5-year old child, a higher bolus administration of 18.4 mg/kg (as opposed to 10 mg/kg maintenance dose) was required for the day 3 pre-dose 15 mg/L target, although producing peaks > 60 mg/L (**Fig. 6A**). In this patient, extended 12 and 24-h infusions and even a multiple fractionated 12-hourly dose would have been safer alternatives (**Fig. 6B**). Increased predicted and optimal dosages were from 13.9 mg/kg (1.4 times higher) to 3.7, 2.6 and 2.2 mg/kg for the multiple fractionated doses and pre-dose targets of 15 mg/L. There was not a significant impact, when the simulated patients had an average age-related eGFR, higher than actual estimates. In these particular cases, they both required slightly increased dosages (≤2%).

The Monte Carlo simulations suggested that the best performing regimen (3 loading doses of 25 mg/kg followed by a daily maintenance dose of 10 mg/kg) only achieved a 30% of patients with Cmin concentrations of 15-60 mg/L and 13% had potentially toxic levels (> 60 mg/L).

**DISCUSSION**

An improved understanding of the PK-PD of teicoplanin is fundamental to the optimal use of this agent (29). In this study, we developed a population PK model in neonates, infants and older children to identify PK variability and its explanatory covariates. After considering the available covariates, the final pharmacokinetic model accounts for only 28% of the observed PK variability (**Fig.2**, top), which is consistent with other population PK studies in children and adults (7, 9). The high and largely unexplained variability is a strong argument for the use of TDM to minimize both sub-optimal and potentially toxic antimicrobial exposures (1, 2). The combination of a pharmacokinetic model with measurements from an individual patient and software-guided dosage adjustment provided a way future target concentrations can be achieved in a timely and optimally precise manner.

For teicoplanin, a relationship between plasma concentration and toxicity has not been established (10, 30–32), which may reduce the incentive for clinicians to routinely monitor the drug. However, exposure control to maximize efficacy should not be neglected. The British National Formulary for Children (BNFC) suggests a therapeutic window of >15 to 60 mg/L for children and adults (3). These recommendations are largely based on retrospective studies of MRSA infection (12, 13, 30, 33). Low drug exposures increase the probability of clinical failure and potentially promote the development of drug resistance (34, 35). This is the predominant argument for the routine monitoring of teicoplanin concentrations and active dosage adjustment.

Teicoplanin dosages that are adjusted by weight and/or renal function improve the achievement of target concentrations in adults (36, 37). However, high and unexplained PK variability makes this approach less effective in children and neonates. Hence, an alternative dosing strategy is required. Bayesian tools offer a way to achieve target concentrations in a timely and optimally precise manner (38). A number of Bayesian forecasting tools can be used to deliver dosage adjustment. In this study, the multiple model algorithm embedded in the software package BestDose was used.

The following steps are required to achieve dosage individualization using the multiple model algorithm. Firstly, the entire patient population is described by a matrix of support points, which consist of individual sets of parameter values. Each support point has an associated probability, which reflects how well it describes individual patients within the population. The population is described by multiple support points, because there are both multiple patients and there is typically considerable inter-individual pharmacokinetic variability. The set of support points constitute the Bayesian prior and are a mathematical summary of drug behavior in the population. In the next step, pharmacokinetic measurements are obtained from the patient whose dosage needs to be individualized. The probabilities of support points that best describe that PK of that patient are then revised. Those points that poorly describe the observed pharmacokinetics have their probability revised downward. Other points that perform better have their probability increased. Hence, each individual patient has the same set of support points as the total population, but with a revised probability distribution. In the final step the dosage required to achieve the target concentration for the individual patient is calculated. This is achieved by calculating the dose that is required for each support point to achieve the desired target concentration. These dosages are then weighted by the probability of each support point and summed to obtain a mean weighted dose.

The approach used in this study has several attractive features. Firstly, dosage individualization can commence immediatley without waiting for steady state. Secondly, patients can be controlled without an explicit understanding of the sources or causes of pharmacokinetic variability. The control of critically ill patients who are clinically unstable (20, 39) represents an ongoing challenge. One limitation of current approaches (including this study) is that a patient’s PK are assumed to be invariant. This can lead to poor fitting if the PK change and ultimately leads to suboptimal control. The only way to circumvent this problem at the current time is to use the most recent pharmacokinetic data to estimate a patient’s PK and updated covariate information. In this case the probability for each support point describing the PK for the new episode are recalculated and are then used to control subsequent dosing. The incorporation of the interacting multiple model approach into dosage adjustment algorithms potentially provides a way to control unstable patients, but this is yet to be done (38).

Another interesting aspect of our work was the use of post-natal age (PNA) divided by serum creatinine (SCr) as a novel marker of renal function. When modeling and controlling drug behavior, it is not necessary to describe renal function using traditional equations that estimate GFR, although we did use the Schwartz equation for the infants >3 months of age. The goal in pharmacometrics is to find the best descriptors of drug behavior, in this case related to renal function and maturation. We feel that PNA/SCr has advantages over any other estimation of renal function, including Schwartz, in that it does not use length (height), which can be notoriously inaccurate in infants. We have previously found PNA/SCr to be a useful predictor for both vancomycin (40) and gentamicin PK (41) in infants.

In conclusion, we present a tool to rapidly and accurately predict teicoplanin concentrations and calculate doses that optimally achieve desired concentrations in pediatrics. We further validate PNA/SCr as a novel predictor of renal drug elimination in neonates and young infants. A number of prospective clinical studies can now be considered. At the simplest level these may consist of studies that have drug exposure as the primary endpoint. More complex studies that have clinical outcomes and/or toxicity as primary endpoints will require a significantly larger number of patients and a multicenter design.

**PATIENTS AND METHODS**

**Pharmacokinetic study of teicoplanin in children and neonates**

Pharmacokinetic data from 57 children (39 children aged 1 month-16 years old and 18 neonates between 26-44 postmenstrual age-PMA- weeks) was available for model building. Patients were prospectively enrolled from two different hospitals in Liverpool (Alder Hey NHS Children´s Foundation Trust and Liverpool Women´s Hospital) over a 20 month-period (April 2013 and January 2015). These PK data have been previously reported in two separate population models (1, 2). In this study, we combined these datasets to develop a joint population PK model fitted to data from neonates to older children that can be used for dosage individualization. Such an approach avoids the problem of having multiple pharmacokinetic models for the same drug, each with an arbitrarily chosen cut-off value for age or size.

The study was approved by the Medicines and Healthcare Products Regulatory Agency (clinical trial authorization number: 21362/00003/001-0001) and the National Research Ethics Service and Regional Committee (REC: 13/NW/0023). The trial was registered with the European Clinical Trials Database Registry. EudraCT: 2012-005738-12. Written informed consent was obtained from parents and/or legal guardians.

Neonates ≤ 44 weeks PMA (post-menstrual age) received a loading dose of 16 mg/kg followed by 8 mg/kg once daily via a 30 minute i.v. infusion. Children > 1 month of age received three loading dosages (LD) of 10 mg/kg every 12 hours, followed by 10 mg/kg once daily via a bolus iv infusion (2-5 min), according to dosages currently recommended by the SPC (11). Plasma samples were collected during the first dosage interval and then at steady state (1, 3, 6, 24 hours post-dose) on days 3-7 of therapy. Neonates < 1000 grams contributed two samples per dosing interval because of constraints on sample volume. The duration of the treatment course was at the discretion of the treating physician. All patients received teicoplanin for proven or suspected methicillin-resistant staphylococcal (either coagulase negative staphylococci-CoNS- or MRSA) sepsis and/or central-line associated bloodstream infection. Demographic variables included weight, height, age in years, post-menstrual age (PMA) in weeks, postnatal age (PNA) in days, albumin (g/L) and serum creatinine. The estimated glomerular filtration rate (eGFR) (Schwartz-Haycock) (16) was also available for each patient.

Teicoplanin concentrations were measured using a commercially available fluorescence polarization immunoassay (FPIA; Thermo Fisher Scientific, Germany). The limit of quantification (LOQ) was < 3.0 mg/L. The dynamic range was 3-100 mg/L and overall precision (intra and inter-day variability) was < 6%.

**Development of a population PK model**

A PK model was fitted to the data using Pmetrics 1.4.2 for R statistical package 3.2.2 that utilizes the non-parametric adaptive grid (NPAG) algorithm (17). The inverse of the estimated assay variance was used to weight the data. Initially, a standard two-compartment model with time-delimited zero-order intravenous (iv) input and first-order elimination from central compartment was developed. The standard model is described by the differential equations 1a and 1b below.

$$\frac{dX\left(1\right)}{dt}=R\left(1\right)-\left(Kcp+Cl/V\right)∙X\left(1\right)+\left[Kpc∙X\left(2\right)\right] (1a)$$

$$\frac{dX\left(2\right)}{dt}=Kcp∙X\left(1\right)-Kpc∙X\left(2\right) (1b)$$

Where X(1) and X(2) represent the amount of teicoplanin (mg) in the central (c) and peripheral (p) compartments, respectively. R(1) is the rate of infusion of drug into the central compartment (mg/h). There is clearance (Cl) from the central compartment measured in L/h, which has Volume (V) measured in liters (L). The central and peripheral compartments are connected by the first-order rate constants Kcp and Kpc (h-1).

Once the standard model was developed, the potential effect of growth (size) and development (maturity) on the PK of teicoplanin was investigated. This was conducted using clinical measures that are readily accesible, such as weight and age. We also examined the relationships between other potentially relevant covariates and the PK (e.g. albumin). The Bayesian individual posterior median estimates for clearance and volume of distribution were obtained from the standard model for each patient. These were then plotted against the covariates of interest to interrogate any possible relationships.

In neonates and children, clearance generally scales with size in a nonlinear manner that is best described using a power function. A scaling exponent of 0.75 is most frequently used (i.e. Clearance is proportional to weight0.75). In addition, physiological maturation may also affect clearance and this is especially important for neonates and young infants (18, 19). In our model building process, we switched from clearance to using Ke (h-1) as the first-order elimination rate constant, where Ke = Cl/V and Ke is proportional to weight-0.25. While it is possible to directly estimate the scaling exponents, we chose to fix these values as previously described by us and others (18–20). There is a theoretical basis for using fixed scaling exponents that is related to fundamental relationships between size and a range of biological functions. Weight for each individual patient was normalized to a 70 kg adult (19, 21). Consequently, values for Ke0 and V0 approximate adult values.

The potential impact of development (or maturation) on teicoplanin elimination was studied by using age (years), and PMA (weeks) and/or PNA (days) for the neonates and younger infants. The effect of age (years) was explored linearly with Ke and by using a sigmoidal maturation factor driven by PMA, as previously described (20). Ultimately, none of these functions were incorporated into the final model.

Finally, we also explored the impact of renal function on the PK of teicoplanin. Before doing this, we inspected the relationship between renal function and age in all patients to ensure appropriate estimates of renal function were used in the model building process. GFR was estimated (eGFR) using the Haycock-Schwartz formula (k\*Height/ serum creatinine) (23). A value for k=0.33 was used for pre-term neonates and k=0.45 for term neonates and older children (k=0.41). The different values of k reflects the smaller percentage of muscle mass in pre-term *vs* term infants (16, 24). If height (or length) was not directly recorded, values from UK pediatric growth charts for age and gender were used. We also considered the use of the post natal age (PNA)/serum creatinine ratio as an alternative measure to eGFR to estimate renal function in relation to age in neonates and young infants.

The final structural took the following form:

$$\frac{dX\left(1\right)}{dt}=R\left(1\right)-\left(Kcp+\left(Ke0∙\left(\frac{wt}{70}\right)^{-0.25}\right)∙Renal\right)∙X\left(1\right)+\left[Kpc∙X\left(2\right)\right] \left(2a\right)$$

$$\frac{dX\left(2\right)}{dt}=Kcp∙X\left(1\right)-Kpc∙X\left(2\right) (2b)$$

With output equation Y(1)=X(1)/V, which described the time course of teicoplanin concentrations.

Where: Ke=(Ke0\*(wt/70)(-0.25))\*Renal (the exponent is -0.25 because Ke0\*(wt/70)-0.25 is algebraically equivalent to (Cl/V)\*(wt/70)0.75); V=(V0\*(wt/70)); where wt is the patient´s weight (kg). A cut-off age in the maturation of renal function was apparent when eGFR was plotted against age (Fig. 1H,I) with an inflection point at 3 months (0.25 years). Hence, renal function (“Renal”) for infants and children >3 months of age was described as the estimated glomerular filtration rate (eGFR) (mL/min/1.73 m2) to an estimated power function (pw). If age was < 0.25 years (i.e. 3 months) “Renal” was the post-natal age (PNA (years)), divided by the serum creatinine (µmol/L). Ke0 and V0 are the weight standardized parameters for the elimination rate constant and volume, respectively.

There were two sampling periods denoted by IOV=1 and IOV=2 for concentrations collected <96 hours and and ≥ 96 hours, respectively. For the first sampling period (i.e. IOV=1) Ke0=Ke01 and V0=V01. For the second sampling period (i.e. IOV=2), Ke0=Ke02 and V0=V02.

The fit of each exploratory model to the data was assessed using a combination of the following: (1) the log-likelihood value, (2) the Akaike information criterion (AIC) (3) the coefficients of determination (r2) from the linear regression of the observed-predicted plots before and after the Bayesian step, (4) minimization of bias and imprecisions of the observed-predicted plots; (5) the NPDE and 6) the distribution of the weighted residual errors. A model comparison was made using the above named diagnostics in order to choose the best final model.

**Building the teicoplanin dose optimisation software**

We incorporated the final population PK model into a teicoplanin multiple-model Bayesian adaptive dosing controller (the software “cartridge”). The controller is based on the concepts and software (BestDose) developed by the University of Southern California Laboratory for Applied Pharmacokinetics and Bioinformatics (LAPKB) (<http://www.lapk.org)> (26, 27). The teicoplanin cartridge included the structural final model equations relating input (dosing information) to output (plasma concentrations) and the discrete joint probability distribution of the values of the equation variables (PK parameters) in the population, consisting of a discrete number of support points and their associated probability (the Bayesian prior). The cartridge was implemented in BestDose version 0.2.4 for R, which used the cartridge and each patient´s weight, age, PNA, serum creatinine, eGFR and teicoplanin dosing- concentration data to find the least biased and most precise dosage regimen relative to a target concentration, as previously described (26).

**Simulations to demonstrate the utility of the dose optimization software**

To show the potential value of the dose optimization software as a clinical tool,the software was used to predict the required dosage by day 2 of therapy to achieve a pre-determined teicoplanin concentration (15 mg/L) from day 3 in two representative subjects selected from the study population chosen based on age: 1) a critically ill infant (5 months old-0.46 years old-, 6.3 kg, eGFR 63.84 ml/min/1.73m2) and 2) a critically ill older child (5.78 years old, 16.3 kg, eGFR 108.41 ml/min/1.73 m2). We used the past real concentration-time and dosing data from these two patients during the first dosing interval plus a 48h trough (n=4 observations) to predict the optimized dose and infusion time to achieve the desired target concentration safely (i.e avoiding peaks > 60 mg/L, regarded as potentially toxic levels (3)). A “past” data-file contained the observed concentrations for each patient. A “future” data-file contained the required timings of future dosages and target, an initial guess of the likely future dose(s) that would be required, as well as the infusion time was prepared. The same patients were also investigated with different simulated age-related average eGFR: 77 and 127 ml/min/1.73m2, respectively) to evaluate the impact of renal function in the patient´s PK profile (28).

The dose optimization software was tested by comparing the estimated predicted PK profile plot against the observations, as well as by the linear regression of the observed versus predicted concentrations for each individual patient. From the predicted concentrations based on the median individual Bayesian posterior parameter distribution, we calculated the bias, which is equal to the mean weighted predicted error (∑ wpe/N), with wpe = /predicted concentration – the actual concentration)/SD for each prediction/observation, and the % bias. We also computed the imprecision, which is the mean bias adjusted weighted squared error (∑ wspe/N-mwpe2), and its respective percentage for each patient and each experimental run. The weighted mean individual PK parameter values and an average 24h AUC estimated by the trapezoidal approximation to hourly predictions for each subject were also computed by the software.

Monte Carlo simulations were performed to assess the proportion of patients receiving fixed regimens with a Cmin (i.e. trough concentration) of 15-60 mg/L by day 3 of therapy and the proportion with potentially toxic concentrations (>60 mg/L). Four candidate regimens were examined: (1) 30 mg/kg x 3 LD every 12 h + 20 mg/kg q24 h; (2) 20 mg/kg x 3 LD q12h + 15 mg/kg q24 h; (3) 25 mg/kg x 3 LD q12 h + 10 mg/kg q24 h; and (4 ) 30 mg/kg x 2 LD q12 h+ 10 mg/kg q24 h. One-hundred concentration-time profiles were simulated for each regimen. The range of the covariates used in the simulations (i.e. weight, age and the renal function descriptor) were the same as the original population. The simulations were performed using Pmetrics.

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**Competing interests**

WWH has received research funding from Pfizer, Gilead, Astellas, AiCuris, Amplyx, Spero Therapeutics and F2G, and acted as a consultant and/or given talks for Pfizer, Basilea, Astellas, F2G, Nordic Pharma,  Medicines Company, Amplyx, Mayne Pharma, Spero Therapeutics, Auspherix, Cardeas and Pulmocide.

**REFERENCES**

1. **Ramos-Martin V**, **Paulus S**, **Siner S**, **Scott E**, **Padmore K**, **Newland P**, **Drew RJ**, **Felton TW**, **Docobo-Perez F**, **Pizer B**, **Pea F**, **Peak M**, **Turner M a.**, **Beresford MW**, **Hope WW**. 2014. Population Pharmacokinetics of Teicoplanin in Children. Antimicrob. Agents Chemother. **58**:6920–6927.

2. **Ramos-Martín V**, **Neely MN**, **McGowan P**, **Siner S**, **Padmore K**, **Peak M**, **Beresford MW**, **Turner MA**, **Paulus S**, **Hope WW**. 2016. Population pharmacokinetics and pharmacodynamics of teicoplanin in neonates: making better use of C-reactive protein to deliver individualized therapy. J. Antimicrob. Chemother. **71**: 3168-3178.

3. **BMJ Group, the Royal Pharmaceutical Society of Great Britain and RPL 2014.** 2015. British National Formulary for Children-Antibacterial drugs-Teicoplanin., 2015th–2016thed. BMJ Group, London.

4. **Pea F**, **Viale P**, **Candoni A**, **Pavan F**, **Pagani L**, **Damiani D**, **Casini M**, **Furlanut M**. 2004. Teicoplanin in Patients with Acute Leukaemia and Febrile Neutropenia. Clin. Pharmacokinet. **43**:405–415.

5. **Dufort G**, **Ventura C**, **Olivé T**, **Ortega JJ**. 1996. Teicoplanin pharmacokinetics in pediatric patients. Pediatr. Infect. Dis. J. **15**:494–8.

6. **Sánchez A**, **López-Herce J**, **Cueto E**, **Carrillo A**, **Moral R**. 1999. Teicoplanin pharmacokinetics in critically ill paediatric patients. J. Antimicrob. Chemother. **44**:407–409.

7. **Zhao W**, **Zhang D**, **Storme T**, **Baruchel A**, **Declèves X**, **Jacqz-Aigrain E**. 2015. Population pharmacokinetics and dosing optimization of teicoplanin in children with malignant haematological disease. Br. J. Clin. Pharmacol. **80**:1197–1207.

8. **Yamada T**, **Nonaka T**, **Yano T**, **Kubota T**, **Egashira N**, **Kawashiri T**, **Oishi R**. 2012. Simplified dosing regimens of teicoplanin for patient groups stratified by renal function and weight using Monte Carlo simulation. Int. J. Antimicrob. Agents **40**:344–348.

9. **Byrne CJ**, **Egan S**, **Fennell JP**, **O’Byrne P**, **Enright H**, **Deasy E**, **Ryder SA**, **D’Arcy DM**, **McHugh J**. 2015. Teicoplanin use in adult patients with haematological malignancy: Exploring relationships between dose, trough concentrations, efficacy and nephrotoxicity. Int. J. Antimicrob. Agents **46**:406–412.

10. **Tobin CM**, **Lovering AM**, **Sweeney E**, **MacGowan AP**. 2010. Analyses of teicoplanin concentrations from 1994 to 2006 from a UK assay service. J. Antimicrob. Chemother. **65**:2155–2157.

11. **The Electronic Medicines Compendium**. 2014. Targocid 200mg - Summary of Product Characteristics (SPC) - (eMC).

12. **Ueda T**, **Takesue Y**, **Nakajima K**, **Ichki K**, **Wada Y**, **Tsuchida T**, **Takahashi Y**, **Ishihara M**, **Tatsumi S**, **Kimura T**, **Ikeuchi H**, **Uchino M**. 2012. Evaluation of teicoplanin dosing designs to achieve a new target trough concentration. J. Infect. Chemother. **18**:296–302.

13. **Harding I**, **MacGowan a P**, **White LO**, **Darley ES**, **Reed V**. 2000. Teicoplanin therapy for Staphylococcus aureus septicaemia: relationship between pre-dose serum concentrations and outcome. J. Antimicrob. Chemother. **45**:835–41.

14. **Kanazawa N**, **Matsumoto K**, **Fukamizu T**, **Shigemi A**, **Yaji K**, **Shimodozono Y**, **Takeda Y**, **Yamada K**, **Ikawa K**, **Morikawa N**. 2011. An initial dosing method for teicoplanin based on the area under the serum concentration time curve required for MRSA eradication. J. Infect. Chemother. **17**:297–300.

15. **Hagihara M**, **Umemura T**, **Kimura M**, **Mori T**, **Hasegawa T**, **Mikamo H**. 2012. Exploration of optimal teicoplanin dosage based on pharmacokinetic parameters for the treatment of intensive care unit patients infected with methicillin-resistant Staphylococcus aureus. J. Infect. Chemother. **18**:10–16.

16. **Schwartz GJ**, **Feld LG**, **Langford DJ**. 1984. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J. Pediatr. **104**:849–54.

17. **Neely MN**, **van Guilder MG**, **Yamada WM**, **Schumitzky A**, **Jelliffe RW**. 2012. Accurate Detection of Outliers and Subpopulations With Pmetrics, a Nonparametric and Parametric Pharmacometric Modeling and Simulation Package for R. Ther. Drug Monit. **34**:467–476.

18. **Anderson BJ**, **Holford NHG**. 2008. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu. Rev. Pharmacol. Toxicol. **48**:303–332.

19. **Germovsek E**, **Barker C**, **Sharland M**, **Standing JF**. 2016. Scaling Clearance in Paediatric Pharmacokinetics: all models are wrong, which are useful? Br. J. Clin. Pharmacol. 1–14.

20. **Holford N**, **Heo Y-A**, **Anderson B**. 2013. A Pharmacokinetic Standard for Babies and Adults. J. Pharm. Sci. **102**:2941–2952.

21. **West GB**, **Brown JH**, **Enquist BJ**. 1999. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science **284**:1677–9.

22. **Rhodin MM**, **Anderson BJ**, **Peters a. M**, **Coulthard MG**, **Wilkins B**, **Cole M**, **Chatelut E**, **Grubb A**, **Veal GJ**, **Keir MJ**, **Holford NHG**. 2009. Human renal function maturation: A quantitative description using weight and postmenstrual age. Pediatr. Nephrol. **24**:67–76.

23. **Martini S**, **Prévot A**, **Mosig D**, **Werner D**, **van Melle G**, **Guignard JP**. 2003. Glomerular filtration rate: measure creatinine and height rather than cystatin C! Acta Paediatr. **92**:1052–7.

24. **Brion LP**, **Fleischman AR**, **McCarton C**, **Schwartz GJ**. 1986. A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: noninvasive assessment of body composition and growth. J. Pediatr. **109**:698–707.

25. **Karlsson MO**, **Sheiner LB**. 1993. The importance of modeling interoccasion variability in population pharmacokinetic analyses. J. Pharmacokinet. Biopharm. **21**:735–50.

26. **Hope WW**, **Van Guilder M**, **Donnelly JP**, **Blijlevens NM a**, **Brüggemann RJM**, **Jelliffe RW**, **Neely MN**. 2013. Software for dosage individualization of voriconazole for immunocompromised patients. Antimicrob. Agents Chemother. **57**:1888–1894.

27. **Neely M**, **Margol A**, **Fu X**, **Van Guilder M**, **Bayard D**, **Schumitzky A**, **Orbach R**, **Liu S**, **Louie S**, **Hope W**. 2015. Achieving target voriconazole concentrations more accurately in children and adolescents. Antimicrob. Agents Chemother. **59**:3090–3097.

28. **Heilbron DC**, **Holliday MA**, **al-Dahwi A**, **Kogan BA**. 1991. Expressing glomerular filtration rate in children. Pediatr. Nephrol. **5**:5–11.

29. **Drusano GL**. 2004. Antimicrobial pharmacodynamics: critical interactions of “bug and drug.” Nat. Rev Microb.

30. **Matthews PC**, **Chue AL**, **Wyllie D**, **Barnett A**, **Isinkaye T**, **Jefferies L**, **Lovering A**, **Scarborough M**. 2014. Increased teicoplanin doses are associated with improved serum levels but not drug toxicity. J. Infect. **68**:43–49.

31. **Yamada T**, **Kubota T**, **Yonezawa M**, **Nishio H**, **Kanno S**, **Yano T**, **Kobayashi D**, **Egashira N**, **Takada H**, **Hara T**, **Masuda S**. 2017. Evaluation of Teicoplanin Trough Values After the Recommended Loading Dose in Children With Associated Safety Analysis. Pediatr. Infect. Dis. J. **36**:398–400.

32. **Yamada T**, **Kubota T**, **Nakamura M**, **Ochiai M**, **Yonezawa M**, **Yano T**, **Kawashiri T**, **Egashira N**, **Hara T**, **Masuda S**. 2014. Evaluation of teicoplanin concentrations and safety analysis in neonates. Int. J. Antimicrob. Agents **44**:458–62.

33. **Strenger V**, **Hofer N**, **Rodl S**, **Honigl M**, **Raggam R**, **Seidel MG**, **Dornbusch HJ**, **Sperl D**, **Lackner H**, **Schwinger W**, **Sovinz P**, **Benesch M**, **Urlesberger B**, **Urban C**. 2013. Age- and gender-related differences in teicoplanin levels in paediatric patients. J. Antimicrob. Chemother. **68**:2318–23.

34. **Drusano GL**. 2004. Antimicrobial pharmacodynamics: critical interactions of “bug and drug.” Nat. Rev. Microbiol. **2**:289–300.

35. **Chang H-J**, **Hsu P-C**, **Yang C-C**, **Siu L-K**, **Kuo A-J**, **Chia J-H**, **Wu T-L**, **Huang C-T**, **Lee M-H**. 2012. Influence of teicoplanin MICs on treatment outcomes among patients with teicoplanin-treated methicillin-resistant Staphylococcus aureus bacteraemia: a hospital-based retrospective study. J. Antimicrob. Chemother. **67**:736–741.

36. **Yamada T**, **Nonaka T**, **Yano T**, **Kubota T**, **Egashira N**, **Kawashiri T**, **Oishi R**. 2012. Simplified dosing regimens of teicoplanin for patient groups stratified by renal function and weight using Monte Carlo simulation. Int. J. Antimicrob. Agents **40**:344–348.

37. **Niwa T**, **Imanishi Y**, **Ohmori T**, **Matsuura K**, **Murakami N**, **Itoh Y**. 2010. Significance of individual adjustment of initial loading dosage of teicoplanin based on population pharmacokinetics. Int. J. Antimicrob. Agents **35**:507–510.

38. **Macdonald I**, **Staatz CE**, **Jelliffe RW**, **Thomson AH**. 2008. Evaluation and Comparison of Simple Multiple Model, Richer Data Multiple Model, and Sequential Interacting Multiple Model (IMM) Bayesian Analyses of Gentamicin and Vancomycin Data Collected From Patients Undergoing Cardiothoracic Surgery. Ther. Drug Monit. **30**:67–74.

39. **Blot SI**, **Pea F**, **Lipman J**. 2014. The effect of pathophysiology on pharmacokinetics in the critically ill patient - Concepts appraised by the example of antimicrobial agents. Adv. Drug Deliv. Rev. **77**:3–11.

40. **Yamada Y**, **Schaiquevich P**, **& Neely M**. 2015. AUC-targeted vancomycin dosing in term and pre-term neonates. 4th Int. Congr. Ther. Drug Monit. Toxicol. Rotterdam, NL, Oct. 11-15, 2015, Abstr. 347.

41. **Neely M**, **Floyd R**. 2015. Schwartz Creatinine Clearance is Not the Best Description of Infant Gentamicin Elimination., p. 1–60. *In* Clinical Pharmacology in Drug Development.

**Tables/Figures**

Table 1. Demographics and clinical characteristics of patients.

|  |  |
| --- | --- |
| Demographic / clinic characteristic | Median (range)  |
|  | Children >1 month | Neonates | Total |
| n. of patients  | 39/39 | 18/18 | 57 |
| Mean observations/patient | 7.6 | 5.3 | 6.9 |
| Sex (male:female) | 21:18 | 12:6 | 33:24 |
| Weight (kg) | 14.8 (3-62.2) | 2.04 (0.69-5.08) | 7.5 (0.69-62.2) |
| Height (cm) | 97.9 (45-170)\* | 48 (36-52)\*\* | 72 (36-170) \*\*\* |
| Age (years) | 3.3 (0.12-15.8) | 0.05 (0.01-0.19) | 0.88 (0.01-15.82) |
| PMA (weeks) | NA | 37 (26-44) | NA |
| PNA (days) | 1204.5 (43.8-5774.3) | 17 (4-69) | 321.2 (4-5774.3) |
| eGFR (mL/min/1.73 m2) | 78.94 (6.43-160.3) | 42.8 (5.4-95.2) | 62.06 (5.4-160.3) |
| Serum Creatinine (μmol/L)  | 41 (27-308) | 44.5 (21-265) | 41 (21-308) |

PMA=post-menstrual age; PNA=post-natal age; eGFR= estimated glomerular filtration rate;\*n=30 provided data; \*\*=UK median length value for gender and age; \*\*\*n=30 provided data for height, the remaining data were obtained from the UK pediatric growth charts as the median value for height corresponding to the gender and age; NA=not-applicable.

Table 2. Model comparison and model diagnostics with and without covariates for models.

|  |  |  |
| --- | --- | --- |
| Model | Standard(without covariates) | Final model(allometric without age) |
| N. of variables | 4 | 7 |
| Log-likelihood value | 2523 | 2360 |
| AIC | 2533 | 2376 |
| Pop/post Bias | 3.8/-0.02 | 1.1/-0.15 |
| Pop/post Imprecision | 72.2/1.5 | 12.3/0.9 |
| Pop r2 | 0.12 | 0.9 |
| Post r2 | 0.8 | 0.92 |

AIC:Akaike information criterion; Pop/post Bias: population and posterior mean weighted error respectively; Pop/post Imprecision: population and posterior mean bias-adjusted weighted squared error; Pop/Post r2 = coefficient of determination for the linear regression of the observed *vs* predicted plots for the population and the posterior fits, respectively.

Table 3. Population PK parameter estimates from the final model.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | Ke01 (h-1) | Ke02 (h-1) | V01 (L) | V02 (L) | Kcp (h-1) | Kpc (h-1) | pw |
| Mean | 0.038 | 0.036 | 22.636 | 22.472 | 0.490 | 0.214 | 0.125 |
| Median | 0.03 | 0.025 | 19.52 | 22.7 | 0.23 | 0.12 | 0.07 |
| SD | 0.04 | 0.03 | 14.23 | 7.95 | 0.48 | 0.27 | 0.15 |
| Ke= Weight normalized rate constant of elimination= Ke0\*(wt/70)-0.25 \*Renal; Renal=eGFRpw or PNA/creatinine if < 0.25 years old; V= Weight normalized volume of the central compartment=V0\*(wt/70); Kcp and Kpc are the first-order intercompartmental rate constants; pw=power function. The suffix 01 and 02 denote the occasion. Ke0=Ke01 and V0=V01 for time < 96 hours; otherwise, Ke0=Ke02 and V0=V02.  |

Table 4. Summary of the individual prediction diagnostics from the dosing optimization software for the two patients(using past-real data in order to obtain a target of 15 mg/L from day 3 of therapy).

|  |  |  |
| --- | --- | --- |
| **Subject** | **1\_Infant** | **2\_Child** |
| **r2** | 1 | 0.97 |
| **Bias** | -0.42 | 0.4 |
| **% Bias** | -2.54 | 8.46 |
| **Imprecision** | 0.3 | 1.64 |
| **% Imprecision** | 0.05 | 1.54 |
| **Median (range) of average 24h AUC (mg\*h/L) along the treatment course** | 493.8 (355.8-574) | 368.1 (318.9-388.4) |
| r2= coefficient of determination of the linear regression of the predicted *vs* observed concentrations; Bias=mean weighted predicted-observed error; % Bias= 100\* [mean weighted predicted-observed error/observed]; Imprecision= bias-adjusted mean squared error; %Imprecision= 100\*[bias-adjusted mean squared error/observed]. |

Figure 1. Relationships between covariates and the Bayesian posterior estimates for clearance (Cl) and volume (V) obtained from the base model.

Panel A) linear and B) log10-log10 relationship between Cl and weight (wt), respectively; C) linear and D) log10-log10 relationship between V and wt, respectively; E) Linear relationship between Cl and age (years), F) V and age (years); G) Cl and eGFR, H) eGFR and age (years); I) eGFR versus age <12 months, which shows two distinct periods of change in eGFR with age (i.e. <0.25 and ≥0.25 years . J) The relationship between eGFR and PMA (weeks), which is less informative than age (years) for the young infants. The continuous line shows the linear regression line and the dashed line shows the LOWESS (locally weighted scatterplot smoothing) or local regression line, which highlights a Cl versus eGFR relationship compatible with a power function, where GFR is the independent variable raised to a constant (pw) in G.

Figure 2. Observed-predicted concentrations scatter plots for the final PK model before (population) (top) and after (individual posteriors) the Bayesian step (bottom) using the median parameter values.

Figure 3. Normalized distribution predicted error (NPDE). A: Q-Q plot of the distribution of the NPDE versus the theoretical N (0,1) distribution; B: a histogram of the distribution of the NPDE with the density of the standard Gaussian distribution overlaid. The results suggest an acceptable fit of the final model to the data.

Figure 4. Weighted residual error (predicted-observations) distributions.

Panel A: weighted residuals vs. predictions; B: weighted residuals vs. time; and C: histogram of residuals with a superimposed normal curve.

Figure 5. Representative plots from an infant patient receiving teicoplanin for a pre-dose target of 15 mg/L from day 3 of therapy following A) bolus administration; B) 12h infusion. [A) Bolus administration: Dose required by day 2: 143.4 mg (22.3 mg/kg); day 3: 97.22 mg (15.4 mg/kg); day 4: 87.74 (13.9 mg/kg); B) 12h infusion: Dose required by day 2: 112.02 mg (17.8 mg/kg); day 3: 81.72 mg (12.97 mg/kg); day 4: 74.64 mg (11.8 mg/kg)].

Figure 6. Representative plots from an older child patient receiving teicoplanin for a pre-dose target of 15 mg/L from day 3 of therapy following A) bolus administration; B) 12h infusion.[A) Bolus administration: Dose required by day 2: 300.62 mg (18.4 mg/kg); day 3: 78.64 mg (4.8 mg/kg); day 4: 61.75 mg (3.8 mg/kg); B) 12h infusion: Dose required by day 2: 276.5 mg (17 mg/kg); day 3: 83.71 mg (5.1 mg/kg) and day 4: 62.38 mg (3.8 mg/kg)].