Title: Revising paediatric vancomycin dosing accounting for nephrotoxicity in a pharmacokinetic-pharmacodynamic model

Running title: Paediatric vancomycin dose revision

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Abstract

This study aimed to suggest an initial paediatric vancomycin dose regimen through population pharmacokinetic-pharmacodynamic modelling. A population pharmacokinetic approach was used to analyse vancomycin concentration-time data from a large paediatric cohort. Pharmacokinetic target attainment for patients with blood stream isolates was compared with clinical outcome using logistic regression and classification and regression trees. Change in serum creatinine during treatment was used as an indicator of acute nephrotoxicity. Probability of acute kidney injury (50% increase from baseline) or kidney failure (75% increase from baseline) was evaluated using logistic regression. An initial dosing regimen was derived, personalised by age, weight and serum creatinine using stochastic simulations. Data from 785 hospitalised paediatric patients (1 day to 21 years) with suspected Gram-positive infections were collected. Estimated (RSE) typical CL, V1, Q and V2 were (standardised to 70 kg) 4.84 (2.38) L/h, 39.9 (8.15) L, 3.85 (17.3) L/h, and 37.8 (10.2) L, respectively. Whilst cumulative vancomycin exposure correlated positively with the development of nephrotoxicity (713 patients) no clear relationship between vancomycin AUC and efficacy was found (102 patients). Predicted probability of acute kidney injury and kidney failure with the optimised dosing regimen at day 5 was 10-15% and 5-10 %, increasing by approximately 50% on day 7 and roughly 100% on day 10 across all age groups. This study presents the first data driven paediatric dose selection to-date accounting for nephrotoxicity and indicated that cumulative vancomycin exposure best described risk of acute kidney injury and acute kidney failure.

Key words: vancomycin; paediatrics; dose optimisation; pharmacokinetics; pharmacodynamics

Introduction

Vancomycin is a glycopeptide antibiotic effective against Gram-positive bacteria and plays a crucial role in the treatment of serious and resistant infections, in both adults and children (1). Previous studies have reported vancomycin pharmacokinetics (PK) in children, and proposed model based dose optimisations (2-11). Dose selection in these studies adopted a 24 hour steady state Area Under the plasma concentration-time Curve (AUC) (12) over MIC ratio greater than 400 mg.h/L (AUC/MIC>400). However, this PKPD endpoint was adopted from adults without further evaluation in children and without taking adverse effects such as nephrotoxicity into account. The overall aim of this study was to revisit the paediatric initial vancomycin dosing regimen and with this in mind there were four main aims.

The first aim was to study vancomycin population PK in a large cohort. Several previous studies have sought to describe paediatric vancomycin PK reporting clearance (median [range] 4.52 [1.00-5.57] l/hr) and steady-state volume of distribution (median [range] 37.8 [31.0-119] l) (2-8). Most of these studies used small sample sizes or focussed on paediatric sub populations such as neonates, meaning parameter comparisons between studies is challenging, not least because important covariates such as age and weight are often not parameterised in a standard way (13). Moreover, vancomycin distribution often requires two and in some cases three disposition compartments (14), although most paediatric vancomycin PK papers have previously reported a one-compartment model (2-7). Vancomycin is mainly bound to albumin in the blood (15) with protein binding ranging between 50% and 55%, resulting in free vancomycin exposure at only half the equivalent of total exposure (14).

The second aim was to identify the target concentration for efficacy in paediatrics. Vancomycin AUC/MIC was found to be more predictive of efficacy than time above MIC in with methicillin-resistant *Staphylococcus aureus* sepsis or with a methicillin-resistant *Staphylococcus aureus* infection of the lower respiratory tract (16, 17). Adult patients with a target AUC/MIC value of ≥ 400 appeared to have a lower risk of treatment failure (16-18) and as free antibiotic concentrations drive the antibacterial effects AUC_{free}/MIC ≥ 200 mg.h/L has consequently been reported as the target efficacy threshold (14).

The third aim was to identify predictors of nephrotoxicity. Nephrotoxicity indices have been defined for paediatric patients (19), and risk factors for nephrotoxicity (20) such as vancomycin loading dose, , duration of vancomycin

65 therapy, concomitant therapy and demographic features have been defined in adult patients (21). Vancomycin
66 trough levels and vancomycin AUC have been defined in both adults and children (22) resulting in a toxicity
67 threshold AUC of 700 mg.h/L for the adult population and 800 mg.h/L for the paediatric population, rendering a
68 therapeutic window of 400 to 700-800 mg.h/L (22, 23).

69 The fourth aim was to further refine initial dosing recommendations, taking into account the findings from the
70 modelling described above. Therapeutic Drug Monitoring (TDM), is often used to ensure that vancomycin
71 concentrations fall within the therapeutic window (2) but optimising the starting dose may limit the need for dose
72 adjustments. Traditionally vancomycin trough concentrations have been preferred for TDM although Bayesian
73 forecasting is now more readily available so AUC is becoming the preferred endpoint (3). It is therefore crucial that
74 efficacy and toxicity thresholds are adequately identified in paediatric patients.

Results

Population pharmacokinetics

A total of 616 patients contributing two or more vancomycin plasma samples, age, bodyweight, creatinine and dosing (intravenous infusion over one hour) data were used to build the PK model and labelled "training data" (Table 1). Data from 169 patients contributing only one vancomycin plasma sample, age, bodyweight, creatinine, and dosing information (intravenous infusion over one hour) data were used for external validation of the population PK model and labelled "test data" (Table 1). Patients were only included if matching records in the TDM system were taken no later than 48 hours after a dose. Sample times reported before 1.5 hours (during or immediately after the infusion) after a dose were considered reporting errors (likely time of sample being left for the porter recorded rather than actual sampling time). These samples were subsequently considered trough values. This yielded vancomycin plasma concentration samples between 1.5 and 48 hours after dose.

A two-compartment disposition model performed substantially better ($p < 0.001$) when compared to a one-compartment model. Inter-individual variability on clearance (CL) and central volume (V_C) displayed reasonably high shrinkage (24) (32% and 41%, respectively) but epsilon-shrinkage was low at 8%. Bodyweight as a continuous covariate on volume and clearance using allometric size scaling, a sigmoidal post-menstrual age maturation function and age corrected creatinine as a continuous covariate on clearance were all included *a priori*. A bodyweight power of 0.632 on elimination clearance provided a better fit to the data compared to a power of 0.75 (ΔOFV=-29.3). Backward exclusion of bodyweight as a continuous covariate on volume and clearance parameters ($p < 0.001$), post-menstrual age as a maturation function on CL ($p < 0.001$) and creatinine on elimination CL ($p < 0.001$) resulted in significant worsening of the model fit and so were retained (Fig. S1).

The model adequately described the vancomycin concentration-time data with a Mean Prediction Error on the test data of 0.96 mg/l (Fig. 1, Table 2, Fig. S2, Fig. S3). The final model was re-estimated on a dataset where the corrected time samples (originally reported before 1.5 hours) were omitted as sensitivity analysis, and this yielded similar parameter estimates: CL (-1.03%), PMA_{50} (-5.78%), Hill (36.9%) and Power Creatinine (-2.31%) which was important as dose optimisations focus on AUC.

Efficacy

Among the included patients 102 had Gram positive bloodstream isolates for which MIC was measured (Table 1). *Coagulase Negative Staphylococcus* infections, which are largely as a result of line infections (25), or contamination, accounted for 80, rendering a limited number of true Gram-positive blood stream infections (Table 1).

In patients with a blood stream organism, treatment failure was defined if at least one of the following criteria was met: 1.) deceased within 30 days of vancomycin treatment initiation, 2.) recurrent infection between 48 hours and 60 days following vancomycin treatment discontinuation, and 3.) microbiologically confirmed growth 7 days after the initiation of therapy but before treatment completion (16). Treatment outcome was classified as successful if none of the above criteria were met. Neither trough concentration/MIC nor AUC/MIC correlated with probability of treatment failure in a multivariate generalised logistic regression model or in a Classification and Regression Tree analysis (Table 3, Fig. S4).

Nephrotoxicity

A total of 713 patients, contributing PK, baseline demographic, nephrotoxicity data and concomitant medication data were included for the characterisation of predictors for nephrotoxicity (Table 1). Urine output data were not available and hence nephrotoxicity severity was defined based on the change in creatinine criteria in the Paediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) score (19). The two outcome classes acute kidney injury and acute kidney failure corresponded to a 50% and 75% increase in plasma creatinine compared to baseline values, respectively.

The multivariable logistic regression model (Table 4), demonstrated an increase in the probability of acute kidney injury or kidney failure with increasing cumulative Area Under the plasma concentration-time Curve up to 8 hours post last dose (AUC_{CUM}) (increase of estimate±standard error 1.17±0.178 per unit increase in $\log(AUC_{CUM})$, $p<0.001$). Similarly an increase in the probability of acute kidney failure with increasing AUC_{CUM} (increase of 1.32±0.237 per unit increase in $\log(AUC_{CUM})$, $p<0.001$) and concomitant therapy with ciclosporin (increase of 0.739±0.358 per unit increase in creatinine, $p<0.05$) was observed. Baseline plasma creatinine displayed a non-significant trend ($p < .01$) of increased probability of acute kidney injury and acute kidney failure (Table 4). Approximately half of the patients had their dose changed during the first week of the treatment, with most of the modifications being dose increases

(Table 1). Consequently, unlike AUC_{CUM}, 24 hour AUC did not come out as a significant predictor for nephrotoxicity in the multivariable logistic regression (Table 4).

The predictive performance of the multivariable logistic regression models for acute kidney injury and acute kidney failure, with only statistically significant predictors included, was further evaluated. The models were trained on 70% of the patients, which were selected at random. The models were subsequently tested on the other 30% of the patients and area under the ROC curve was used as diagnostic tool. If the area under the ROC curve was ≥ 0.6 the logistic regression model was refitted on the full dataset (26). AUC_{CUM} was included *a priori* in the predictive logistic regression models for acute renal injury (Table S1) with ciclosporin concomitant therapy on top for acute renal failure (Table S2) and displayed an area under the ROC curve of 0.640 and 0.643, respectively. The predictive logistic regression model for acute renal injury on full data had an area under the ROC curve of 0.676 (Table S3) and the predictive logistic regression model for acute renal failure on full data had an area under the ROC curve of 0.685 (Table S4).

Dose optimisation

Current paediatric initial vancomycin dosing regimens, 15 mg/kg 8 hourly for children 0-1 month, 10-15 mg/kg 6 hourly for children 1 month – 11 years and 15-20 mg/kg 8-12 hourly for children 12 years and above (1), were revisited using the developed population pharmacokinetic model and 2,000 stochastic simulations. As the efficacy analysis in this study did not yield target levels in the paediatric patient population, a vancomycin AUC target attainment ≥ 400 was adopted from an adults (16-18). Most of patients achieved target attainment when vancomycin after the current standard dosing regimens were stratified by bodyweight although a clear positive correlation with increased plasma creatinine was apparent, hence patients in the lower creatinine band displayed a lower vancomycin AUC (Fig. 2). Further stratification of the vancomycin dosing regimen by baseline plasma creatinine yielded target attainment for most of the patients, both when stratified by bodyweight and baseline plasma creatinine (Table 5; Fig. 2). Estimated Glomerular Filtration Rate (eGFR) for each baseline plasma creatinine and age group, using the Schwartz formula (27), indicated that the proposed dosing regimen remained untested for paediatric patients with kidney failure, with all eGFR estimates above 20 mL/min (Table 5).

Subsequently, correlations between vancomycin AUC_{CUM} and probability of acute kidney injury or acute kidney failure, with the optimised initial vancomycin dosing regimen, was studied using the predictive multivariable logistic

regression models for acute kidney injury and acute kidney failure and 500 stochastic simulations. The predicted probability of acute kidney injury and kidney failure at day 5 for children 0-1 month was 13.3 [4.95-27.3] % and 5.55 [2.00-12.3]%, increasing to 19.4 [7.88-37.2]% and 8.36 [3.21-18.0]% on day 7 and 27.7 [12.4-48.5%] and 12.6 [5.13-25.8]% on day 10 (Fig. 3). A similar probability of acute kidney injury and kidney failure was predicted at day 5 for children 1 month –2 years at 14.2 [2.29-30.2] % and 6.78 [2.27-19.1]%, increasing to 20.4 [8.20-40.2] % and 10.0 [3.54-26.7]% on day 7 and to 28.7 [12.6-51.5] % and 14.8 [5.52-36.2] % on day 10 (Fig. 3). Also for children 2-11 years predicted probability of acute kidney injury and kidney failure was similar with 12.9 [4.69-28.0] % and 6.10 [2.02-17.9]% after 5 days of treatment, increasing to 18.7 [7.33-37.8]% and 9.07 [3.16-25.2] % on day 7 and 26.6 [11.4-49.2] % and 13.5 [4.95-34.5]% on day 10 (Fig. 3). Day 5 predictions for probability of acute kidney injury and acute kidney failure in the eldest children of 12 years and above were in a similar range at 14.6 [5.24-31.1] % and 6.33 [2.15-15.8]%, increasing to 21.1 [8.29-41.6] % and 9.47 [3.42-22.6] % on day 7 and 29.8 [12.9-53.1] % and 14.1 [5.44-31.6] % on day 10 (Fig. 3). For comparison, approximately 6.38% and 3.55% of the patients in the data had observed acute kidney injury or acute renal failure at day 5 and approximately 13.0% and 4.63% of the patient in the data had observed acute kidney injury and acute renal failure at day 10.

Discussion

This study provides a comprehensive evaluation of vancomycin PKPD in a paediatric population with to our knowledge the largest sample size to date. Our major finding is that AUC_{CUM} is associated with risk of nephrotoxicity. The optimised dosing regimen resulted in a predicted 10-15% and 5-10 % probability of acute kidney injury and kidney failure at day 5, increasing by approximately 50% on day 7 and roughly 100% on day 10 across all age groups (Fig. 3).

Population pharmacokinetics

In general, vancomycin population PK characteristics were in agreement with those previously published literature. For example, creatinine levels, relative to the mean age adjusted creatinine levels for the individual patient, displayed a negative exponential correlation with vancomycin elimination clearance, similar to other renally cleared drugs such as gentamicin (28). Unlike in most other paediatric vancomycin PK studies, where mostly a one-compartment disposition model was identified, a two-compartment disposition model was identified in this paediatric patient population due to 1 hour post infusion sampling taken in a part of our dataset (Fig. 1, Table 2, Fig. S2, Fig. S3).

A 0.632 bodyweight power on CL was evaluated in addition to the conventional 0.75 power as vancomycin is eliminated renally. The 0.632 power provided a superior model fit (ΔOFV=-29.3) over the 0.75 power which could be explained by renal maturation and therefore drug elimination (29). The power function on inter-compartmental clearance was fixed to 0.75 and to 1 for distribution volumes based on tissue blood flow and proportional growth between body size, respectively.

Efficacy

Neither vancomycin trough concentrations or AUC correlated with treatment failure in this paediatric patient population with a variety of blood stream infections (Table 3, Fig. S3) although several studies in adults with methicillin resistant *Staphylococcus aureus* blood stream infections concluded that the PKPD endpoint of AUC/MIC ≥ 400 mg.h/L was clinically relevant (16-18). A plausible explanation for this discrepancy is the large number of *Coagulase Negative Staphylococcus* infections (Table 1). *Coagulase Negative Staphylococcus* infections are likely to be a result of line infections (25) or contamination and cause limited morbidity. For the remaining 22 Gram-positive

blood stream infections there was insufficient statistical power to refute AUC target attainment ≥ 400 mg.h/L (16-18). The fact that we only had 22 in 785 patients with confirmed Gram-positive isolates on blood culture highlights the lack of infections at the study centre, possibly due to good infection control procedures, and shows how difficult running prospective paediatric antimicrobial clinical trials is when so few patients have identifiable infections.

Nephrotoxicity

Validation of renal toxicity biomarkers in children is lacking which directly stipulates the limitation of the nephrotoxic results presented in this investigation. The most commonly studied renal biomarkers have limited use and validity, e.g. urinary and serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) – this biomarker rises with creatinine but also with white cell count, procalcitonin and C-Reactive Protein so its use is limited in the setting of infection/acute inflammation. “Normal ranges” are also lacking e.g. Smertka et al found similar NGAL levels in babies with and without renal impairment (30).

Acute kidney injury and acute kidney failure corresponded to a 50% and 75% increase in plasma creatinine compared to baseline values in this study. Even though such increases in creatinine as a percentage of baseline levels may be high, creatinine level may be still in range further complicating the interpretation of the biomarker.

Nonetheless, duration of treatment turned out to be an important risk factor for renal disease, underwritten by a significant correlation between acute kidney injury or acute kidney failure and AUC_{CUM} (Table 4). The predictive performance of AUC_{CUM} aligns with the previously described delay in nephrotoxicity, which has been found to occur late in the first week of vancomycin therapy (31). Creatinine levels should therefore be monitored carefully in patients on vancomycin to facilitate early detection and intervention. Moreover, vancomycin treatment for more than 7 days should be carefully considered and weighted against the probability of acute kidney injury and acute kidney failure. It should be noted here that our simulations show the probability of nephrotoxicity without dose adjustment.

Whilst recently *Zasowski et al* suggested a toxicity threshold AUC of 700 mg x h/L, and thereby a therapeutic window of 400-700 mg.h/L (23) no significant correlation between acute kidney injury or acute kidney failure and AUC could be identified in our data (Table 4). The fact that almost half of the patients in this study had their doses changed during the first seven days of treatment, with the majority of the dose changes being dose increases (Table 1) may

be responsible. This may highlight that the use of 24 hour AUC as predictive variable for kidney injury and kidney failure is inappropriate in a clinical setting.

Dose optimisation

Vancomycin dosing recommendations have changed since the data collection period (32) with 15 mg/kg 8 hourly for children 0-1 month, 10-15 mg/kg 6 hourly for children 1 month – 11 years and 15-20 mg/kg 8-12 hourly for children 12 years and above as most recent dosing recommendations (1). Using currently recommended vancomycin dosing we stratified the mg per kg doses by baseline creatinine level (Table 5). Even after stratifying mg per kg dose by age and creatinine, it is clear that TDM will continue to be required since target attainment is low in some categories (Fig. 2). Also from a nephrotoxicity perspective TDM continues to be required, hence vancomycin TDM is focused on avoiding renal failure. At day 5 approximately 6.38% and 3.55% of the patients had observed acute kidney injury or acute renal failure and at day 10, approximately 13.0% and 4.63% of the patient had observed acute kidney injury and acute renal failure. This was substantially lower compared to simulations in Figure 3 highlighting the impact of TDM as the virtual patient population remained on the initial dosing regimen for the entire duration of the simulated treatment whereas the real observed patients underwent TDM guided dose reduction.

Although trough levels of 10-15 mg/l and 15-20 mg/l have been recommended (32, 33), we chose to target AUC > 400 hr.mg/l, a target that is now becoming a preferred PK endpoint with increasing availability of Bayesian TDM software. It should be noted that this target has not been evaluated in children, and our attempt at modelling efficacy was hampered by the limited number of patients in our study having non-coagulase negative Staphylococcus Gram positive blood stream infections.

In summary, although we present one of the largest paediatric datasets, our study did have some limitations. A relatively high between patient variability and shrinkage on elimination clearance (Table 2) emphasises the need for caution with regards to the interpretation of dose optimisation results and the need for a confirmatory, prospective clinical study. Our centre does not have a maternity unit and hence only a small fraction of our patients were neonates (Table 1), most of whom were admitted for surgery. Moreover, eGFR might be most relevant for vancomycin dosing personalisation although patients heights were not routinely recorded making individual level eGFR calculations (27) impossible. Instead, baseline plasma creatinine band was used to further stratify initial paediatric vancomycin dosing and indicative eGFR values were reported for each age and baseline creatinine group

(Table 5). The use of eGFR for personalised initial paediatric vancomycin dosing has to be further evaluated in prospective clinical studies. Furthermore, whilst our PK model could potentially be used for extrapolation to the pre-term neonatal population, given our similar maturation parameters (Table 2) to previous studies (28), in-depth evaluation of PD and nephrotoxicity in neonatal patients is required.

The current paediatric dosing regimen for vancomycin adequately accounts for changes in bodyweight although variability could be substantially reduced by taking creatinine levels into account. Combining creatinine, age and bodyweight can reduce the risk of toxicity by reduced variability in target attainment, although TDM continues to be required in order to ensure vancomycin exposure is adequate. This work indicates that paediatric target attainment from an efficacy perspective tends to be adequately reached although monitoring of kidney function remains important in view of the increased probability of acute kidney injury or acute kidney failure with prolonged vancomycin treatment.

Materials and methods

Experimental design

This study was a retrospective analysis of paediatric patients treated with vancomycin at a large tertiary paediatric hospital (Great Ormond Street Hospital) in London, United Kingdom. De-identified data were extracted from electronic health records with ethical approval without the requirement for written informed consent provided (17/LO/0008). Patients included in the study were hospitalised between 2010 and 2016 and contributed vancomycin drug level, dosing (intravenous infusion over one hour) and demographic data. For a selection of patients, MIC was available for bloodstream isolates and these patients were included in the PKPD efficacy study.

Vancomycin assay

Vancomycin quantification in plasma was undertaken at the department of medical microbiology of the Great Ormond Street Hospital, London, United Kingdom using Indiko Plus (a CE marked assay). Indiko Plus is fully atomised and uses a Quantitative Microsphere System immunoassay. The assay is based on the competition between drug in the sample, and drug coated onto a micro particle for antibody binding sites and the rate of absorbance change, measured photometrically. The lower and upper limits of detection were 2.0 and 100 µg/ml.

Plasma creatinine assay

Plasma creatinine was measured using an enzymatic creatinine method on Vitros 5600 clinical chemistry auto analyser (Ortho Clinical Diagnostics, High Wycombe, UK). The assay is traceable to a gas chromatography isotopic dilution mass spectroscopy method and National Institute of Standards and Technology (NIST) SRM 914 creatinine standard reference material. The coefficient of variance for the assay was 2.1% at 76 µmol/L and 2.5% at 479 µmol/L. The limit of quantification is 4 µmol/L.

MIC determination

The MICs of vancomycin were determined by E-strips (manufactured by Oxoid) and Mueller-Hinton Agar. The laboratory has maintained full accreditation with CPA and now UKAS LTD under Standard: ISO 15189:2012 - Medical Laboratories.

Data analysis

Population pharmacokinetics

Vancomycin concentration-time data transformed into their natural logarithm was modelled using a First Order Conditional Estimation method with interaction in NONMEM v.7.3.0 with a gfortran compiler on a Windows 10 operating system. The supporting software packages PsN v.4.2.0 (http://psn.sourceforge.net/) and R v.3.2.3 (https://www.r-project.org/) were used for model building.

One- and two-compartment disposition models were tested in combination with bodyweight as the continuous covariate for clearance and volume parameters, with allometric scaling standardised to a 70 kg individual included a priori (34). A sigmoidal maturation factor based on postmenstrual age (PMA) (34) was estimated, and the effect of deviation from age standardised serum creatinine was also tested using a power model (35, 36). Hierarchical models, developed using the model building data was evaluated and compared Normalised Prediction Distributed Error (NPDE) and the objective function (-2 x log likelihood) (37). Inter individual variability was calculated as $100 \times \sqrt{e^{\eta} - 1}$ and relative standard errors were derived non-parametric bootstraps in NONMEM (n = 1,000) as $100 \times \frac{Standard\ deviation}{Mean}$. The best performing model was subsequently externally evaluated using a visual predictive check (37) ($n_{simulations}$=2,000) on the test data and the Mean Prediction Error was calculated ($MPE = \frac{\sum_{i=1}^{n} DV_i - IPRED_i}{n}$).

Efficacy

Steady state vancomycin AUC and trough concentrations after three doses of vancomycin were derived using Empirical Bayes Estimates (EBE-) parameter estimates for all patients in the training dataset and test dataset who also contributed MIC data. Logistic regression ($p < 0.05$) was used to identify the impact of vancomycin trough concentration, AUC, creatinine levels, bodyweight and post-natal age on treatment efficacy and breakpoints were identified using Classification and Regression Tree analysis ($p < 0.05$) (38). Besides a full Classification and Regression Tree analysis for treatment efficacy, another Classification and Regression Tree analysis was performed. AUC/MIC was excluded in the latter analysis to identify break points relevant for clinical use when Bayesian forecasting software is not available.

Nephrotoxicity

Under the assumption that cumulative drug exposure may be important for nephrotoxicity development vancomycin AUC_{CUM}, during the first treatment episode, was derived using EBE-parameter estimates for all patients in the training dataset and test dataset, where treatment episode was defined as a period of continuous vancomycin treatment of 48 hours or longer without disruption. Logistic regression ($p < 0.05$) was conducted to identify the impact of AUC_{CUM}, baseline creatinine, post-natal age and concomitant therapy with aminoglycosides, diuretics, NSAIDs, ciclosporin and colistin on acute kidney injury (50% increase from baseline) and acute kidney failure (75% increase from baseline) (19). A predictive logistic regression model ($p < 0.05$) was developed using the variables that were significantly associated with acute kidney injury or acute kidney failure.

Dose optimisations

Dose optimisations were carried out aiming to optimise target attainment, AUC > 400 hr.mg/l in a virtual patient population (n=750) comprising demographics from patients in the training and test datasets with baseline creatinine levels of ≥ 15 µmol/l. First vancomycin AUC after 15 mg/kg 8 hourly for children 0-1 month, 10-15 mg/kg 6 hourly for children 1 month – 11 years and 15-20 mg/kg 8-12 hourly for children 12 years and above (1) were simulated (n = 2,000) to elucidate the impact of bodyweight and creatinine in four distinct age ranges i.e. 0 – 1 month (n = 48), 1 month – 2 years (n = 254), 2 – 12 years (n = 389) and older than 12 years (n = 94).

Subsequently, dosages were refined based on baseline plasma creatinine band to ensure adequate exposure throughout the entire virtual patient population. The probability on AUC > 400 was compared between the standard and optimised treatment using 2,000 stochastic simulations of the identical virtual patient population characteristics as used for exploratory purposes. Corresponding eGFR for each of the age and baseline plasma creatinine level groups was calculated using the Schwartz formula: $(\frac{k \times Height}{Plasma\ creatinine})$ with 0.413 for k, height in cm and plasma creatinine in mg/dL (27). Average height for age, derived from WHO tables, was 51.9, 76.1, 121 and 168 cm for children 0-1 month, 1 month – 2 years, 2-12 years and >12 years, respectively (39, 40). Median plasma creatinine was 0.255, 0.452, 0.792, and 1.02 mg/dl for the (15-30], (30-50], (50-90], and >90 µmol/l baseline creatinine band, respectively. Dose optimisations for patients with creatinine levels < 10 and creatinine levels > 100 µmol/l were considered unreliable and therefore should be interpreted with caution.

Predictive generalised linear models for acute kidney injury or acute kidney failure and AUC_{CUM} and ciclosporin concomitant therapy were used to evaluate the nephrotoxicity risk profile during 10 days of treatment with the optimised vancomycin dosing schedule in a virtual patient population with baseline creatinine levels ≥ 15 µmol/l and for which concomitant therapy data was available (n=680).

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Conflict of Interest

The authors have declared that no competing interests exist.

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Table 1: Summary of patient data mean [range].

	Pharmacokinetic analysis	
	Training data	Test data
Study size (n)	616	169
Sample size (n)	4137	169
Samples per patient (n)	7 [2-50]	1 [1-1]
Treatment length (days)	8 [0-83]	3 [0-15.2]
First episode[a]	*9 [0-83]*	*3 [0-15.2]*
Consecutive episodes[a]	*7 [0-43.7]*	*2 [0-3.6]*
Age (months)	61 [0.03-255]	63 [0.08-204]
0-1 month (n)	*39*	*9*
1 month – 2 years (n)	*195*	*59*
2 – 12 years (n)	*314*	*75*
> 12 years (n)	*68*	*26*
Body weight (kg)	19 [0.742-95]	20 [1.18-107]
Creatinine (µmol/l)	39 [5-892]	35 [8-291]
Creatinine samples per patient (n)	14 [1-118]	3 [1-13]
	Pharmacokinetic-pharmacodynamic analysis of efficacy	

	Study size	Died	Recurrence	Microbiological failure	MIC (mg/l)	AUC/MIC
All	102	3	6	7	2 [0.12-4]	320 [50-2755]
CoNS	80	3	5	7	2 [0.5-4]	260 [50-846]
M. luteus	1	0	0	0	0.12	2755
Unknown	10	0	1	0	1 [0.5-2]	348 [127-620]
S. aureus	9	0	0	0	2 [0.5-2]	369 [125-1007]
V. streptococci	2	0	0	0	1 [0.5-1]	1155 [364-1947]

Pharmacokinetic-pharmacodynamic analysis of nephrotoxicity

	All data	Normal kidney function	Kidney injury	Kidney failure
Study size (n)	713	618	41	54
Aminoglycosides (n)	405 (56.8 %)	336 (54.4 %)	30 (73.2 %)	39 (72.2 %)
Diuretics (n)	219 (30.7 %)	172 (27.8 %)	18 (43.9 %)	29 (53.7 %)
NSAIDs (n)	166 (23.3 %)	149 (24.1 %)	8 (19.5 %)	9 (16.7 %)
Ciclosporin (n)	112 (15.7 %)	78 (12.6 %)	11 (26.8 %)	23 (42.6 %)
Colistin (n)	6 (0.842 %)	5 (0.809 %)	1 (2.44 %)	0 (0 %)
No dose change	381	346	16	19
One dose change	200	170	12	18

Fraction increased dose	*0.732*	*0.75*	*0.72*	*0.6*
Two dose changes	102	80	11	11
Fraction increased dose	*0.682*	*0.676*	*0.672*	*0.706*
Three dose changes	21	17	1	3
Fraction increased dose	*0.8*	*0.773*	*1*	*0.833*
Four dose changes	8	5	0	3
Fraction increased dose	*0.667*	*0.6*	-	*1*
Five dose changes	1	0	1	0
Fraction increased dose	*1*	-	*1*	-

[a] A treatment episode was defined as consecutive dosing no longer than 48 hours apart and 0 represents patients only having received one dose of vancomycin. CoNS: Coagulase negative staphylococcus

Table 2: Summary of population pharmacokinetic parameter estimates.

	Fixed effects (RSE)	IIV (RSE)
Cl (l/h)	4.84 (2.38)	50.4 (11.8)
PMA_{50}	50.2 (3.34)	-
HILL	3.52 (14.8)	-
$Power_{Creatinine}$	-0.692 (5.28)	-
V_C (l)	39.9 (8.15)	232 (17.2)
Q (l/h)	3.85 (17.3)	-
V_P (l)	37.8 (10.2)	-
RUV	0.243 (4.85)	-
η_{CL}-η_{Vc}	0.535 (11.2)	-

CL: elimination clearance, V_C: distribution volume central compartment, Q: inter-compartmental clearance, V_P: distribution volume peripheral compartment, PMA_{50}: Post-natal age half-maximum organ maturation, $Power_{Creatinine}$: exponent on creatinine function, RUV: additive residual variability on log transformed data and η_{CL}-η_{Vc}: correlation between variability on clearance and distribution volume central compartment. Clearance and volume parameters were centralised around a 70 kg patient using 0.632, 0.75 and 1 as power functions for CL, Q and the distribution volumes (V_C and V_P), respectively. IIV: Inter Individual Variability ($100 \times \sqrt{e^{\eta} - 1}$) and RSE: relative standard errors were derived from 962 (out of 1000) converged non-parametric bootstraps in NONMEM as $100 \times \frac{Standard\ deviation}{Mean}$.

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Table 3: Summary of pharmacokinetic-pharmacodynamic analysis of efficacy.

	AUC/MIC				C_{trough}/MIC			
	Estimate	Std. Error	z-value	Pr(>|z|)	Estimate	Std. Error	z-value	Pr(>|z|)
Intercept	-4.18	2.8	-1.49	0.135	-1.88	0.826	-2.27	0.0231*
Log(AUC/MIC)	0.487	0.498	0.977	0.329	.	.	.	.
Log(Ct_{rough}/MIC)	.	.	.	.	0.296	0.331	0.894	0.371
M. luteus	-18.5	6520	-0.00284	0.998	-18	6520	-0.00277	0.998
Unknown	-1.14	1.16	-0.982	0.326	-1.08	1.14	-0.941	0.347
S. aureus	-17.3	2140	-0.00806	0.994	-17.1	2120	-0.00803	0.994
V. streptococci	-18.8	4490	-0.00418	0.997	-18.4	4580	-0.00401	0.997
Creatinine	0.000607	0.0147	0.0413	0.967	0.00116	0.0148	0.0786	0.937
Age	0.0151	0.0127	1.19	0.234	0.0145	0.0128	1.14	0.256
Bodyweight	-0.0384	0.0683	-0.562	0.574	-0.0406	0.0679	-0.599	0.549
Age:bodyweight	-0.0000234	0.000376	-0.0624	0.95	-0.00000403	0.000375	-0.0107	0.991

462 Unknown: unidentified bacterial species.

463 * $p < 0.05$

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Table 4: Summary of pharmacokinetic-pharmacodynamic analysis of nephrotoxicity.

	AUC and kidney injury or failure				AUC and kidney failure			
	Estimate	Std. Error	z-value	Pr(>|z|)	Estimate	Std. Error	z-value	Pr(>|z|)
Intercept	-0.333	1.84	-0.18	0.857	-1.48	2.33	-0.639	0.523
Log(AUC)	-0.186	0.342	-0.544	0.586	0.0277	0.428	0.0647	0.948
Aminoglycosides	0.372	0.263	1.41	0.158	0.17	0.341	0.498	0.618
Diuretic	0.704	0.244	2.89	0.0039**	0.808	0.313	2.58	0.00995**
NSAIDs	-0.0129	0.313	-0.0412	0.967	0.0201	0.42	0.0479	0.962
Ciclosporin	1.17	0.274	4.26	0.0000209**	1.44	0.341	4.23	0.0000234**
Colistin	0.203	1.13	0.179	0.858	-14	955	-0.0147	0.988
Creatinine	-0.051	0.0203	-2.52	0.0118*	-0.0811	0.0276	-2.94	0.0033**
Age	-0.00523	0.00419	-1.25	0.212	-0.0117	0.00504	-2.32	0.0203*
Creatinine:Age	0.000281	0.000122	2.31	0.0211*	0.000484	0.000156	3.1	0.00192**
	AUC_{CUM} and kidney injury or failure				AUC_{CUM} and kidney failure			
Intercept	-11.5	1.42	-8.12	4.68E-16**	-13.4	1.92	-6.96	3.29E-12**
Log(AUC_{CUM})	1.17	0.178	6.55	5.71E-11**	1.32	0.237	5.57	0.000000026**
Aminoglycosides	0.276	0.276	1	0.317	0.0584	0.358	0.163	0.87

Diuretic	0.179	0.258	0.696	0.486	0.216	0.328	0.657	0.511
NSAIDs	0.0274	0.327	0.0839	0.933	0.104	0.435	0.239	0.811
Ciclosporin	0.549	0.291	1.88	0.0596	0.739	0.358	2.06	0.0391*
Colistin	1.12	1.16	0.962	0.336	-13	923	-0.0141	0.989
Creatinine	0.00591	0.00321	1.84	0.0655	0.00643	0.00361	1.78	0.0751
Age	-0.00369	0.00256	-1.44	0.15	-0.00556	0.00332	-1.68	0.0938
Creatinine:Age	-0.000000257	0.0000283	-0.00911	0.993	0.00000702	0.0000303	0.232	0.817

* p < 0.05 ** p < 0.01

Table 5: Overview refined paediatric initial dosing regimen (mg/kg).

Creatinine band (µmol/l)	0-1 month		1-month-2 years		2-12 years		>12 years	
	eGFR	Dosage	eGFR	Dosage	eGFR	Dosage	eGFR	Dosage
(15-30]	84.2	20 q8h	123	20 q6h	197	20 q6h	272	35 q8h
(30-50]	47.4	15 q8h	69.4	15 q6h	111	15 q6h	153	25 q8h
(50-90]	27.1	10 q8h	39.7	10 q6h	63.2	10 q6h	87.5	15 q8h
>90	21.1	10 q8h*	30.9	5 q6h	49.2	5 q6h	68.0	7.5 q8h

466 * Not supported by data as no patients were available in this category. eGFR: estimated Glomerular Filtration Rate

467 ($\frac{k \times Height}{Plasma\ creatinine}$) in mL/min.

468

Figure 1: The left panel represents the simulation based goodness of fit plots on the training data including Normalised Prediction Distributed Error (NPDE) versus population predictions (on natural logarithm scale), NPDE versus Time After Dose, density distribution of NPDE and a qq-plot for NPDE. The right panel represents a visual predictive check of 2,000 simulated concentration-time profiles using the final model, for the test data. Points represent the observations, black lines represent the 2.5th, 50th, and 97.5th percentiles, and the shaded areas represent the 95% confidence intervals of the corresponding predicted vancomycin concentration percentiles. The x-axis of visual predictive check was constrained between 1.5 and 12 hours leaving 14 scattered samples between 12 and 48 hours not shown.

478 Figure 2 Vancomycin trough concentrations versus creatinine levels (top row) and bodyweight (bottom row) after
479 the standard dosing regimen (green and red) and optimised dosing regimen (blue). Results were stratified for age
480 group (by column). The dashed black horizontal lines represent the target exposure (i.e. 400 hrxmg/l). Dots
481 represent the mean median values from 2,000 simulations and the error bars represent the mean 5th and 95th
482 percentiles. The "(" parentheses on the x-axes indicates equal and larger and the "]" parentheses indicates smaller
483 than.

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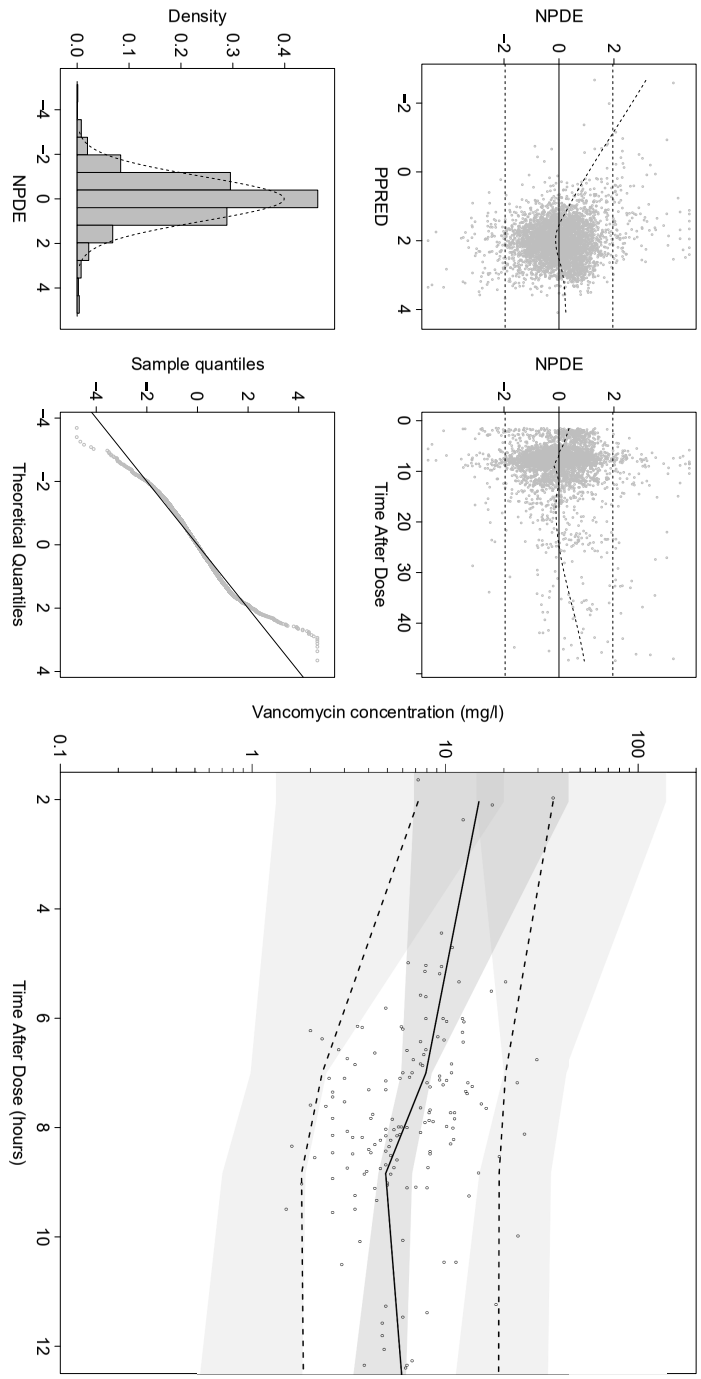
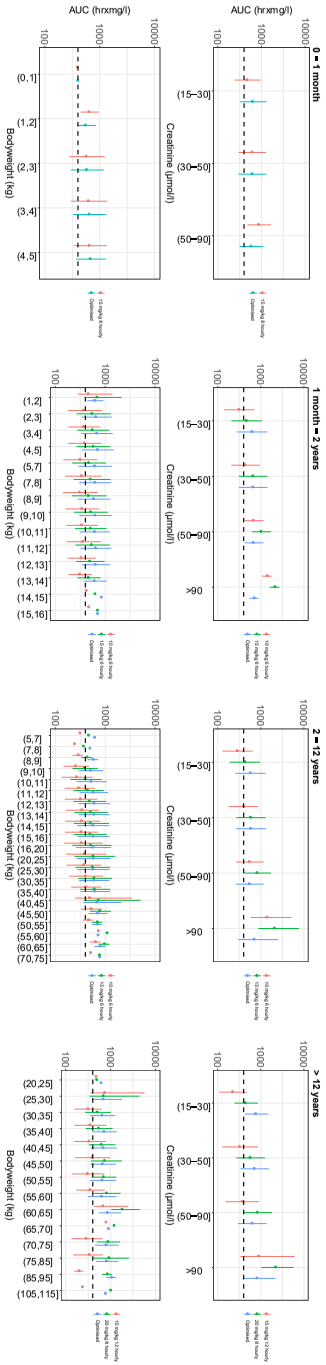
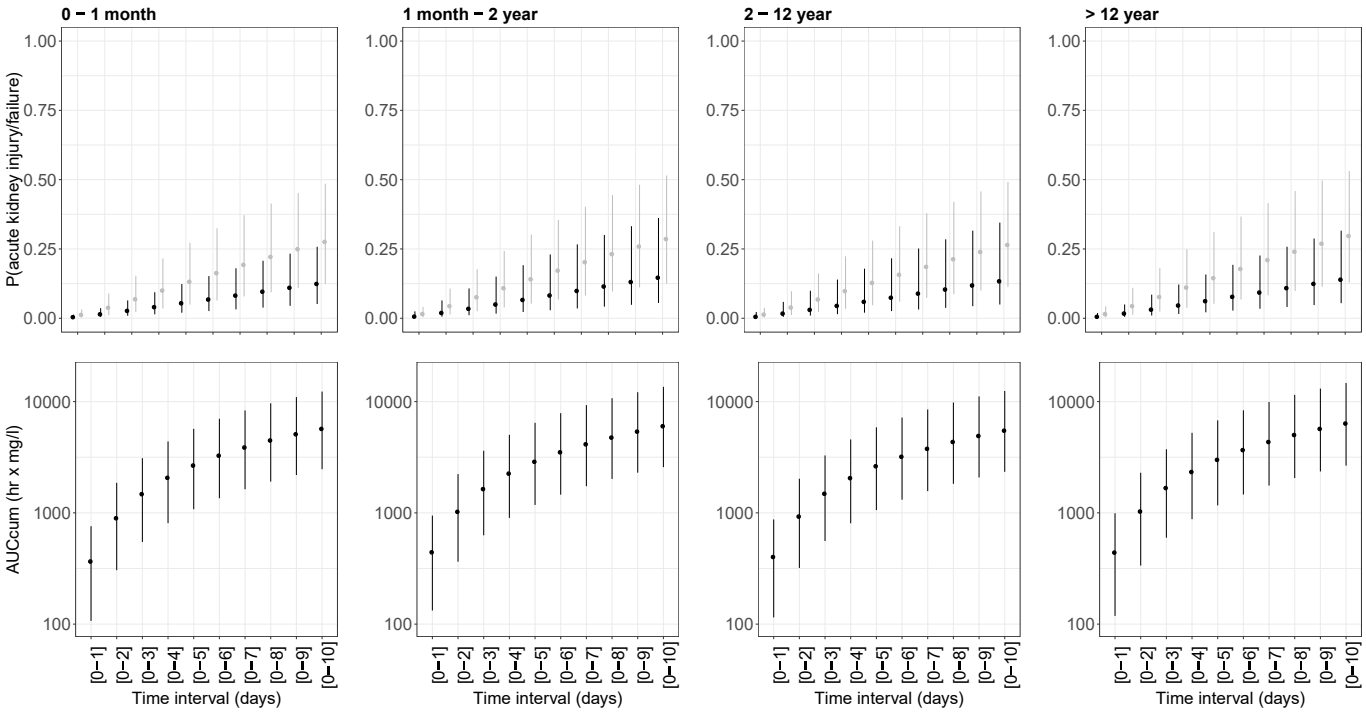
485 Figure 3: Probability of nephrotoxicity (top row, grey: acute kidney injury and black: acute kidney failure) and
486 vancomycin exposure (bottom row) for treatment with the optimised dosing regimen for different durations. Results
487 were stratified for age group (by column). Dots represent the mean median values from 500 simulations and the
488 error bars represent the mean 5th and 95th percentiles.







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