

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

3 Running title: Paediatric vancomycin dose revision

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## 20 Abstract

21 This study aimed to suggest an initial paediatric vancomycin dose regimen through population pharmacokinetic-  
22 pharmacodynamic modelling. A population pharmacokinetic approach was used to analyse vancomycin  
23 concentration-time data from a large paediatric cohort. Pharmacokinetic target attainment for patients with blood  
24 stream isolates was compared with clinical outcome using logistic regression and classification and regression trees.  
25 Change in serum creatinine during treatment was used as an indicator of acute nephrotoxicity. Probability of acute  
26 kidney injury (50% increase from baseline) or kidney failure (75% increase from baseline) was evaluated using logistic  
27 regression. An initial dosing regimen was derived, personalised by age, weight and serum creatinine using stochastic  
28 simulations. Data from 785 hospitalised paediatric patients (1 day to 21 years) with suspected Gram-positive  
29 infections were collected. Estimated (RSE) typical CL, V1, Q and V2 were (standardised to 70 kg) 4.84 (2.38) L/h, 39.9  
30 (8.15) L, 3.85 (17.3) L/h, and 37.8 (10.2) L, respectively. Whilst cumulative vancomycin exposure correlated positively  
31 with the development of nephrotoxicity (713 patients) no clear relationship between vancomycin AUC and efficacy  
32 was found (102 patients). Predicted probability of acute kidney injury and kidney failure with the optimised dosing  
33 regimen at day 5 was 10-15% and 5-10 %, increasing by approximately 50% on day 7 and roughly 100% on day 10  
34 across all age groups. This study presents the first data driven paediatric dose selection to-date accounting for  
35 nephrotoxicity and indicated that cumulative vancomycin exposure best described risk of acute kidney injury and  
36 acute kidney failure.

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

## 39 Introduction

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

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

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

63 The third aim was to identify predictors of nephrotoxicity. Nephrotoxicity indices have been defined for paediatric  
64 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.

## 75 Results

### 76 Population pharmacokinetics

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

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

95 The model adequately described the vancomycin concentration-time data with a Mean Prediction Error on the test  
96 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  
97 time samples (originally reported before 1.5 hours) were omitted as sensitivity analysis, and this yielded similar  
98 parameter estimates: CL (-1.03%),  $\text{PMA}_{50}$  (-5.78%), Hill (36.9%) and Power Creatinine (-2.31%) which was important  
99 as dose optimisations focus on AUC.

## 100 Efficacy

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

104 In patients with a blood stream organism, treatment failure was defined if at least one of the following criteria was  
105 met: 1.) deceased within 30 days of vancomycin treatment initiation, 2.) recurrent infection between 48 hours and  
106 60 days following vancomycin treatment discontinuation, and 3.) microbiologically confirmed growth 7 days after  
107 the initiation of therapy but before treatment completion (16). Treatment outcome was classified as successful if  
108 none of the above criteria were met. Neither trough concentration/MIC nor AUC/MIC correlated with probability of  
109 treatment failure in a multivariate generalised logistic regression model or in a Classification and Regression Tree  
110 analysis (Table 3, Fig. S4).

## 111 Nephrotoxicity

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

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

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

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

### 138 Dose optimisation

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

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

153 regression models for acute kidney injury and acute kidney failure and 500 stochastic simulations. The predicted  
154 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  
155 [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-  
156 25.8%] on day 10 (Fig. 3). A similar probability of acute kidney injury and kidney failure was predicted at day 5 for  
157 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  
158 [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  
159 predicted probability of acute kidney injury and kidney failure was similar with 12.9 [4.69-28.0] % and 6.10 [2.02-  
160 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-  
161 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  
162 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  
163 [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-  
164 31.6] % on day 10 (Fig. 3). For comparison, approximately 6.38% and 3.55% of the patients in the data had observed  
165 acute kidney injury or acute renal failure at day 5 and approximately 13.0% and 4.63% of the patient in the data had  
166 observed acute kidney injury and acute renal failure at day 10.



## 167 Discussion

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

## 173 Population pharmacokinetics

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

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

## 186 Efficacy

187 Neither vancomycin trough concentrations or AUC correlated with treatment failure in this paediatric patient  
188 population with a variety of blood stream infections (Table 3, Fig. S3) although several studies in adults with  
189 methicillin resistant *Staphylococcus aureus* blood stream infections concluded that the PKPD endpoint of  $AUC/MIC \geq$   
190 400 mg.h/L was clinically relevant (16-18). A plausible explanation for this discrepancy is the large number of  
191 *Coagulase Negative Staphylococcus* infections (Table 1). *Coagulase Negative Staphylococcus* infections are likely to  
192 be a result of line infections (25) or contamination and cause limited morbidity. For the remaining 22 Gram-positive

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

### 197 **Nephrotoxicity**

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

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

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

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

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

### 221 Dose optimisation

222 Vancomycin dosing recommendations have changed since the data collection period (32) with 15 mg/kg 8 hourly for  
223 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  
224 12 years and above as most recent dosing recommendations (1). Using currently recommended vancomycin dosing  
225 we stratified the mg per kg doses by baseline creatinine level (Table 5). Even after stratifying mg per kg dose by age  
226 and creatinine, it is clear that TDM will continue to be required since target attainment is low in some categories  
227 (Fig. 2). Also from a nephrotoxicity perspective TDM continues to be required, hence vancomycin TDM is focused on  
228 avoiding renal failure. At day 5 approximately 6.38% and 3.55% of the patients had observed acute kidney injury or  
229 acute renal failure and at day 10, approximately 13.0% and 4.63% of the patient had observed acute kidney injury  
230 and acute renal failure. This was substantially lower compared to simulations in Figure 3 highlighting the impact of  
231 TDM as the virtual patient population remained on the initial dosing regimen for the entire duration of the simulated  
232 treatment whereas the real observed patients underwent TDM guided dose reduction.

233 Although trough levels of 10-15 mg/l and 15-20 mg/l have been recommended (32, 33), we chose to target AUC >  
234 400 hr.mg/l, a target that is now becoming a preferred PK endpoint with increasing availability of Bayesian TDM  
235 software. It should be noted that this target has not been evaluated in children, and our attempt at modelling  
236 efficacy was hampered by the limited number of patients in our study having non-coagulase negative Staphylococcus  
237 Gram positive blood stream infections.

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

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

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

## 257 Materials and methods

### 258 Experimental design

259 This study was a retrospective analysis of paediatric patients treated with vancomycin at a large tertiary paediatric  
260 hospital (Great Ormond Street Hospital) in London, United Kingdom. De-identified data were extracted from  
261 electronic health records with ethical approval without the requirement for written informed consent provided  
262 (17/LO/0008). Patients included in the study were hospitalised between 2010 and 2016 and contributed vancomycin  
263 drug level, dosing (intravenous infusion over one hour) and demographic data. For a selection of patients, MIC was  
264 available for bloodstream isolates and these patients were included in the PKPD efficacy study.

### 265 Vancomycin assay

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

### 271 Plasma creatinine assay

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

### 277 MIC determination

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

## 281 Data analysis

### 282 Population pharmacokinetics

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

287 One- and two-compartment disposition models were tested in combination with bodyweight as the continuous  
288 covariate for clearance and volume parameters, with allometric scaling standardised to a 70 kg individual included a  
289 priori (34). A sigmoidal maturation factor based on postmenstrual age (PMA) (34) was estimated, and the effect of  
290 deviation from age standardised serum creatinine was also tested using a power model (35, 36). Hierarchical models,  
291 developed using the model building data was evaluated and compared Normalised Prediction Distributed Error  
292 (NPDE) and the objective function (-2 x log likelihood) (37). Inter individual variability was calculated as  $100 \times$   
293  $\sqrt{e^{\eta} - 1}$  and relative standard errors were derived non-parametric bootstraps in NONMEM (n = 1,000) as  
294  $100 \times \frac{\text{Standard deviation}}{\text{Mean}}$ . The best performing model was subsequently externally evaluated using a visual predictive  
295 check (37) ( $n_{\text{simulations}}=2,000$ ) on the test data and the Mean Prediction Error was calculated ( $MPE = \frac{\sum_{i=1}^n DV_i - IPRED_i}{n}$ ).

### 296 Efficacy

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

### 305 Nephrotoxicity

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

### 314 Dose optimisations

315 Dose optimisations were carried out aiming to optimise target attainment,  $AUC > 400$  hr.mg/l in a virtual patient  
316 population ( $n=750$ ) comprising demographics from patients in the training and test datasets with baseline creatinine  
317 levels of  $\geq 15$   $\mu\text{mol/l}$ . First vancomycin AUC after 15 mg/kg 8 hourly for children 0-1 month, 10-15 mg/kg 6 hourly for  
318 children 1 month – 11 years and 15-20 mg/kg 8-12 hourly for children 12 years and above (1) were simulated ( $n =$   
319 2,000) to elucidate the impact of bodyweight and creatinine in four distinct age ranges i.e. 0 – 1 month ( $n = 48$ ), 1  
320 month – 2 years ( $n = 254$ ), 2 – 12 years ( $n = 389$ ) and older than 12 years ( $n = 94$ ).

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

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



## 335 Funding

336 No specific funding was received for this study. FK (MR/P014534/1) and JFS (MR/M008665/1) have conducted the  
337 research as part of their Medical Research Council fellowships. The Medical Research Council had no role in study  
338 design, data collection and analysis, decision to publish, or preparation of the manuscript. Support at institution level  
339 came from the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital  
340 for Children NHS Foundation Trust and University College London. Louise F Hill is supported by the National Institute  
341 for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's  
342 College Hospital NHS Foundation Trust. The views expressed are those of the author[s] and not necessarily those of  
343 the NHS, the NIHR or the Department of Health and Social Care.

344 **Conflict of Interest**

345 The authors have declared that no competing interests exist.

346

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- 458

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]
<i>First episode<sup>a</sup></i>	9 [0-83]	3 [0-15.2]
<i>Consecutive episodes<sup>a</sup></i>	7 [0-43.7]	2 [0-3.6]
Age (months)	61 [0.03-255]	63 [0.08-204]
<i>0-1 month (n)</i>	39	9
<i>1 month – 2 years (n)</i>	195	59
<i>2 – 12 years (n)</i>	314	75
<i>&gt; 12 years (n)</i>	68	26
Body weight (kg)	19 [0.742-95]	20 [1.18-107]
Creatinine ( $\mu\text{mol/l}$ )	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]
<i>M. luteus</i>	1	0	0	0	0.12	2755
Unknown	10	0	1	0	1 [0.5-2]	348 [127-620]
<i>S. aureus</i>	9	0	0	0	2 [0.5-2]	369 [125-1007]
<i>V. streptococci</i>	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

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

459 <sup>a</sup> 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:

460 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 <sub>50</sub>	50.2 (3.34)	-
HILL	3.52 (14.8)	-
Power <sub>Creatinine</sub>	-0.692 (5.28)	-
V <sub>C</sub> (l)	39.9 (8.15)	232 (17.2)
Q (l/h)	3.85 (17.3)	-
V <sub>P</sub> (l)	37.8 (10.2)	-
RUV	0.243 (4.85)	-
$\eta_{CL}-\eta_{Vc}$	0.535 (11.2)	-

CL: elimination clearance, V<sub>C</sub>: distribution volume central compartment, Q: inter-compartmental clearance, V<sub>P</sub>: distribution volume peripheral compartment, PMA<sub>50</sub>: Post-natal age half-maximum organ maturation, Power<sub>Creatinine</sub>: exponent on creatinine function, RUV: additive residual variability on log transformed data and  $\eta_{CL}-\eta_{Vc}$ : 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<sub>C</sub> and V<sub>P</sub>), 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  $100 \times \frac{\text{Standard deviation}}{\text{Mean}}$ .

461

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

	AUC/MIC				C <sub>trough</sub> /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(C <sub>trough</sub> /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	-0.0000403	0.000375	-0.0107	0.991

462 Unknown: unidentified bacterial species.

463 \* p &lt; 0.05

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 <sub>CUM</sub> and kidney injury or failure				AUC <sub>CUM</sub> and kidney failure			
Intercept	-11.5	1.42	-8.12	4.68E-16**	-13.4	1.92	-6.96	3.29E-12**
Log(AUC <sub>CUM</sub> )	1.17	0.178	6.55	5.71E-11**	1.32	0.237	5.57	0.00000026**
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	-0.00000257	0.0000283	-0.00911	0.993	0.00000702	0.0000303	0.232	0.817
465	*	p	<	0.05	**	p	<	0.01

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

Creatinine band ( $\mu\text{mol/l}$ )	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  $\left(\frac{k \times \text{Height}}{\text{Plasma creatinine}}\right)$  in mL/min.

468

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

477

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 hr $\times$ mg/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.

484

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.







