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Optimization of vancomycin initial dose in term and preterm neonates by Machine Learning

Laure Ponthier^{1,2}, Pauline Ensuque², Alexandre Destere^{1,3}, Pierre Marquet^{1,4}, Marc Labriffe^{1,4}, Evelyne Jacqz-Aigrain⁵, Jean-Baptiste Woillard^{1,4}

1 Pharmacology & Transplantation, INSERM U1248, Université de Limoges, Limoges, France

2 Department of Pediatrics, University Hospital of Limoges, Limoges, France

3 Department of Pharmacology and Toxicology, University Hospital of Nice, Nice, France

4 Department of Pharmacology, Toxicology and Pharmacovigilance, University Hospital of Limoges, Limoges, France

5 Pediatric Pharmacology, Department of Biological Pharmacology, Saint-Louis University hospital, Assistance Publique - Hôpitaux de Paris, France

Corresponding author:

Jean-Baptiste Woillard

Title: PharmD, PhD

ORCID: 0000-0003-1695-0695

Address:

Univ. Limoges, INSERM U1248 P&T, 2 rue du Pr Descottes, F-87000 Limoges, France.

Phone: +33 5 55 05 61 40

Fax: +33 5 55 05 61 62

Email: jean-baptiste.woillard@unilim.fr

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Abstract

Introduction: Vancomycin is one of the antibiotics most used in neonates. Continuous infusion has many advantages over intermittent infusions, but no consensus has been achieved regarding the optimal initial dose. The objectives of this study were: to develop a Machine learning (ML) algorithm based on pharmacokinetic profiles obtained by Monte Carlo simulations using a population pharmacokinetic model (POPPK) from the literature, in order to derive the best vancomycin initial dose in preterm and term neonates, and to compare ML performances with those of an literature equation (LE) derived from a POPPK previously published.

Materials and methods: The parameters of a previously published POPPK model of vancomycin in children and neonates were used in the mrgsolve R package to simulate 1900 PK profiles. ML algorithms were developed from these simulations using Xgboost, GLMNET and MARS in parallel, benchmarked and used to calculate the ML first dose. Performances were evaluated in a second simulation set and in an external set of 82 real patients and compared to those of a LE.

Results: The Xgboost algorithm yielded numerically best performances and target attainment rates: 46.9% in the second simulation set of 400-600 AUC/MIC ratio vs. 41.4% for the LE model ($p=0.0018$); and 35.3% vs. 28% in real patients ($p=0.401$), respectively). The Xgboost model resulted in less AUC/MIC >600 , thus decreasing the risk of nephrotoxicity.

Conclusion: The Xgboost algorithm developed to estimate the initial dose of vancomycin in term or preterm infants has better performances than a previous validated LE and should be evaluated prospectively.

Introduction

Vancomycin is a bactericidal glycopeptide antibiotic that inhibits cell wall synthesis of gram-positive bacteria. Late-onset sepsis due to coagulase-negative-staphylococcus is frequent in neonatology, particularly in patients requiring intensive care, and vancomycin is one of the antibiotics most used in neonates [1]. Vancomycin shows a large interindividual pharmacokinetic variability of renal elimination and distribution volume among preterm and term neonates [2]. Research identified that weight, age and renal function, reflecting both growth and maturation of organ functions were predictors of vancomycin clearance [2]. Accordingly vancomycin initial doses are most often based on body weight, plasma creatinine, post-menstrual age (PMA) and/or post-natal age (PNA) [3]. Due to this variability and the drug narrow therapeutic index, therapeutic drug monitoring (TDM) is required in this population [4]. Indeed, low concentrations may lead to poor antibacterial efficacy and high concentrations increase the risk of nephrotoxicity [5,6]. Recently, guidelines meant for adults and children recommended a ratio of 24-hour Area under the curve (AUC_{0-24h}) to minimum inhibitory concentration (MIC) between 400 and 600 mg*h/L to achieve clinical efficacy while reducing the incidence of nephrotoxicity [7].

Vancomycin continuous IV infusion has many advantages over intermittent infusions: it shortens the time to achieve target concentrations and increases the probability of drug concentrations in the therapeutic range [8], reduces drug toxicity and the need for plasma drug measurements [9,10]. Studies dealing with continuous infusion of vancomycin in pediatric patients are heterogenous, and the optimal dosage is still to be identified, which will require studies in larger population [11]. Adding a loading dose is recommended to increase the proportion of early target attainment [4]. In the meantime, artificial intelligence, particularly machine learning, may help to best use the sparse existing data to derive an initial dose with the best probability of achieving target serum concentrations. The development of machine learning algorithms requires large datasets [3,12], but we have recently demonstrated that ML algorithms could be efficiently trained on simulated data, obtained using a validated population pharmacokinetic (POPPK) model from the literature [13].

The objectives of this study were: (i) to obtain a Machine learning algorithm able to estimate the best vancomycin initial dose in term or preterm neonates, trained on PK profiles obtained by means of Monte Carlo simulations using a POPPK model from the literature; and (ii) to compare its performances on a second PK simulated profiles with a previously published and validated equation derived from a POPPK model (literature equation; LE).

Materials and Methods

Simulation of vancomycin pharmacokinetic profiles in neonates

The parameters of a previously published POPPK model of vancomycin in children and neonates [14] were used in the `mrgsolve` R package [12] to simulate 1900 PK profiles (corresponding to 100 profiles for the 19 gestational ages between 24 and 42 weeks usually met in Neonatal intensive care unit). It was a 2-compartment model with linear elimination from the central compartment, whose parameters were used with a few modifications with respect to the values reported in the original paper [14]: inter-occasion variability was not implemented and we performed in parallel one set of simulation with the original residual error (additive error = 1.57 µg/L and proportional error = 0.22 %) and one with the residual error decreased (additive error = 0.1 µg/L and proportional error = 0.01%) in order to obtain less noisy and more realistic simulated PK profiles [15].

The covariates used in the model for the simulation of PK profiles were created as follow: Gestational age (GA) between 23 and 42 weeks, simulated using a uniform distribution; Birth Weight (BW) simulated based on a truncated normal distribution according to gestational age using the Fenton growth chart [16]; the time at which infection occurrence after birth (= Post-Natal Age= PNA) [17], simulated using a truncated normal distribution; Post Menstrual Age (PMA) at first infection, calculated as $PMA = GA + PNA$; weight gain per day [18], simulated using a truncated normal distribution; Current Weight (CW), calculated as $CW = BW + PNA * \text{weight gain per day}$; and plasma creatinine (CREA), simulated using a truncated normal distribution between 40 and 145 µmol/L, independently of the other covariates [19]. All the values of covariates and the code used to simulate them is provided as Supplemental material (ESM_1).

The reference AUC_{48-72h} (=AUC_{48-72h_{ref}}) was calculated by multiplying the concentration simulated at 48 hours by 24. A filter was applied to remove AUC_{48-72h_{ref}} outliers, i.e. values outside the 5%-95% interval of simulated values (<264 mg*h/L or > 1164 mg*h/L). We also performed an analysis without removing the outlier values to highlight the decrease in performance. Finally, 1717 simulated PK profiles were used for the next step (simulation set n°1) after applying the filters.

The dose usually prescribed in our NICU Department at Limoges university Hospital based on PMA and CREA was used for the simulations and was considered as the Reference Dose to be beaten by the ML algorithms and LE [20]. Loading dose was calculated with post menstrual age and current weight (10 mg/kg for PMA below 32 weeks and 15 mg/kg for PMA after 32 weeks). Its calculation method is provided in a Supplemental Table (ESM_2).

Machine learning analysis

All pre-processing and machine learning analyses were performed using the `tidymodels` framework in R version 4.0.5 [21]. Data were split into a training set (75%) and a test set (25 %) by random selection of patients. The training set was secondarily split into an analysis set (80%) and an assessment set (20%) in order to benchmark different ML algorithms and select the one with the best performances without wasting the test set for this purpose.

Preprocessing consisted in normalization (centering and scaling) of numeric variables, and one hot encoding of categorical features. Xgboost (eXtreme Gradient Boosting Training) [22], MARS (Multivariate Adaptive Regression Splines) [23] and GLMNET (generalized linear model via penalized maximum likelihood) algorithms [24] were employed in parallel. For each algorithm, the hyperparameters were tuned using ten-fold

cross-validations in the analysis set. Once optimized, the ML algorithms were comparatively evaluated in the assessment set in order to select the one with the best performances. The models with the best performances in terms of Root mean square error (RMSE, expressed in mg*h/L) and r^2 with respect to the AUC48-72h_{ref} were evaluated by calculating:

- the relative mean prediction error (MPE): $rMPE (\%) = \frac{AUC48-72h_{pred} - AUC48-72h_{ref}}{AUC48-72h_{ref}}$
- the relative RMSE: $rRMSE (\%) = \sqrt{\frac{\sum (rMPE)^2}{n}}$
- and the number of AUC48-72h_{pred} profiles out of the +/- 20% rMPE interval compared to the AUC48-72h_{ref}

This best algorithm was refined using the analysis and assessment sets combined and was finally evaluated in the test set. The relative importance of each features was determined using random permutations and variable importance plot was drawn. The AUC48-72h_{pred} was estimated with the best ML algorithm and the initial dose resulting in AUC48-72h_{target} = 500 mg*h/L (corresponding to a steady-state concentration (C_{ss}) of 20.8 mg/L) was derived as follows: ML dose = AUC48-72h_{target} *dose administered/AUC48-72h_{pred}.

Robustness evaluation using an independent simulation set

An independent simulation set was created using the same procedure as that mentioned above (modification of the seed used for simulations). The target attainment rate for reference doses was defined as the percentage of patients with a vancomycin serum AUC48-72h_{ref} within the target window of 400 to 600 mg*h/L calculated using a sample taken 48 h after starting vancomycin treatment.

The reference doses (currently used in our hospital) and their target attainment rate were compared to those of the ML algorithm and the LE [25] doses. The LE dose was calculated from an equation derived from a POPPK model based on Birth Weight, Current Weight, creatinine and Post Natal Age following this formula:

$$Dose = 20 \times 24 \times 0.0571 \times \frac{CW}{1416} \times 0.513 \times \frac{BW^{0.599}}{1010} \times \left(1 + 0.282 \times \frac{PNA}{17}\right) \times \frac{1^{0.525}}{42}$$

With CW being the current weight (g), BW being the birth weight (g), PNA being the postnatal age (Weeks of amenorrhoea) and CREA being the creatinine value (μM).

The AUC48-72h extrapolated derived from the dose proposed by each algorithm was extrapolated as follows:

$$AUC48 - 72h \text{ extrapolated} = AUC48 - 72h \times \frac{\text{Reference dose}}{\text{Proposed dose}}$$

Finally, the number/proportion of AUC48-72h extrapolated below (<400 mg*h/L), within (400 – 600 mg*h/L) and above (>600 mg*h/L) the therapeutic range were evaluated between the two approaches and a chi-square test investigating the probability of being vs no being in the AUC target was performed.

External validation in actual patients

Deidentified data from 82 patients (43 from University Hospital in Limoges and 39 from Robert Debré Hospital in Paris) for whom TDM was performed as part of routine care with a sample drawn at least 24h after drug initiation were used to externally evaluate the algorithms. The dose administered based on standard practice (reference dose) was compared to the doses proposed by the best ML algorithm and the literature equation and the number and proportion of extrapolated AUC_{48-72h} from these 3 doses: below (<400 mg*h/L), within (400 – 600 mg*h/L) and above (>600 mg*h/L) target range were evaluated. Finally, a chi-square test investigating the probability of being vs no being in the AUC target was performed.

Ethic statement concerning actual patients

Parental informed consent was obtained for all infants. The study protocol was approved by institutional ethics committee (CPP SOOM 4, Limoges, France). The authors confirmed that they have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Results

After removing extreme values, 1717 profiles were exploitable in the simulation set n°1 (spaghetti plot in ESM_3). The distribution of simulated AUC_{48-72h} is presented in Figure 1. Characteristics of the simulated profiles in the analysis, assessment and test subsets, the robustness evaluation set n°2 and the external validation set of 82 patients are summarized in Table 1. Two independent random typical patients drawn with the original and with the decreased error model are presented in ESM_4.

Development of the Machine Learning algorithm

The performances of the algorithms trained in the analysis (resampling) and the assessment sets with each ML algorithm are available in Table 2 (with the original and decreased error). The use of the original error model led to the worst performances that led us to select the decreased error model for the next step. Similarly, the inclusion of outlier values exhibits large decreased performances in comparison to the ML developed after filtering out the outliers (ESM_5). Xgboost was associated with the best performances in terms of rMPE and rRMSE and was selected for calculating the ML doses (rRMSE = 36.1, rMPE = 7.2 and number out of the $\pm 20\%$ interval (%) = 703 (54.7%) and rRMSE = 35.7, rMPE = 8.6 and number out of the $\pm 20\%$ interval (%) = 234 (54.7%) in the train set and the test set, respectively). The variable importance plot showed that the creatinine, the loading dose (derived from PMA and current weight) and the PMA were the most important, in this order (Figure 2).

Robustness evaluation in an independent simulation set (simulation set n°2)

Paired boxplots comparing the 3 dose proposals are presented in Figure 3. They show that overall, XGboost proposed lower doses than the reference when the $AUC_{48-72h_{ref}}$ is above target (>600 mg*h/L), and similar doses when the $AUC_{48-72h_{ref}}$ is in the target range. When split into within or outside the target, the best target attainment rate was obtained with the ML doses (46.9%, N= 793/1692) in comparison to the reference doses (34.5%, N=583/1692; $p<0.0001$) and to the LE doses (41.4%, N= 702/1692; $p = 0.0018$) (Table 3).

External validation in a database from actual patients

With real patient data, numerical but not significant best target attainment rate was obtained with the ML doses (35.3%, 29/82) vs LE doses (28%, 23/82; $p=0.401$) while no difference between ML and reference was observed reference doses (35.3%, 29/82; $p = 1.000$). Paired plots and contingency tables for comparisons are presented in Figure 4 and Table 4, respectively.

Discussion

In the present study, we developed a ML algorithm using simulated PK profiles able to predict the first dose of vancomycin in preterm and term neonates with greater efficacy than our previous reference method, and we compared its performances to a formula derived from a published LE model. Even if the differences were not highly clinically different, we observed that the ML algorithm had significant better performances in comparison to the literature formula in simulations but only numerically better performances in real patients (probably in relation with the small sample size in the real patient dataset). We have chosen this equation because it showed good performances, relevant covariables and was prospectively validated [25]. With our ML estimator, we improved the estimation performance from 41.4% with the literature formula up to 46.9%. The performances in an actual clinical database were less good but showed the same improvement from 28% up to 35% of patients in the target range with the literature formula and our XGboost estimator, respectively. It is important to note that the performances of the literature formula were largely worse than those of the original study (28% vs. 70% in real patients) [25]. It may be explained by the narrower target range that we used in the present article (400-600 vs. 360-600 mg*h/L) and the differences in patient characteristics (term = 30 vs. 33.8 weeks of amenorrhea and weight = 1300 vs. 1700g in Leroux's study). Indeed, a recent prospective study targeting 360 to 600 mg*h/L showed an attainment of 74.6% using this formula [26]. We considered, following recent recommendations [2] that an interdose AUC target at steady-state should be > 400 mg*h/L (corresponding to $C_{ss} > 17$ mg/L) even if some studies question this threshold [27].

It is very important to quickly reach the AUC target for rapid efficacy. Administrating a loading dose helps in reaching this target in most but not all cases. Indeed, premature neonates with sepsis have a high mortality rate and may have many morbidities such bronchopulmonary dysplasia, necrotizing enterocolitis, prematurity retinopathy, prolonged hospitalization and long term adverse neurodevelopment outcomes [28]. Nephrotoxicity occurs in 1-9% neonates receiving the currently recommended dose of vancomycin [5]. The percentage of

overexposure observed in this study was lower with ML doses than with the LE, potentially resulting in a decreased occurrence of nephrotoxicity.

Inter-individual pharmacokinetic variability is higher in neonates than in adults and the former are characterized by a higher distribution volume and a lower clearance [29]. Among the factors influencing vancomycin PK variability in neonates, one can cite the increasing glomerular filtration rate depending on gestational age and post-natal age, the presence of intra-uterine growth restriction and co-administration of cyclo-oxygenase inhibitors, amikacin or dopamine [3]. Based on our personal experience, the urinary output is also an important factor of variability. Even with ML initial dose estimation, the exposure target attainment rate still exhibits values around 35% in real patients, meaning that two third of the patients would receive a suboptimal initial dose. It means that there is still room for improvement, owing to the many variability factors that are currently not accounted for.

In this study, the PK profiles used to train the ML algorithms were obtained from Monte Carlo simulations using a previously published POPPK model [14]. The simulations were based on published covariables and their distributions, in order to obtain the most realistic and representative “simulated population” as possible. We did not simulate covariates with covariance. However, we simulated independently each week of GA and weight using the Fenton curves. This granularity (1 week per one week) in the simulations prevents unrepresentative combinations. This is also the reason why we removed extreme values, and the residual error was set to values close to 0 since they are applied to concentrations and not to PK parameters, leading to unrealistic gaps between 2 consecutive concentrations. We however choose to perform a sensitivity analysis in which we kept the original error model and a second one in which we kept the extreme values. As expected, the performances obtained were largely worse than the one without extreme value and with the decreased error model. We previously used this methodology successfully for the estimation of tacrolimus AUC from simulated concentrations [13]. However, the principle of the analysis in the present article was different as the goal was to estimate vancomycin initial dose *a priori*, without observed data.

In this study, we compared the performances of 3 ML algorithms. We choose Xgboost, an ensemble tree approach that use boosting because it has shown very good performances in our previous works [13,30]. We select MARS algorithm that uses splines because it also capture nonlinear relationships using and is not based on trees and has also been previously used in our team with very good performances [30] and a linear model with penalization for evaluating a linear algorithm.

As performed in our previous study, the best ML estimator was validated against actual data. However, since we were dealing with retrospective analysis of the initial dose, we could only indirectly assess the performances of our estimators. Indeed, if an administered dose gave exposure below target, we proposed a higher dose and we had to estimate the resulting AUC using a cross-product, which implies a strong linearity hypothesis. This is probably the main limit of this work. However, we used the same approach for our ML estimator and the literature formula, thus allowing direct comparison.

The ML algorithm was evaluated in a second simulated set which was developed like the first one. In this case, the joint distribution of the variables in the second sample is identical to that of the first simulated set and therefore the performances of the models should be the same as those observed on the test set. That was a way to measure sampling fluctuation but that could also have been done by simulating an unique larger sample dataset.

However, we used the first simulated data to estimate the performances in terms of rMPE and rRMSE while we used the second to estimate the proportion of AUC extrapolated in or out the target range.

Our study had some other limitations. For the ML estimator development, we chose the concentration at 48 hours by learning the $AUC_{48-72h_{ref}}$. Even if a loading dose was used in all simulated patients, some profiles had probably not reached steady-state by then, especially for simulated patients with the highest creatinine values. However, this time point corresponds to the clinical blood draw in clinical care in most of the time for the monitoring of vancomycin continuous infusion. In the external set, the median weight was lower than in the simulations because we had more premature patients and the median weight observed is in accordance with the weights observed in a NICU department. However, the goal of this work was to develop an algorithm for preterm and term neonates that explains range of weight observed in the simulation. Another limitation is the small number of variables used for ML estimator development. However, as this ML algorithm was trained on simulated data generated using a previously published POPPK model, we were limited to the covariates selected in the POPPK model[14]. This POPPK model was chosen mainly because: it was developed in a large group of patients; it (still) included many covariates; and it was different from that used to derive the formula considered as a comparator in the present study. Finally, no simple equation can be directly derived from the developed ML algorithm and to overcome that, we developed a shiny.app (https://vanco.shinyapps.io/app_vanco_neonate/) for demonstration. The boundary used in the Shiny.app were current weight between 500 and 5000 grams, Post-natal age between 24 and 45 weeks and creatinine values between 40 and 145 μM . The source code is available at: <https://github.com/LaureP87/vancomycin.git>

Conclusion

In conclusion, the ML estimator that we have developed to estimate vancomycin initial dose in term or preterm neonates improves the exposure target attainment rate, with a lower likelihood of overexposure that might decrease the incidence of nephrotoxicity. Further prospective investigations are needed to confirm its clinical relevance in this population.

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Conflict's interest

The authors have no competing interests to declare in relation to this work

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Authors contributions statement

LP & JBW: made substantial contributions to the conception, design of the work; acquisition, analysis, interpretation of data and drafted the work, PE : made substantial contributions to the acquisition and analysis, PM and ML made substantial contributions to the interpretation of data and EJA made substantial contributions to the acquisition, interpretation of data and draft. AD built the shiny application.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table 1: Characteristics of the simulated profiles in the analysis, assessment and test sets, robustness evaluation in an independent simulation set (n°2) and external validation using a database of real patients.

Variables	Simulation set n°1				Simulation set n°2	Real patients
	Analysis set N= 1025	Assesment set N=260	Training set (Analysis+ assessment set) N=1285	Test set N=432	Robustness evaluation in an independent simulation set N=1692	External validation N=82
Birth weight (grams)	1801.01 [1077.63, 2925.62]	1913.05 [1091.69, 2887.65]	1827.31 [1080.84, 2923.72]	2024.63 [1107.60, 3032.46]	1873.77 [1081.80, 2899.82]	1230.00 [786.00, 1889.80]
Gestational age (weeks)	33.08 [28.61, 38.09]	33.59 [29.06, 37.42]	33.19 [28.61, 38.03]	34.01 [29.28, 38.19]	33.33 [28.90, 38.05]	30.57 [27.43, 34.54]
Weight gain (gr/days)	13.80 [11.54, 15.54]	13.82 [11.45, 15.66]	13.80 [11.54, 15.61]	13.68 [11.56, 15.46]	12.55 [10.13, 14.47]	9.80 [2.98, 20.69]
Post-Natal Age (days)	27.29 [17.47, 48.61]	27.57 [15.68, 46.69]	27.44 [17.43, 48.61]	27.36 [17.47, 48.61]	27.66 [14.20, 47.72]	20.5 [5.50, 24.50]
Current weight (grams)	2342.42 [1545.14, 3405.38]	2388.31 [1594.33, 3307.68]	2346.50 [1558.37, 3399.46]	2498.15 [1616.10, 3497.05]	2339.26 [1526.54, 3334.02]	1748.00 [987.00, 2257.00]
Post Menstrual Age (weeks)	38.03 [33.15, 42.60]	37.99 [33.38, 42.39]	38.02 [33.17, 42.49]	38.38 [33.61, 42.94]	38.20 [33.19, 42.59]	32.71 [30.43, 37.3]
Creatinine (µmol/L)	70.92 [58.13, 94.98]	67.26 [57.34, 86.65]	70.62 [57.50, 92.29]	70.62 [57.17, 100.65]	71.04 [55.59, 94.01]	41.50 [28.50, 62.50]
Continuous Dose (mg)	64.19 [35.26, 118.29]	65.76 [37.23, 115.51]	64.65 [35.78, 118.04]	74.88 [38.48, 122.40]	67.41 [35.91, 116.23]	37.50 [24.30, 68.75]
AUC48-72h (mg*h/L)	597.90 [453.03, 782.00]	600.30 [455.77, 779.31]	597.90 [454.12, 782.00]	599.31 [454.05, 782.78]	593.03 [454.06, 765.31]	395.00 [304.80, 460.80]

Continuous variables are presented as median [IQR].

Table 2: Comparative performances of three ML algorithms in the analysis and assessment sets.

	residual error decreased			Original residual error		
	Relative MPE (%)	Relative RMSE (%)	Number of estimates out of \pm the 20% interval n (%)	Relative MPE (%)	Relative RMSE (%)	Number of estimates out of \pm the 20% interval n (%)
XGBOOST *Analysis set	6.85	35.4	568(55.4)	13.8	47.75	684(66.7)
XGBOOST Assesment set	5.66	38.14	147 (56.5)	12.4	44.95	164(63.2)
GLMNET *Analysis set	10.16	37.05	530(51.7)	15.41	47.61	685(66.8)
GLMNET Assesment set	9.44	39.25	147(56.5)	9.10	37.75	146(56.1)
MARS *Analysis set	9.90	36.72	547(53.3)	14.99	48.00	680(66.4)
MARS Assesment set	9.30	39.78	143(55.0)	14.88	47.01	176(67.6)

*Results in the analysis set were obtained after 10-fold cross validation; GLMNET is LASSO and Elastic-Net Regularized Generalized Linear Models, XGBOOST is extreme gradient boosting and MARS is Multivariate Adaptive Regression Splines, MPE is mean prediction error, RMSE is root mean square error.

Table 3: Number of patients with theoretical AUC below, within, or above the therapeutic range calculated using the references doses, machine learning (ML) doses and literature equation (LE) doses [25] in the independent simulated set n°2

		AUC (mg*h/L) ML doses			Total
		<400	400-600	>600	
AUC(mg*h/L) with references doses	<400	231	49	0	280
	400-600	193	356	34	583
	>600	26	388	415	829
Total		450	793	449	1692

		AUC (mg*h/L) with LE doses [24]			Total
		<400	400-600	>600	
AUC (mg*h/L) with ML doses	<400	328	119	3	450
	400-600	97	494	202	793
	>600	1	89	359	449
Total		426	702	564	1692

		AUC (mg*h/L) with LE doses [24]			Total
		<400	400-600	>600	
AUC (mg*h/L)with references doses	<400	201	75	4	280
	400-600	170	320	93	583
	>600	55	307	467	829
Total		426	702	564	1692

AUC is area under the curve

Table 4: Number of patients with theoretical AUC below, within, or above the therapeutic range calculated using the references doses, machine learning (ML) doses and literature equation (LE) doses [25] in the external database from actual patients (n=82).

		AUC48-72h (mg*h/L) with LE doses [24]			Total
		<400	400-600	>600	
AUC48-72h (mg*h/L)with ML doses	<400	39	7	3	49
	400-600	11	14	4	29
	>600	0	2	2	4
Total		50	23	9	82

		AUC48-72h (mg*h/L) ML doses			Total
		<400	400-600	>600	
AUC48-72h (mg*h/L) references doses	<400	36	6	0	42
	400-600	10	18	1	29
	>600	3	5	3	11
Total		49	29	4	82

		AUC48-72h (mg*h/L) with LE doses [24]			Total
		<400	400-600	>600	
AUC48-72h (mg*h/L) with references doses	<400	32	8	2	42
	400-600	14	13	2	29
	>600	4	2	5	11
Total		50	23	9	82

AUC is area under the curve

Figure legends

Figure 1: Distribution of the simulated vancomycin $AUC_{48-72h_{ref}}$ values used for the development of machine learning algorithms using three different algorithms (AUC is area under the curve in $mg \cdot h/L$)

Figure 2: Xgboost variable importance plot in the analysis set.

Figure 3: Paired boxplots comparing the log of the 3 dose proposals (reference, literature equation [25] and ML doses) and split into 3 groups: AUC calculated with references doses in the target range (400-600 $mg \cdot h/L$), below the target ($mg \cdot h/L < 400$) and above the target ($> 600 mg \cdot h/L$) in the independent simulated set ($n = 2$).

Figure 4: Paired boxplots comparing the log of the 3 dose proposals (reference, literature equation [25] and ML doses) and split into 3 groups: AUC calculated with references doses in the target range (400-600 $mg \cdot h/L$), below the target ($mg \cdot h/L < 400$) and above the target ($> 600 mg \cdot h/L$) in the external database from actual patients ($n = 82$).