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Drug Clearance in Neonates: A Combination of Population Pharmacokinetic Modelling and Machine Learning Approaches to Improve Individual Prediction

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Running title: Combining Population Pharmacokinetic Modelling and Machine Learning Approaches to Improve Prediction of Neonatal Clearance

87 **Abstract**

88 **Background.** Population pharmacokinetic evaluations have been widely used
89 in neonatal pharmacokinetic studies, while machine learning has become a
90 popular approach to solving complex problems in the current era of big-data.
91 The objective of this proof-of-concept study was to evaluate whether combining
92 population pharmacokinetic and machine learning approaches could provide a
93 more accurate prediction of the clearance of renally eliminated drugs in
94 individual neonates.

95 **Methods.** Six drugs that are primarily eliminated by the kidneys were selected
96 (vancomycin, latamoxef, cefepime, azlocillin, ceftazidime, amoxicillin) as “proof
97 of concept” compounds. Individual estimates of clearance obtained from
98 population pharmacokinetic models were used as reference clearances, and
99 diverse machine learning methods and nested cross-validation were adopted
100 and evaluated against these reference clearances. The predictive performance
101 of these combined methods was compared to the performance of two other
102 predictive methods: a covariate based maturation model; and a postmenstrual
103 age and body weight scaling model. Relative error was used to evaluate the
104 different methods.

105 **Results.** The extra tree regressor was selected as the best-fit machine learning
106 method. Using the combined method, more than 95% of predictions for all six
107 drugs had a relative error of less than 50% and the mean relative error was

reduced by an average of 44.3% and 71.3% compared to the other two predictive methods.

Conclusion. A combined population pharmacokinetic and machine-learning approach provided improved predictions of individual clearances of renally cleared drugs in neonates. For a new patient treated in clinical practice, individual clearance can be predicted a priori using our model code combined with demographic data.

Key Points

1. The objective of this study was to investigate whether the combination of population pharmacokinetic modelling and a machine-learning approach provides more accurate predictions of the individual clearances of 6 renally eliminated drugs using data from 2272 neonates.
2. The prediction models that combine population pharmacokinetic modelling and machine learning approaches can provide improved predictions of the individual clearances of renally cleared drugs in neonates compared to two other predictive population pharmacokinetic models.
3. The final prediction models are available as a package in Python. The individual clearance of a new patient who is being treated in clinical practice can be predicted a priori using our model code and demographic data. As a consequence, the initial dose can be determined more precisely.

1. Introduction

Despite governmental regulations to promote drug research in neonates in the United States and Europe, most drugs in this vulnerable population are still used off-label. Drug development to support neonatal drug dose requirements is limited because many innovative technologies cannot be directly applied to neonates [1, 2]. Furthermore, such patients present many challenges due to rapid maturational changes during early life, resulting in extensive inter-individual variability in pharmacokinetics and pharmacodynamics [3]. Consequently, clinical pharmacology research is a crucial component of drug dose optimization for neonates. Population pharmacokinetic analysis has been widely used in neonatal pharmacology and optimal drug dosages based on model-based simulation techniques have been proposed [4-6]. Machine learning, a data-driven approach, uses algorithms to learn from data, and then makes decisions and predictions about events in the real world. Unlike traditional software programs that solve specific tasks with hard coding, machine learning uses training data to learn how to accomplish tasks through various algorithms [7]. It has become indispensable for solving complex problems in this era of “big data”, and has opened up many new possibilities for clinical applications. Examples include prediction of either cardiovascular or all-cause mortality [8], enhancement of radiology decisions [9], prediction of mental illness [10], and optimization of antibiotic dosing strategies [11].

Combining population pharmacokinetics with machine learning approaches may result in more computationally powerful data science tools that could enhance the achievement of precision medicine in this vulnerable, neonatal population [12, 13].

For renally eliminated drugs, clearance in neonates is often expressed as a function of growth (size), maturation (gestational, postnatal or postmenstrual age) and kidney function; all based on developmental population pharmacokinetic analyses [14]. In this proof-of-concept study, we hypothesized that we could predict individual clearance values by combining population pharmacokinetics with machine learning approaches. Six drugs that are primarily eliminated by the kidneys: vancomycin, cefepime, latamoxef, amoxicillin, azlocillin and ceftazidime were selected as “proof of concept” compounds. The objective of the study was to evaluate whether a combination of the two methods could accurately predict the individual clearances of renally eliminated drugs in neonates.

2. Methods

This study consisted of three steps: population pharmacokinetic analysis, machine learning analysis, and predictive performance comparison. The essential information for each step is summarized in Figure 1. The study

protocol was applied to all six drugs. Six different models were built using this combined approach.

2.1 Population pharmacokinetic model analysis

Pharmacokinetic data were extracted from previous studies of vancomycin, cefepime, latamoxef, amoxicillin, azlocillin, and ceftazidime [4, 15, 16, 5, 17, 18]. These studies had been approved by the institutional ethics committees and were conducted according to the ethical principles of the Declaration of Helsinki.

Population pharmacokinetic analysis was carried out using the nonlinear mixed-effects modeling program NONMEM V 7.4 (Icon Development Solutions, USA). This part repeated the analyses conducted to determine the original six pharmacokinetic models. The first-order conditional estimation (FOCE) method with interaction was used to estimate pharmacokinetic parameters, inter-individual variability and residual variability. Covariate analysis followed a standard forward and backward selection process.

Individual estimates of clearances were obtained for each neonate from these population pharmacokinetic models via Bayesian estimation and defined as “reference clearances”, i.e. the “reference clearance” is the post hoc clearance derived from individual concentration data and the population pharmacokinetic model for each antibiotic.

2.2 Machine learning analysis

To fit individual reference clearances derived from step 1, diverse state-of-the-art machine learning methods were adopted for exploratory analyses, including k-nearest neighbor (KNN) [19], decision tree [20], adaptive boosting (Adaboost) [21], extra tree regressor (ETR) [22], random forest (RF) [23], gradient boosted regression with trees (GBR) [24] and logistic regression with ridge [25], lasso [26] and elastic net regularization (EN) [27].

The input predictors were birth weight (BW), current weight (CW), gestational age (GA), postnatal age (PNA), postmenstrual age (PMA), and serum creatinine valueconcentration (CREA). (For the data format, see *Supplementary Material* “Input data example”). All machine learning models were implemented in “scikit-learn” (sklearn) using Python 3.6 [28].

Nested cross-validation (NeCV) was used to validate all machine learning models. NeCV has been accepted widely in the machine learning community as “state-of-the-art”, as it has been found to be an (almost) unbiased model assessment method when estimating the true error [29, 30]. The inner cross-validation is used to select the best parameters while the outer cross-validation is used to evaluate the performance of the model using the best parameters of the inner cross-validation selection (see figure 2).

The detailed data set partition information was as follows (figure 2):

(1) The whole data set was randomly divided into five parts, on average.

(2) One part was selected as the outer testing set and the remaining four parts as the outer training set. This step was repeated five times, each time taking a different part as the outer testing set.

(3) The inner training set was randomly divided into five parts on average. One part was then selected as the inner test set and the remaining four parts as the inner training set.

(4) Each inner training set was used for initial model fitting and the inner testing data set was used to tune and optimize the parameters of the model. The best machine learning model was then chosen across tested scenarios.

(5) The outer test set was then used to evaluate the best machine learning model.

(Through each training of the ML algorithm, each outer test set of reference clearances was not used for model development.)

Graphical and statistical criteria were used to select the optimal machine learning approach and validate the performance of the final model. Scatterplots of individual reference clearances (dependent variable) versus individual predicted clearances were initially used for diagnostic purposes. Two statistical metrics, the coefficient of determination (r^2 score) and the mean squared error (MSE), were used to assess the performance of the machine learning model. The coefficient of determination is the squared correlation coefficient between the estimated values (reference clearances) and the predictor values, which

normally ranges from 0 to 1. The bigger value of the r^2 score represents a better prediction of the model. MSE is an estimator that measures the average of the square of the errors.

Individual predicted clearances were obtained using the final optimal approach and parameters. The importance of each clinical factor was calculated and visualized using Python [31].

2.3 Comparison of predictive performances

In this part, we compared the predictive performances of the following three prediction methods:

Predictive method 1: proposed combined model (population pharmacokinetic and machine learning)

Predictive method 2: maturation model

Predictive method 3 [32]: PMA and body weight scaling model

For predictive method 1, individual predicted clearances were obtained using the final, combined model.

For predictive methods 2 and 3, the predicted individual clearances were parameterized as follows:

$$CL_{prediction} = \theta_{CL} * F_{size} * F_{age} * F_{renal}$$

Where θ_{CL} represents the typical value of clearance and F_{size}, F_{age}, and F_{renal} represent the effects of size, age, and renal function, respectively.

For predictive method 2, F_{size}, $F_{age,}$ and F_{renal} were estimated according to different population pharmacokinetic models (step 1). For example, for latamoxef, F_{size} characterizes the effect of current weight (CW), F_{age} the effects of birth weight (BW) and postnatal age (PNA) and F_{renal} is 1 (no effect). Detailed equations for the six drugs are as follows:

vancomycin [4], $CL=0.068*(CW/1.35)^{0.863}*(PMA/32)^{0.544}*1/(0.72*CREA/54)^{0.666}$;

cefepime [15], $CL=0.589*(CW/3.35)^{0.75}*(PMA/40)^{1.16}*1/(CREA/28.5)^{0.218}$;

latamoxef [16], $CL=0.268*(CW/3.22)^{0.75}*(BW/3.10)^{0.288}*(PNA/8)^{0.214}$;

amoxicillin [5], $CL=0.812*(CW/3.21)^{0.75}*(GA/38.1)^{4.19}*(PNA/7)^{0.281}$;

azlocillin [17], $CL=0.440*(CW/3.34)^{0.75}*(BW/3.39)^{0.907}*(PNA/3)^{0.367}$;

ceftazidime [18], $CL=0.356*(CW/3.08)^{0.75}*(GA/38.6)^{1.57}*(PNA/11)^{0.22}$;

where CW is current weight, BW is birth weight, GA is gestational age; PNA is postnatal age; PMA is postmenstrual age; CREA is creatinine.

For predictive method 3, proposed by Wang et al, [32], fixed and unified functions of F_{size} and F_{age} were applied and θ_{CL} represents adult clearance. The functions were as follows:

$$F_{size} = (Weight / Weight_{std})^{0.75}$$

$$F_{age} = PMA^{3.4} / (PMA^{3.4} + 47.7^{3.4})$$

where $Weight_{std}$ is the standard adult weight of 70 kg and PMA is postmenstrual age. The detailed equations for the six drugs are as follows:

vancomycin, $CL=5.9*(CW/70)^{0.75}*(PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$;

cefepime, $CL=7.74*(CW/70)^{0.75}*(PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$;

latamoxef, $CL=5.2*(CW/70)^{0.75}*(PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$;

amoxicillin, $CL=18*(CW/70)^{0.75}*(PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$;

azlocillin, $CL=10.5*(CW/70)^{0.75}*(PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$;

ceftazidime, $CL=11.4*(CW/70)^{0.75}*(PMA^{3.4}/(PMA^{3.4}+47.7^{3.4}))$;

θ_{CL} values of 5.9, 7.74, 5.2, 18, 10.5, and 11.4 L/h represent the adult clearance values for each drug.

Five data sets (the five outer test data sets in the machine learning analysis step) were used as the evaluation data sets for the three methods. The prediction performance of the three predictive methods was evaluated using relative errors, which were calculated as follows:

$$Relative\ errors = | CL_{prediction} - CL_{reference} | / CL_{reference}$$

Where $CL_{prediction}$ represents predicted clearance values and $CL_{reference}$ represents individual “reference clearances”.

3. Results

3.1 Population pharmacokinetic model analysis

A total of 2272 neonates were included. The mean (SD) values of CW and PMA were 2.99 (1.18) (range 0.415 to 11.4) kilograms and 34.7 (5.6) (range 23.3 to 52.4) weeks. Correlations between BW and GA and between PMA and CW had coefficients of 0.920 and 0.868, respectively. Patient characteristics

293 and the population pharmacokinetic models of the six renally-eliminated drugs
294 are presented in Table 1 [4, 5, 15-17].

295 **3.2 Machine Learning analysis**

296 The Machine Learning analysis was applied separately to each of the six
297 drugs and the results of the different machine learning approaches are
298 presented in Table 2. ETR (extra tree egressor) was the optimal machine
299 learning approach for latamoxef, amoxicillin and ceftazidime and although it
300 was not the best approach, it also performed well for vancomycin, cefepime
301 and azlocillin. Consequently. ETR was selected as the final uniform machine
302 learning approach. Detailed results of the final ML outcomes for the five outer
303 test data sets can be found in the ESM (“ML outcomes for the five outer test
304 data sets”).

305 Goodness-of-fit results for the final models of all six drugs are shown in the
306 scatterplots presented in Figure 3. In order to show the results more intuitively,
307 only one of the five test sets was selected for display. Good predictions of
308 individual clearances were achieved with the combined method.

309 The relative importance of the main factors influencing the individual
310 clearances of each of the six drugs is presented in Figure 4. Current weight was
311 the most important predictor for cefepime, amoxicillin, azlocillin and ceftazidime,
312 whereas PMA was the most important predictor for vancomycin and PNA for
313 latamoxef.

3.3 Comparison of predictive performance

Table 3 shows the mean relative errors for all three methods for all antibiotics. The mean relative errors for the combined predictive method (method 1), were 15.4%, 2.2%, 2.8%, 16.9%, 10.1% and 2.0% for vancomycin, cefepime, latamoxef, amoxicillin, azlocillin and ceftazidime, respectively. With the exception of method 2 for azlocillin (9.9%) all the mean relative errors were higher with methods 2 and 3 than with method 1. The overall mean relative error of the combined method was 8.24%, which was lower by an average of 44.3% and 71.3% than the other two predictive methods (14.8% and 28.7%), respectively.

Figure 5 shows the percentages of patients whose relative errors were within 10%, 30% and 50% for each of the three analysis methods. The highest percentages were consistently achieved with method 1; differences were particularly notable in the 10% and 30% ranges. For all six drugs, method 1 achieved more than 95% of predictions for all antibiotics within a relative error of 50%.

4. Discussion

To the best of our knowledge, this is the first study to demonstrate an innovative method that uses a combination of population pharmacokinetic models and machine learning approaches to predict individual clearances of

renally eliminated drugs in neonates. Since the introduction of population pharmacokinetics by Sheiner in the 1970s [33], several developments have led to models based on mechanistic and pharmacological principles that support a biological interpretation of parameters [34]. Individual pharmacokinetic profiles can be described and the pharmacokinetic behavior of many individuals can be characterized by simultaneously quantifying the covariates that are known to be sources of variability [35]. Population pharmacokinetic methods also facilitate the analysis of sparse data, which reduces the burden of multiple sample collection [36]. This is particularly relevant for neonates, from whom only sparse samples can be collected due to ethical and practical limitations. In clinical practice, Bayesian parameter estimation can then be used to estimate parameters and adjust dosage regimens for individual patients by combining a validated pharmacokinetic model with observed concentration data.

Despite these developments, prediction of individual neonatal parameters from a population pharmacokinetic model has its challenges. For renally eliminated drugs, clearance is often expressed as a function of growth (size or current weight), renal maturation, and/or renal function (serum creatinine/estimated glomerular filtration rate). Due to the colinearity of the covariates, size correction is necessary and current weight is typically incorporated into the basic model using an allometric size approach [37]. Different age indicators, such as birth weight (BW), postmenstrual age (PMA), postnatal age (PNA),

gestational age (GA) and combination formulas have been incorporated into different models without a clear consensus on the best approach. This is illustrated by Wade et al., who used a combination of GA and PNA in their fluconazole model [38], Li et al., who used BW and PNA to describe the population pharmacokinetics of piperacillin [39] and Cohen-Wolkowiez et al. who used PMA to describe renal maturation changes in their piperacillin model [40]. Serum creatinine concentration is commonly used as a biomarker for the glomerular filtration rate in population models. However, this approach has limitations as in the first few days after birth, creatinine concentration is significantly affected by maternal levels and does not reflect neonatal renal function [41].

Neonates have extensive intra- and inter-subject variability in drug disposition and clinical response due to rapid physiological changes and specific pathophysiology [42]. Population pharmacokinetic studies have often found that a large proportion of inter-subject variability cannot be explained by covariates (fixed effects) and is instead captured as random effects. For example, Wang et al. described a renal maturation model based on size, age and renal function that could predict the clearances of renally eliminated drugs in newborns [32]. The model resulted in high uncertainty with prediction results ranging from 0.6-2.0 (prediction bias) [32]. This demonstrates that fixed-effect

models are not always able to explain sufficiently the variability found in clinical settings.

In recent years, machine learning methodology has become increasingly popular in different domains. These approaches can handle large numbers of predictors and allow the use of new types of data, whose sheer volume or complexity would previously have made their analysis unimaginable [43]. Machine learning is not based on the results of programming, its processing is not a causal logic, but a correlation conclusion drawn through inductive thinking. Furthermore, machine learning is a data-driven approach, thereby eliminating the need for mechanistic assumptions. From a pharmacological perspective, these features might be considered as a “black-box” method, and pharmacologists and clinical researchers may be reluctant to embrace this approach without making assumptions based on developmental pharmacology [35]. Even though machine learning has been successfully applied in the prediction of preterm infant survival rate [44] and neonatal hyperbilirubinemia [45], predicting neonatal drug clearance is a challenge due to fast-changing maturation processes and a lack of diagnostic feature values. Moreover, the selection of influencing factors has additional challenges to ensure that they are physiologically relevant and easily available in clinical practice.

Based on the above challenges, combining population pharmacokinetic and machine learning approaches may prove useful. The population approach

can utilise basic knowledge of physiology and pharmacological development while machine learning models can implement physiologically significant covariates preselected by the population model as part of the study design. In the present study, it was found that for all six drugs, the combined approach achieved more than 95% of predictions within a 50% relative error (Figure 5), a result that was superior to those obtained with the 'stand-alone' pharmacometric models (predictive methods 2 and 3). This improvement in predictive performance demonstrates that a combination of machine learning and population pharmacokinetics is feasible and accurate.

The final prediction models have been incorporated into a package in Python and the codes for these models can be accessed in the *Supplementary Material* "final model code". The models can be used to predict individual clearances of each drug in neonates, based on the patient's demographic data (e.g. BW, CW, GA, PNA, PMA, CREA). These clearance estimates can then be used to determine a more accurate, personalized, starting dosage regimen for each patient. Further optimization of this initial dosage regimen to achieve target concentrations or exposure would involve MAP Bayesian analysis to determine revised individual parameter estimates by combining information from measured concentrations with parameters from the population pharmacokinetic model.

Even though developmental, pharmacology-based clinical characteristics were used in building the machine learning models, the contributory factors for each drug were still different in the final prediction models. This may be explained by differences in drug properties (e.g. plasma protein binding, molecular mass) and mechanisms of elimination. Renal elimination consists of glomerular filtration, tubular secretion, tubular reabsorption, and intracellular enzymatic processing [46] but even for a renally excreted drug, non-renal pathways, such as biliary excretion, or other (unknown) pathways frequently exist. The adult values of the various elimination processes of the six drugs in this study are summarized in Table 4 [32, 47-52]. The percentage of renal clearance ranges from 55% to 90% and the magnitudes of drug metabolism and other elimination routes are also variable, which may result in different predictive combinations and variability in drug clearance assessments. In neonates, differences in prediction performances might also be related to varying contributions of renal clearance to total drug clearance.

Amoxicillin and azlocillin had the worst machine learning model testing set results based on MSE and r^2. The reason may be that the mechanism of drug elimination is complex. Pharmacokinetic information on the mechanisms and proportions of renal and non-renal elimination are very sparse in this patient group and further research is required.

In the population pharmacokinetic analyses of this study, an opportunistic sampling strategy was used for all six models and this was assumed to provide reasonable estimates of clearance compared with a standard, predetermined sampling strategy [53]. All models have previously been evaluated by external validation methods [54] and one has also been validated clinically [17]. In addition, the ETA shrinkage (%) of clearance for all drugs was less than 30%. These findings demonstrate the reliability of the population pharmacokinetic models and justify the use of individual clearance estimates derived from these models as reference values.

Our study has some limitations. Firstly, the methods are only valid within the covariate space used to build the models. Secondly, although serum creatinine, a widely used biomarker of renal function, is included in the model, residual, maternally derived creatinine or different creatinine assay methods may render this biomarker less than ideal to predict renal function in neonates [55, 54]. In the present study, serum creatinine was found to contribute more than 20% (20/100) when the relative importance of factors was assessed for vancomycin and cefepime. These two drugs have the highest percentage of renal clearance, lack significant tubular secretion and have low protein binding. Alternative biomarkers are needed to better reflect renal function in neonates.

Building complex machine learning models from sparse data always carries a risk of data memorization and this study was not designed to identify the

number of neonates required to accurately predict the clearance of renally eliminated drugs using this approach. Nevertheless, the predictive performances were consistently good with patient numbers ranging from small (cefepime, 85 patients) to large (vancomycin, 1631 patients). Moreover, differences in age distribution were not considered. Although the key covariates associated with maturation were included in the current study, some drug-related covariates were missing. Plasma protein binding affects the free drug concentrations that determine drug elimination and is influenced by various maturational factors, leading to high variability in the unbound fraction in neonates [38, 39]. Disease-related factors were also missing. Future studies using a combined population pharmacokinetic and machine learning analysis approach should evaluate the impact of these covariates on the prediction of individual clearances, examine drug clearance following non IV routes of administration and identify predictors for drugs that are also metabolized.

5. Conclusion

A combined population pharmacokinetic and machine-learning approach provided consistent descriptions of individual clearances of renally drugs in neonates. For new neonatal patients treated in clinical practice, individual clearances can be predicted in advance using the model code and demographic data and used to individualize the initial dosing regimen.

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CONFLICT OF INTEREST

Bo-Hao Tang, Zheng Guan, Karel Allegaert, Yue-E Wu, Efthymios Manolis, Stephanie Leroux, Bu-Fan Yao, Hai-Yan Shi, Xiao Li, Xin Huang, Wen-Qi Wang, A-Dong Shen, Xiao-Ling Wang, Tian-You Wang, Chen Kou, Hai-Yan Xu, Yue Zhou, Yi Zheng, Guo-Xiang Hao, Bao-Ping Xu, Alison H. Thomson, Edmund V. Capparelli, Valerie Biran, Nicolas Simon, Bernd Meibohm, Yoke-Lin Lo, Remedios Marques, Jose-Esteban Peris, Irja Lutsar, Jumpei Saito, Jacobus Burggraaf, Evelyne Jacqz-Aigrain, John van den Anker and Wei Zhao declare

that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

ETHICS APPROVAL

All the data were obtained from previous studies. These studies were approved by the institutional ethics committee.

CONSENT TO PARTICIPATE

All participants received written informed consent in the previous studies.

CONSENT FOR PUBLICATION

Written informed consent for publication was obtained from previous studies.

AVAILABILITY OF DATA AND MATERIAL

Research data are not shared.

CODE AVAILABILITY

Research code available.

AUTHORS' CONTRIBUTIONS

Bo-Hao Tang and Zheng Guan contributed equally to the interpretation of the data for the work, drafting of the initial manuscript, and revising of the manuscript. Bo-Hao Tang, Yue-E Wu, Bu-Fan Yao, Hai-Yan Shi, Xiao Li, Xin Huang, Wen-Qi Wang, Yue Zhou, Yi Zheng and Guo-Xiang Hao analyzed data. Zheng Guan, A-Dong Shen, Xiao-Ling Wang, Tian-You Wang, Chen Kou, Hai-Yan Xu and Bao-Ping Xu performed PK research. Karel Allegaert, Efthymios Manolis, Stephanie Leroux, Alison H. Thomson, Edmund V. Capparelli, Valerie

Biran, Nicolas Simon, Bernd Meibohm, Yoke-Lin Lo, Remedios Marques, Jose-Esteban Peris, Irja Lutsar, Jumpei Saito, Jacobus Burggraaf, Evelyne Jacqz-Aigrain and John van den Anker provided advice and data sets, critically reviewed and revised the manuscript. Wei Zhao designed the work, critically reviewed and revised the manuscript.

SUPPLEMENTARY INFORMATION (SI)

Supplementary Material -1: “Input data example”

Supplementary Material -2: “ML outcomes for the five outer test data sets”

Supplementary Material -3: “Final model code”

References

1. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin DK, Jr., Smith PB et al. Medication use in the neonatal intensive care unit. Am J Perinatol. 2014;31(9):811-21. doi:10.1055/s-0033-1361933.

2. Riou S, Plaisant F, Maucort Boulch D, Kassai B, Claris O, Nguyen K-A. Unlicensed and off-label drug use: a prospective study in French NICU. Acta Paediatrica. 2015;104(5):e228-e31. doi:10.1111/apa.12924.

3. Coppini R, Simons SHP, Mugelli A, Allegaert K. Clinical research in neonates and infants: Challenges and perspectives. Pharmacol Res. 2016;108:80-7. doi:10.1016/j.phrs.2016.04.025.

4. Jacqz-Aigrain E, Leroux S, Thomson AH, Allegaert K, Capparelli EV, Biran V et al. Population pharmacokinetic meta-analysis of individual data to design the first randomized efficacy trial of vancomycin in neonates and young infants. J Antimicrob Chemother. 2019;74(8):2128-38. doi:10.1093/jac/dkz158.

5. Tang BH, Wu YE, Kou C, Qi YJ, Qi H, Xu HY et al. Population Pharmacokinetics and Dosing Optimization of Amoxicillin in Neonates and Young Infants. Antimicrob Agents Chemother. 2019;63(2). doi:10.1128/AAC.02336-18.

6. Bradley JS, Sauberan JB, Ambrose PG, Bhavnani SM, Rasmussen MR, Capparelli EV. Meropenem pharmacokinetics, pharmacodynamics, and Monte

Carlo simulation in the neonate. Pediatr Infect Dis J. 2008;27(9):794-9. doi:10.1097/INF.0b013e318170f8d2.

7. Murphy KP. Machine learning : a probabilistic perspective. 2012.

8. Al'Aref SJ, Anchouche K, Singh G, Slomka PJ, Kolli KK, Kumar A et al. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. Eur Heart J. 2019;40(24):1975-86. doi:10.1093/eurheartj/ehy404.

9. Choy G, Khalilzadeh O, Michalski M, Do S, Samir AE, Pianykh OS et al. Current Applications and Future Impact of Machine Learning in Radiology. Radiology. 2018;288(2):318-28. doi:10.1148/radiol.2018171820.

10. Rutledge RB, Chekroud AM, Huys QJ. Machine learning and big data in psychiatry: toward clinical applications. Curr Opin Neurobiol. 2019;55:152-9. doi:10.1016/j.conb.2019.02.006.

11. Smith NM, Lenhard JR, Boissonneault KR, Landersdorfer CB, Bulitta JB, Holden PN et al. Using machine learning to optimize antibiotic combinations: dosing strategies for meropenem and polymyxin B against carbapenem-resistant Acinetobacter baumannii. Clin Microbiol Infec. 2020;26(9):1207-13. doi:10.1016/j.cmi.2020.02.004.

12. Zhu H, Huang SM, Madabushi R, Strauss DG, Wang Y, Zineh I. Model-Informed Drug Development: A Regulatory Perspective on Progress. Clin Pharmacol Ther. 2019;106(1):91-3. doi:10.1002/cpt.1475.

573 13. Goulooze SC, Zwep LB, Vogt JE, Krekels EHJ, Hankemeier T, van den
574 Anker JN et al. Beyond the Randomized Clinical Trial: Innovative Data
575 Science to Close the Pediatric Evidence Gap. Clin Pharmacol Ther.
576 2020;107(4):786-95. doi:10.1002/cpt.1744.
577 14. Wilbaux M, Fuchs A, Samardzic J, Rodieux F, Csajka C, Allegaert K et al.
578 Pharmacometric Approaches to Personalize Use of Primarily Renally
579 Eliminated Antibiotics in Preterm and Term Neonates. Journal of Clinical
580 Pharmacology. 2016;56(8):909-35. doi:10.1002/jcph.705.
581 15. Zhao Y, Yao BF, Kou C, Xu HY, Tang BH, Wu YE et al. Developmental
582 Population Pharmacokinetics and Dosing Optimization of Cefepime in
583 Neonates and Young Infants. Front Pharmacol. 2020;11:14.
584 doi:10.3389/fphar.2020.00014.
585 16. Qi H, Kou C, Qi YJ, Tang BH, Wu YE, Jin F et al. Population
586 pharmacokinetics and dosing optimization of latamoxef in neonates and
587 young infants. Int J Antimicrob Agents. 2019;53(3):347-51.
588 doi:10.1016/j.ijantimicag.2018.11.017.
589 17. Wu YE, Wang T, Yang HL, Tang BH, Kong L, Li X et al. Population
590 pharmacokinetics and dosing optimization of azlocillin in neonates with early-
591 onset sepsis: a real-world study. J Antimicrob Chemother. 2020.
592 doi:10.1093/jac/dkaa468.

18. Li X, Qi H, Jin F, Yao B-F, Wu Y-E, Qi Y-J et al. Population Pharmacokinetics-Pharmacodynamics of Ceftazidime in Neonates and Young Infants: dosing optimization for neonatal sepsis. European Journal of Pharmaceutical Sciences. 2020;Revision.

19. Sahigara F, Ballabio D, Todeschini R, Consonni V. Defining a novelk-nearest neighbours approach to assess the applicability domain of a QSAR model for reliable predictions. Journal of Cheminformatics. 2013;5(1):27.

20. Kamiński B, Jakubczyk M, Szufel P. A framework for sensitivity analysis of decision trees. Central European Journal of Operations Research. 2017;26(1):135-59. doi:10.1007/s10100-017-0479-6.

21. Kégl, Balázs. The return of AdaBoost.MH: multi-class Hamming trees. Computer Science. 2013.

22. Geurts P, Ernst D, Wehenkel L. Extremely randomized trees. Machine Learning. 2006;63(1):3-42.

23. SVETNIK V. Random Forest : A Classification and Regression Tool for Compound Classification and QSAR Modeling. Journal of Chemical Information & Computer Sciences. 2003;43.

24. Friedman JH. Greedy Function Approximation: A Gradient Boosting Machine. The Annals of Statistics. 2001;29(5):1189-232.

25. Dorugade A V, N KD. Alternative method for choosing ridge parameter for regression. Applied Mathematical Sciences. 2010;4(9):447-56.

614 26. Robert, Tibshirani. Regression Shrinkage and Selection via the Lasso.
615 Journal of the Royal Statistical Society. 1996;Series B: Methodological:273-
616 82.
617 27. Hui, Zou, Trevor, Hastie. Regularization and Variable Selection via the
618 Elastic Net.
619 28. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O et
620 al. Scikit-learn: Machine Learning in Python. J Mach Learn Res.
621 2011;12:2825-30.
622 29. Krstajic D, Buturovic LJ, Leahy DE, Thomas S. Cross-validation pitfalls
623 when selecting and assessing regression and classification models. J
624 Cheminformatics. 2014;6. doi:Artn 10
625 10.1186/1758-2946-6-10.
626 30. Varma S, Simon R. Bias in error estimation when using cross-validation
627 for model selection. Bmc Bioinformatics. 2006;7. doi:Artn 91
628 10.1186/1471-2105-7-91.
629 31. Brownlee J. Data Preparation for Machine Learning: Data Cleaning,
630 Feature Selection, and Data Transforms in Python, Machine Learning
631 Mastery. 2020.
632 32. Wang J, Kumar SS, Sherwin CM, Ward R, Baer G, Burckart GJ et al.
633 Renal Clearance in Newborns and Infants: Predictive Performance of

Population-Based Modeling for Drug Development. Clin Pharmacol Ther. 2019;105(6):1462-70. doi:10.1002/cpt.1332.

33. Sheiner LB, Rosenberg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm. 1977;5(5):445-79. doi:10.1007/bf01061728.

34. Brussee JM, Calvier EA, Krekels EH, Valitalo PA, Tibboel D, Allegaert K et al. Children in clinical trials: towards evidence-based pediatric pharmacotherapy using pharmacokinetic-pharmacodynamic modeling. Expert Rev Clin Pharmacol. 2016;9(9):1235-44. doi:10.1080/17512433.2016.1198256.

35. Koch G, Pfister M, Daunhawer I, Wilbaux M, Wellmann S, Vogt JE. Pharmacometrics and machine learning partner to advance clinical data analysis. Clin Pharmacol Ther. 2020. doi:10.1002/cpt.1774.

36. Graaf PH. Introduction to population pharmacokinetic/pharmacodynamic analysis with nonlinear mixed effects models. CPT Pharmacometrics Syst Pharmacol. 2014;3:e153. doi:10.1038/psp.2014.51.

37. Meibohm B, Laer S, Panetta JC, Barrett JS. Population pharmacokinetic studies in pediatrics: issues in design and analysis. AAPS J. 2005;7(2):E475-87. doi:10.1208/aapsj070248.

653 38. Wade KC, Wu D, Kaufman DA, Ward RM, Benjamin DK, Jr., Sullivan JE
654 et al. Population pharmacokinetics of fluconazole in young infants. Antimicrob
655 Agents Chemother. 2008;52(11):4043-9. doi:10.1128/AAC.00569-08.
656 39. Li Z, Chen Y, Li Q, Cao D, Shi W, Cao Y et al. Population
657 pharmacokinetics of piperacillin/tazobactam in neonates and young infants.
658 Eur J Clin Pharmacol. 2013;69(6):1223-33. doi:10.1007/s00228-012-1413-4.
659 40. Cohen-Wolkowiez M, Watt KM, Zhou C, Bloom BT, Poindexter B, Castro
660 L et al. Developmental pharmacokinetics of piperacillin and tazobactam using
661 plasma and dried blood spots from infants. Antimicrob Agents Chemother.
662 2014;58(5):2856-65. doi:10.1128/AAC.02139-13.
663 41. Kuppens M, George I, Lewi L, Levtchenko E, Allegaert K. Creatinaemia at
664 birth is equal to maternal creatinaemia at delivery: does this paradigm still
665 hold? J Matern Fetal Neonatal Med. 2012;25(7):978-80.
666 doi:10.3109/14767058.2011.602144.
667 42. Allegaert K, van de Velde M, van den Anker J. Neonatal clinical
668 pharmacology. Paediatr Anaesth. 2014;24(1):30-8. doi:10.1111/pan.12176.
669 43. Obermeyer Z, Emanuel EJ. Predicting the Future - Big Data, Machine
670 Learning, and Clinical Medicine. N Engl J Med. 2016;375(13):1216-9.
671 doi:10.1056/NEJMp1606181.
672 44. Podda M, Bacciu D, Micheli A, Bellu R, Placidi G, Gagliardi L. A machine
673 learning approach to estimating preterm infants survival: development of the

674 Preterm Infants Survival Assessment (PISA) predictor. Sci Rep.
675 2018;8(1):13743. doi:10.1038/s41598-018-31920-6.
676 45. Bartz-Kurycki MA, Green C, Anderson KT, Alder AC, Bucher BT, Cina RA
677 et al. Enhanced neonatal surgical site infection prediction model utilizing
678 statistically and clinically significant variables in combination with a machine
679 learning algorithm. Am J Surg. 2018;216(4):764-77.
680 doi:10.1016/j.amjsurg.2018.07.041.
681 46. Schreuder MF, Bueters RR, Allegaert K. The interplay between drugs and
682 the kidney in premature neonates. Pediatr Nephrol. 2014;29(11):2083-91.
683 doi:10.1007/s00467-013-2651-0.
684 47. Van der Auwera P, Santella PJ. Pharmacokinetics of cefepime: a review.
685 J Antimicrob Chemother. 1993;32 Suppl B:103-15.
686 doi:10.1093/jac/32.suppl_b.103.
687 48. Shepherd AM, Hardin TC, Ludden TM, Miner DJ, Coleman DL. Latamoxef
688 (moxalactam) kinetics in volunteers studied by a specific HPLC assay
689 technique. J Antimicrob Chemother. 1983;12(4):377-86.
690 doi:10.1093/jac/12.4.377.
691 49. Mastrandrea V, Ripa S, La Rosa F, Tarsi R. Human intravenous and
692 intramuscular pharmacokinetics of amoxicillin. Int J Clin Pharmacol Res.
693 1984;4(3):209-12.

694 50. Singlas E, Haegel C. [Clinical pharmacokinetics of azlocillin]. Presse Med.
695 1984;13(13):788-96.
696 51. Gundert-Remy U, Weber E. Elimination of azlocillin in patients with biliary
697 t-tube drainage. Eur J Clin Pharmacol. 1982;22(5):435-9.
698 doi:10.1007/BF00542549.
699 52. Ljungberg B, Nilsson-Ehle I. Comparative pharmacokinetics of ceftazidime
700 in young, healthy and elderly, acutely ill males. Eur J Clin Pharmacol.
701 1988;34(2):179-86. doi:10.1007/BF00614556.
702 53. Leroux S, Turner MA, Guellec CB, Hill H, van den Anker JN, Kearns GL et
703 al. Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic
704 Sampling Design. Clin Pharmacokinet. 2015;54(12):1273-85.
705 doi:10.1007/s40262-015-0291-1.
706 54. Zhao W, Kaguelidou F, Biran V, Zhang D, Allegaert K, Capparelli EV et al.
707 External Evaluation of Population Pharmacokinetic Models of Vancomycin in
708 Neonates: The transferability of published models to different clinical settings.
709 Br J Clin Pharmacol. 2013;75(4):1068-80. doi:10.1111/j.1365-
710 2125.2012.04406.x.
711 55. Abitbol CL, DeFreitas MJ, Strauss J. Assessment of kidney function in
712 preterm infants: lifelong implications. Pediatr Nephrol. 2016;31(12):2213-22.
713 doi:10.1007/s00467-016-3320-x.
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Table and Figure Legends

Tab. 1: Patient characteristics and model information extracted from the published studies and from unpublished data.

Tab. 2: Test sets performance measures for all regressors of all six drugs.

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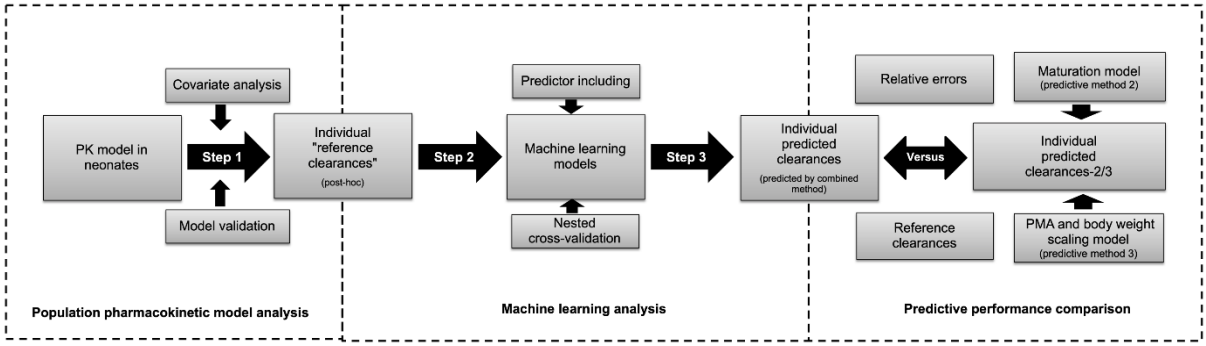
Fig.1 The different steps of this study for all six drugs.

Fig.2 Diagram representation of the nested cross-validation algorithm used in this study.

Fig.3 Goodness-of-fit results for the final model. A) vancomycin B) cefepime C) latamoxef D) amoxicillin E) azlocillin F) ceftazidime. $CL_{prediction}$ represents individual predicted clearance values using the combined method, $CL_{reference}$ represents individual “reference clearances”. Solid circles represent training dataset results, open circles points represent testing dataset results (In order to show the results more intuitively, one of five test sets was selected to display).

Fig.4 The relative importance of factors. 100 represent the most important factor and the values for other factors are relative to this factor.

Fig.5 Predictive performance of drug clearance (percentage of patients achieving relative error within 10%, 30%, and 50%) using three different predictive methods: 1 is the combined method of population pharmacokinetics and machine learning, 2 is the maturation model and 3 is the scaling model based on postmenstrual age and body weight 3 [32]



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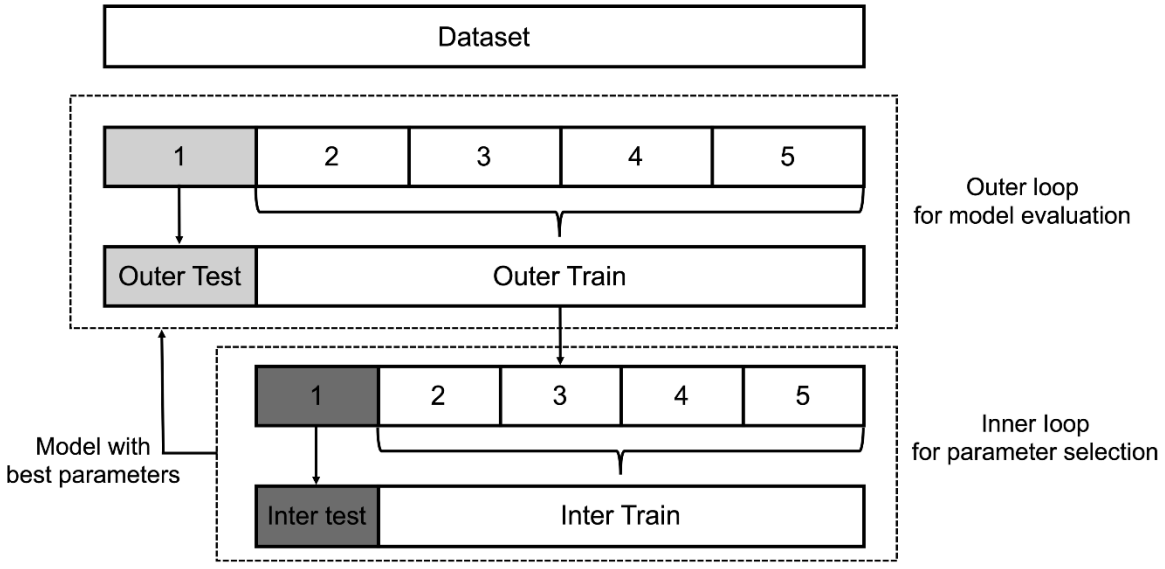

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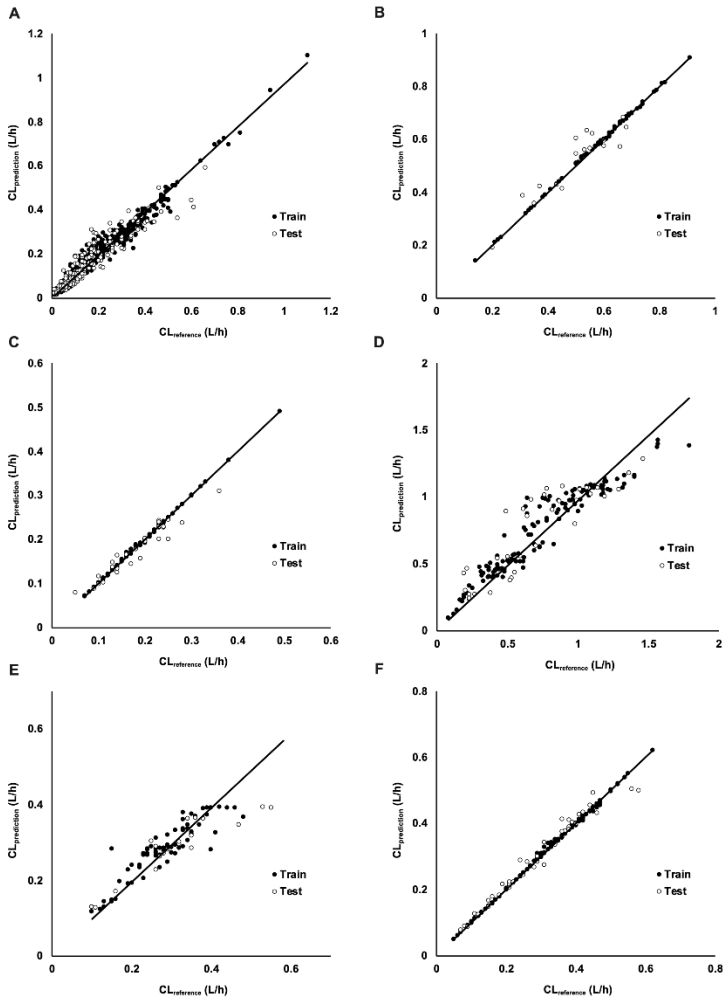
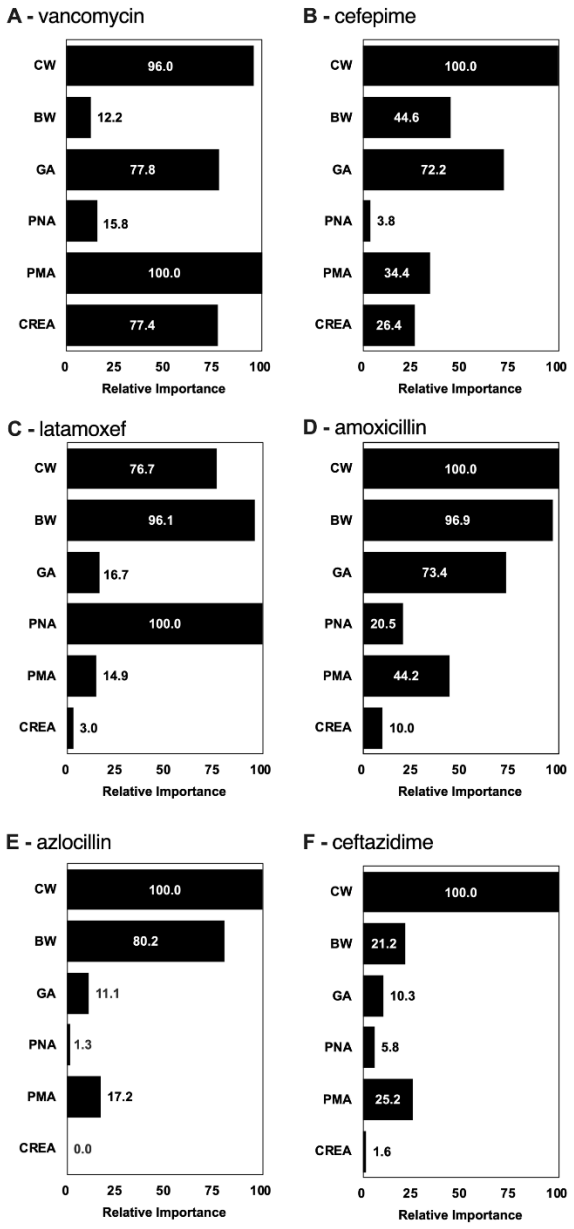


Fig.4 The relative importance of clinical factors in the prediction of clearance. 100 represent the most important factor and values for the other factors are relative to this factor.



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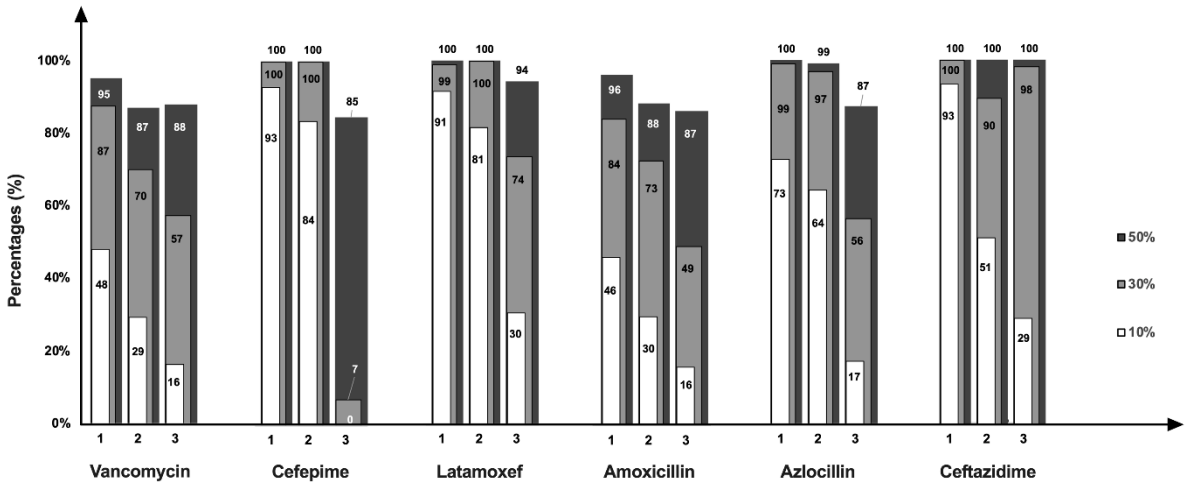

774 **Table 1.** Patient characteristics and model information extracted from the published studies and unpublished data [4, 5, 15-18].

	Vancomycin	**Cefepime**	**Latamoxef**	**Amoxicillin**	**Azlocillin**	**Ceftazidime**
Patients	1631	85	128	187	95	146
Samples	4894	100	165	224	167	203
BW (kg)	1.24 (0.362-4.81)	3.12 (0.980-4.21)	3.10 (1.01-4.58)	3.05 (1.04-4.60)	3.39 (1.80-4.85)	3.00 (0.740-4.65)
CW (kg)	1.35 (0.415-11.4)	3.35 (0.950-4.35)	3.22 (1.00-4.60)	3.21 (1.06-4.58)	3.34 (1.72-4.69)	3.08 (0.900-4.50)
GA (weeks)	30.0 (22.3-42.1)	39.0 (28.0-41.6)	38.3 (27.3-41.4)	38.1 (28.3-41.4)	39.4 (31.6-41.4)	38.6 (26.0-43.4)
PNA (days)	11.0 (1.00-90.0)	8.00 (1.00-25.0)	8.00 (1.00-54.0)	7.00 (1.00-37.0)	3.00 (1.00-6.00)	11.0 (1.00-81.0)
PMA (weeks)	32.0 (23.3-52.4)	40.1 (30.6-45.1)	39.7 (28.4-46.1)	39.0 (28.4-46.3)	40.1 (32.1-42.0)	40.3 (26.1-47.4)
PMX Model						
Compartment	Two	One	Two	Two	One	One
Clearances (L/h)	0.0798 (0.0101-1.10)	0.605 (0.141-0.933)	0.248 (0.0614-0.516)	0.742 (0.0793-2.04)	0.429 (0.133-0.805)	0.317 (0.0469-0.787)
Clearances (L/h/kg)	0.0572 (0.0120-0.281)	0.180 (0.128-0.243)	0.0861 (0.0498-0.142)	0.250 (0.0683-0.592)	0.130 (0.0696-0.202)	0.110 (0.0521-0.185)
$CL=\theta_{CL}*F_{size}*F_{age}*F_{RF}$						
θ_{CL}	0.0680	0.589	0.268	0.812	0.440	0.356
F_{size}	$(CW/1.35)^{\theta1}$	$(CW/3.35)^{\theta1}$	$(CW/3.22)^{\theta1}$	$(CW/3.21)^{\theta1}$	$(CW/3.34)^{\theta1}$	$(CW/3.08)^{\theta1}$
θ1	0.863	0.75 fix	0.75 fix	0.75 fix	0.75 fix	0.75 fix
F_{age}	$(PMA/32)^{\theta2}$	$(PMA/40)^{\theta2}$	$(BW/3.10)^{\theta2}\times(PNA/8)^{\theta3}$	$(GA/38.1)^{\theta2}\times(PNA/7)^{\theta3}$	$(BW/3.39)^{\theta2}\times(PNA/3)^{\theta3}$	$(GA/38.6)^{\theta2}\times(PNA/11)^{\theta3}$
θ2	0.544	1.16	0.288	4.19	0.907	1.57
θ3	-	-	0.214	0.281	0.367	0.220
F_{RF}	$1/(\theta4\times CREA/54)^{\theta5}$	$1/(CREA/28.5)^{\theta4}$	1	1	1	1
θ4	0.720	0.218	-	-	-	-
θ5	0.666	-	-	-	-	-
CL-IIV (%)	18.2	15.3	15.8	40.0	22.6	24.7
IOV (%)	19.1	-	-	-	-	-
RUV(%)[a]	-[b]	36.6	40.6	35.0	32.2	(1)29.5 (2)0.192μg/mL

775 Patient demographic characteristics and clearance values are presented as median (range)

PMX Model: population pharmacokinetic model**; CW**: current weight; **BW**: birth weight; **GA**: gestational age; **PNA**: postnatal age; **PMA**: postmenstrual age; **CREA**: creatinine; **IIV**: inter-individual variability; **IOV**: interoccasion variability; **RUV**: residual variability

[a]: Residual error models: exponential model was used for amoxicillin, latamoxef, azlocillin; proportional model was used for cefepime; combined additive and proportional model was used for vancomycin and ceftazidime ((1) is proportional part, (2) is additive part.)

[b]: For vancomycin, each analytical method was separate estimated in the residual variability.

Table 2. Test sets performance measures for all regressors of six drugs.

Methods	*VAN*		*CEP*		*MOX*		*AML*		*AZL*		*CAZ*	
	R^2	MSE	R^2	MSE	R^2	MSE	R^2	MSE	R^2	MSE	R^2	MSE
RF	0.882	0.0016	0.844	0.0039	0.896	0.00064	0.597	0.058	0.775	0.0022	0.927	0.0012
Ridge	0.756	0.0033	0.874	0.0032	0.871	0.00078	0.591	0.057	0.759	0.0023	0.864	0.0021
Lasso	0.753	0.0035	0.877	0.0031	0.859	0.00108	0.606	0.056	0.785	0.0021	0.871	0.0021
EN	0.758	0.0032	0.872	0.0032	0.874	0.00078	0.596	0.056	0.785	0.0019	0.859	0.0022
KNN	0.783	0.0030	0.822	0.0049	0.790	0.00116	0.624	0.050	0.725	0.0027	0.855	0.0023
DTR	0.826	0.0024	0.725	0.0063	0.811	0.00140	0.473	0.077	0.765	0.0023	0.878	0.0019
ABR	0.852	0.0020	0.848	0.0039	0.892	0.00073	0.609	0.055	0.772	0.0022	0.906	0.0015
GBR	0.884	0.0015	0.809	0.0041	0.920	0.00049	0.567	0.063	0.790	0.0020	0.941	0.0009
ETR	0.877	0.0017	0.865	0.0034	0.934	0.00045	0.631	0.051	0.778	0.0022	0.944	0.0009
XGBR	0.887	0.0015	0.829	0.0038	0.907	0.00054	0.565	0.061	0.784	0.0020	0.937	0.0010

MSE: mean squared error; **VAN**: vancomycin; **CEP**: cefepime; **MOX**: latamoxef; **AML**: amoxicillin; **AZL**: azlocillin; **CAZ**: ceftazidime; **RF**: random forest; **EN**: Elastic Net; **KNN**: K-nearest Neighbor **DTR**: Decision Tree Regressor; **ABR**: Ada Boost Regressor; **GBR**: Gradient Boosting Regressor; **ETR**: Extra Trees Regressor; **XGBR**: Extreme Gradient Boosting Regressor

Table 3. Mean relative error results of six drugs using three predictive methods.

	Predictive method 1 (combined model)		Predictive method 2		Predictive method 3	
	Mean (CV%) [a]	Median (range) [a]	Mean (CV%) [a]	Median (range) [a]	Mean (CV%) [a]	Median (range) [a]
Vancomycin	15.4% (116)	10.7% (0-282%)	25.6% (97.7)	18.9% (0-215%)	31.3% (98.0)	26.8% (0-373%)
Cefepime	2.19% (208)	1.12% (0-24.8%)	5.56% (99.6)	3.73% (0-29.1%)	43.1% (16.5)	43.1% (22.3-56.6%)
Latamoxef	2.82% (230)	1.91% (0-59.9%)	5.56% (84.5)	4.42% (0.1-24.3%)	20.7% (75.5)	18.2% (0.2-65.2%)
Amoxicillin	16.9% (107)	11.6% (0-126%)	28.5% (122)	17.7% (0.3-781%)	33.9% (121)	30.5% (0.1-478%)
Azlocillin	10.1% (110)	7.32% (0-89.0%)	9.90% (130)	6.32% (0.1-109%)	30.1%(76.0)	26.3% (0-152%)
Ceftazidime	2.01% (166)	0.68% (0-20.2%)	13.4% (82.4)	9.80% (0.1-43.0%)	12.9% (50.1)	11.7% (0.5-41.4%)
MEAN[b]	8.24%	5.55%	14.8%	10.1%	28.7%	26.1%

a: For methods 1, 2, and 3, the Mean(CV%) and Median(range) represent the mean(CV%) and median(range) values using five evaluation data sets(results of integration).

b: MEAN represents the mean value of the mean/median of the six drugs.

CV: Coefficient of Variation

Table 4. Summary of published adult values of drug clearance and renal clearance for all renally cleared drugs examined in the study.

Drugs	Total Clearance (mL/min)	Renal Clearance (mL/min)	% Renal Clearance	Binding rate of plasma protein	Note
Vancomycin	98.3	88.3	~90%	~30%	Biliary excretion ~10% Metabolism
Cefepime	122-136	96-116	~83%	16-19%	No secretion
Latamoxef	87	66	76%	~50%	Low secretion Biliary excretion No metabolism
Amoxicillin	~300	~166	~55%	~20%	Low biliary excretion ~24% metabolism
Azlocillin	150-200	100-140	~65%	30-40%	Low secretion 15% metabolized ~5% biliary excretion
Ceftazidime	190	140	~74%	5-10%	No secretion No reabsorption Low biliary excretion No metabolism