AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

Population Pharmacokinetics of Teicoplanin in Preterm and Term Neonates: Is It Time for a New Dosing Regimen?

A. Kontou,[a] K. Sarafidis,[a] O. Begou,[b,d] H. G. Gika,[c,d] A. Tsiligiannis,[e] K. Ogungbenro,[f] A. Dokoumetzidis,[e] E. Agakidou,[a] E. Roilides[g]

[a]1st Department of Neonatology, Aristotle University School of Health Sciences, Hippokration General Hospital, Thessaloniki, Greece
[b]Laboratory of Analytical Chemistry, School of Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece
[c]Department of Medicine, Laboratory of Forensic Medicine & Toxicology, Aristotle University School of Health Sciences, Thessaloniki, Greece
[d]Center for Interdisciplinary Research of the Aristotle University of Thessaloniki (KEDEK), Thessaloniki, Greece
[e]Department of Pharmacy, University of Athens, Athens, Greece
[f]Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom
[g]Infectious Diseases Unit, 3rd Department of Pediatrics, Aristotle University School of Health Sciences, Hippokration General Hospital, Thessaloniki, Greece

ABSTRACT Our objective was to develop a population pharmacokinetic (PK) model in order to evaluate the currently recommended dosing regimen in term and preterm neonates. By using an optimal design approach, a prospective PK study was designed and implemented in 60 neonates with postmenstrual ages (PMA) of 26 to 43 weeks. A loading dose of 16 mg/kg was administered at day 1, followed by a maintenance dose of 8 mg/kg daily. Plasma concentrations were quantified by high-pressure liquid chromatography–mass spectrometry. Population PK (popPK) analysis was performed using NONMEM software. Monte-Carlo (MC) simulations were performed to evaluate currently recommended dosing based on a pharmacodynamic index of area under the concentration-time curve (AUC)/MIC ratio of ≥400. A two-compartment model with linear elimination best described the data by the following equations: clearance (CL) = 0.0227 × (weight [wt]/1,765)$^{0.75}$ × (estimated creatinine clearance [eCRCL]/22)$^{0.672}$, central compartment volume of distribution (V1) = 0.283 (wt/1,765), intercompartmental clearance (*Q*) = 0.151 (wt/1,765)$^{0.75}$, and peripheral compartment volume (V2) = 0.541 (wt/1,765). The interindividual variability estimates for CL, V1, and V2 were 36.5%, 45.7%, and 51.4%, respectively. Current weight (wt) and estimated creatinine clearance (eCRCL) significantly explained the observed variability. MC simulation demonstrated that, with the current dosing regimen, an AUC/MIC ratio of ≥400 was reached by only 68.5% of neonates with wt of <1 kg when the MIC was equal to 1 mg/kg, versus 82.2%, 89.7%, and 92.7% of neonates with wt of 1 to <2, 2 to <3, or ≥3 kg, respectively. Augmentation of a maintenance dose up to 10 or 11 mg/kg for preterm neonates with wt of 1 to <2 or <1 kg, respectively, increases the probability of reaching the therapeutic target; the recommended doses seem to be adequate for neonates with wt of ≥2 kg. Teicoplanin PK are variable in neonates, with wt and eCRCL having the most significant impact. Neonates with wt of <2 kg need higher doses, especially for *Staphylococcus* spp. with an MIC value of ≥1 mg/liter.

KEYWORDS teicoplanin, population pharmacokinetics, Monte Carlo simulation, neonates, preterm neonates, premature neonates

Neonates represent a unique population that features distinct characteristics, such as developmental immaturity and extensive variability. Not surprisingly, prematurity is a major reason for hospitalization, whereas peculiarities of the immune system at

Citation Kontou A, Sarafidis K, Begou O, Gika HG, Tsiligiannis A, Ogungbenro K, Dokoumetzidis A, Agakidou E, Roilides E. 2020. Population pharmacokinetics of teicoplanin in preterm and term neonates: is it time for a new dosing regimen? Antimicrob Agents Chemother 64:e01971-19. https://doi.org/10.1128/AAC.01971-19.

Address correspondence to E. Roilides, roilides@med.auth.gr.

Received 3 October 2019
Returned for modification 26 October 2019
Accepted 2 January 2020
Accepted manuscript posted online 13 January 2020
Published 24 March 2020

birth render neonates particularly vulnerable to infections. Late-onset sepsis (LOS) remains a significant cause of neonatal morbidity and mortality, and, therefore, empirical antimicrobial therapy is a frequent part of treatment. Moreover, as Gram-positive cocci are the predominant pathogens in LOS, glycopeptides, including teicoplanin, are among the most commonly prescribed drugs in neonates (1–4).

Teicoplanin has bactericidal activity against Gram-positive bacteria such as methicillin-resistant staphylococci, including coagulase-negative staphylococci (CoNS), and an efficacy comparable to that of vancomycin (5). Nevertheless, despite the similar mode of action to that of vancomycin, teicoplanin has different pharmacokinetic (PK) properties. Unlike vancomycin, for which binding to plasma proteins is approximately 30 to 55% and the elimination half-life in adult patients with normal renal function is 6 to 12 h, teicoplanin is mainly bound (90%) to human serum albumin and has a longer elimination half-life that ranges from 100 to 170 h (6, 7). Furthermore, it can be given intravenously or intramuscularly (7). Additionally, existing evidence shows a lower incidence of adverse events caused by teicoplanin than by vancomycin, including that of nephrotoxicity, whereas its long serum half-life enables its administration once daily (8, 9). It is for these reasons that neonatologists probably choose to use teicoplanin in LOS, making it one of the 12 most frequently administered antimicrobial agents in European neonatal intensive care units (NICUs) (3).

Recently, teicoplanin has been licensed in Europe for the treatment of children from birth, according to the summary of product characteristics (SPC), last updated February 2018 (10). There is growing evidence that teicoplanin PK display considerable variability in children in comparison to adults, suggesting that therapeutic drug monitoring (TDM) should be a routine practice (11). In addition, the recommended posology for adults has been changed, as well as the recommended trough concentrations (C_{trough}) (10). In the last version of the SPC, the proposed targeted C_{trough} value for complicated skin and soft tissue infections, pneumonia, and complicated urinary tract infections was >15 mg/liter, for bone and joint infections, >20 mg/liter, and for infective endocarditis, >30 mg/liter, instead of the >10 mg/liter previously proposed only "for severe infections" (10). Nevertheless, limited data still exist in terms of teicoplanin PK/pharmacodynamic (PD) studies in neonates; the optimal dosing, especially in preterm infants, remains questionable. In a recent study with 18 neonates, the PK of teicoplanin were found to be highly variable, leading investigators to propose the routine use of TDM for optimal teicoplanin use (12). Targeting optimal efficacy and safety, teicoplanin administration should be based on integrated knowledge concerning evolving neonates' physiological characteristics and the PK/PD of the specific drug. Our aim was to determine the PK of teicoplanin and to evaluate the currently recommended dosing regimen in preterm and term neonates, designing a single prospective population PK study in a large number of subjects.

(This work was partially presented at the 35th annual meeting of the European Society for Pediatric Infectious Diseases [ESPID], Madrid, Spain, 23 to 27 May 2017, and the 36th annual meeting of ESPID, Malmö, Sweden, 28 May to 2 June 2018.)

RESULTS

Optimal design. An optimal design method was used to determine the sampling design of the teicoplanin study. It was performed with PopDes scripts, using prior information from Lukas et al. (13), and resulted in 3 sampling groups (A, B, and C) comprising 50%, 28%, and 22% of the total, respectively. Group A considered samples at 3 h and 20 h after the loading dose and the 5th dose, group B at 0.5 h and 5 h after the loading dose and the 5th dose, and group C at 0.5 h and 16 h after the loading dose and the 5th dose. A simulated study of 50 virtual neonates with these sampling times was estimated in NONMEM and resulted in precise and accurate estimation of the parameters, i.e., the parameter estimates were close to the nominal values, and the corresponding standard errors were small; the simulated study also exhibited robustness, as demonstrated by a bootstrap test (shown in Table S1).

TABLE 1 Demographics and clinical characteristics of patients at time of enrollment and major neonatal problems before enrollment

Demographic or characteristic[c]	Value
Demographics	
Number of enrolled patients	60
Gender (male) (no. [%] of patients)	25 (41.6)
Birth wt in g (median [IQR])	1,550 (1,115–2,072)
Gestational age in wks (median [IQR])	31.6 (29–34.3)
Postmenstrual[a] age in wks (median [IQR])	33.6 (30.7–36)
Postnatal age in days (median [IQR])	10 (6–17.7)
Current wt in g (median [IQR])	1,645 (1,262–2,215)
Small for gestational age (no. [%] of patients)[b]	8 (13.3)
Cesarean section (no. [%] of patients)	43 (72)
No. of days of teicoplanin treatment (median [IQR])	8 (6–11)
Clinical conditions at study initiation (no. [%] of patients)	
Proven sepsis	7 (11.7)
Culture-negative sepsis	14 (23.3)
Probable NEC	10 (16.6)
NEC (stage 2 or 3)/surgical NEC	14 (23.3)/2 (3.5)
Ventilation-associated pneumonia	1 (1.6)
Suspicion of sepsis until definite negative work-up	14 (23.3)
Major neonatal problems up to study initiation (no. [%] of patients)	
Respiratory morbidity	39 (65)
Patent ductus arteriosus	3 (5)
Bronchopulmonary dysplasia	2 (3.5)
Intraventricular hemorrhage III or IV, post-hemorrhagic hydrocephalus	4 (6.6)
Comedication(s) (no. [%] of patients)	
Cefepime	35 (58.3)
Meropenem	25 (41.6)
Amikacin, ciprofloxacin, amphotericin B	2 (3.3), 1 (1.6), 2 (3.3)
Caffeine	40 (66.6)
Vitamin D, Ferrum	11 (18.3)
Diuretics, fentanyl	2 (3.3), 4 (6.6)
Inotropes	1 (1.6)

[a]Postmenstrual age = gestational age + postnatal age.
[b]Small for gestational age neonates were defined as neonates with birth weight below the 10th percentile for gestational age or >2 standard deviations below the mean for gestational age.
[c]IQR, interquartile range; NEC, necrotizing enterocolitis.

Demographic and clinical characteristics and microbiology results. A total of 60 neonates (25 males) met the eligibility criteria and were enrolled in the study. All of them were treated with intravenous (i.v.) teicoplanin for a minimum of 5 days; teicoplanin was started as part of the initial empirical antimicrobial treatment for sepsis or necrotizing enterocolitis. Demographics, clinical characteristics, and comedications of the studied population are presented in Table 1. The numbers of enrolled patients according to gestational age (GA) were 15 (25 to 28 weeks), 22 (29 to 32 weeks), 18 (33 to 36 weeks), and 5 (37 to 40 weeks).

Seven neonates had microbiologically proven sepsis (11.7%) and 14 (23.3%) had culture-negative sepsis. Gram-positive pathogens were isolated in the blood cultures of 4 neonates, and these were susceptible to teicoplanin, as follows: *Staphylococcus aureus* ($n = 1$, MIC = 0.5 mg/liter), *Staphylococcus epidermidis* ($n = 2$, MIC = 0.5 mg/liter), and *Enterococcus* sp. ($n = 1$, MIC = 0.5 mg/liter). Gram-negative bacteria were isolated from the blood of 3 neonates (*Klebsiella* spp. [$n = 2$] and *Serratia* spp. [$n = 1$]). The latter 3 patients were also included in the PK analysis, as they received 5 doses of teicoplanin during the time period in which definitive blood culture results were pending. All neonates except one were hemodynamically stable, with normal blood pressure and heart rate, without impairment of peripheral perfusion, and with no need of vasoactive/pressor medication. At the initiation of teicoplanin therapy 14 neonates were on mechanical ventilation that was either noninvasive ($n = 6$; 10%) or invasive ($n = 8$; 13.3%). Teicoplanin was well tolerated, with no adverse events detected. As shown in

TABLE 2 Laboratory indicators of kidney and liver function and platelet counts (blood values)[a]

Laboratory indicator[b]	Median (IQR) at:				
	Day 1	Day 3	Day 5	EOT[c]	Day 25 ± 5
Urea (mg/dl)	27.5 (18.7–40.2)	29.5 (22.2–46.5)	26 (17.7–34)	20 (15–27.5)	14 (10–21)
Creatinine (mg/dl)	0.68 (0.57–0.79)	0.60 (0.53–0.69)	0.58 (0.5–0.7)	0.57 (0.45–0.66)	0.53 (0.47–0.6)
SGOT (IU/liter)	26 (18.7–35.2)	23 (17–28)	23 (18–28)	23 (18–28.7)	25.5 (18.7–33)
SGPT (IU/liter)	8 (6–14)	8 (7–10)	8 (7–12)	11 (7–14)	12 (8.7–17)
γ-GT (IU/liter)	65 (39.5–116.5)	62.5 (39.7–112)	63 (43–112)	59 (46.5–123)	78 (43–135)
Total bilirubin (mg/dl)	4.6 (1.4–7.3)	4.6 (1.4–7.8)	3.4 (1–5.5)	2.2 (0.8–4)	1.2 (0.5–3.3)
Total protein (g/dl)	5 (4.7–5.5)	5.3 (4.7–5.6)	5 (4.47–5.5)	4.9 (4.6–5.5)	4.9 (4.4–5.2)
Albumin (g/dl)	3.2 (3.0–3.5)	3.4 (3.0–3.5)	3.3 (2.9–3.5)	3.3 (3.1–3.4)	3.3 (3.0–3.4)
Platelets ($\times 10^3/\mu l$)	329 (211–460)	278 (185.7–415.5)	406 (283–527)	423 (290–517)	426 (288–520)

[a]From day 1 to day 25 ± 5 after the initiation of teicoplanin therapy.
[b]SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; γ-GT, gamma-glutamyl transpeptidase.
[c]EOT, end of teicoplanin treatment;

Table 2, none of the patients presented abnormal renal or liver function during teicoplanin treatment, nor did they present thrombocytopenia.

The full sets of PK samples required were taken from 56 neonates according to the study protocol, whereas incomplete sets were taken from 4 subjects (5 samples missed); namely, 2 PK samples were not taken from 1 neonate and 1 PK sample was missed in each of the other 3 neonates. Moreover, in order to avoid any bias in the development of the PK model, 4 teicoplanin plasma concentrations were excluded from subsequent PK analysis because they were too low, specifically, below the limit of quantification (LOQ) of the method, so they were considered not reliable. Finally, 231 predefined plasma samples, according to the D-optimal design, were included in the PK modeling. Additionally, in 12 randomly assigned neonates, one more sample was taken at 24 h after the 5th dose (C_{trough}), in coordination with the routine laboratory exams. So, teicoplanin concentrations were eventually analyzed in 243 samples. Grouping of enrolled neonates according to gestational age and PK time schedule is shown in Table 3.

Development of the population PK model. A two-compartment model with linear elimination best described the data. This was parameterized as clearance (CL), volume of distribution of the central compartment (V1), intercompartmental clearance (*Q*), and volume of distribution of the peripheral compartment (V2), corresponding to the NONMEM subroutine ADVAN 3 TRANS 4. Interindividual variability (IIV)was included in CL, V1, and V2, while a correlation between CL and V1 was also supported by the data. A proportional error model was used to describe the residual variability. The base model parameter values, together with their standard errors, are listed in Table S2.

Covariate search revealed that the allometric model of the effect of weight (wt), scaled by the average weight of 1,765 g, on CL and volume with fixed exponents of 0.75 and 1, respectively, significantly reduced the objective function value (OFV) by more than 37 units (Table S3). Inclusion of the effect of wt on Q and V2 further reduced the OFV by another 12 units. Also, eCRCL was found to be a significant covariate on drug CL, reducing the OFV by 15 units, which corresponds to a *P* value of <0.001. Apart from

TABLE 3 Number of enrolled patients in each group according to gestational age and PK sampling schedule

Gestational age (wks)	No. of patients enrolled in group:			Total no. of patients
	A	B	C	
25–28	7	6	2	15
29–32	9	5	8	22
33–36	8	5	5	18
37–40	2	1	2	5
All ages	26	17	17	60

TABLE 4 Final model parameter estimates and parameter values from the bootstrap run[b]

	Estimate		Bootstrap value		
Parameter[a]	Mean	%RSE	Mean	%RSE	95% CI
CL (liters/h)	0.0227	5.8	0.0236	5.9	0.0202–0.0253
V1 liters)	0.283	8.8	0.286	8.8	0.239–0.334
Q (liters/h)	0.151	9.8	0.157	15.6	0.128–0.205
V2 (liters)	0.541	10.8	0.549	10.7	0.438–0.661
eCRCL on CL	0.672	22.6	0.670	26.5	0.323–1.044
IIV_{CL} (% [shrinkage %])	36.5 [7.6]	7.4	0.359	11.2	0.282–0.443
IIV_{V1} (% [shrinkage %])	45.7 [8.3]	13.2	0.456	15.4	0.319–0.585
IIV_{V2} (% [shrinkage %])	51.4 [28.7]	14.1	0.502	15.2	0.335–0.642
CL-V1 correlation (r^2)	0.98	3.4	0.951	7.8	0.754–1.000
Proportional error (σ)	0.272	4.7	0.266	8.1	0.223–0.307

[a]CL, clearance; V1, central compartment volume of distribution; *Q*, intercompartmental clearance; V2, peripheral compartment volume; eCRCL, estimated creatinine clearance; IIV, interindividual variability.
[b]RSE, relative standard error.

BW and eCRCL, all other covariates tested were not found to have a statistically significant effect and therefore were not included in the model. The final model parameter values with the corresponding standard errors are shown in Table 4. Furthermore, the shrinkage terms for CL and V1 are relatively low, 7.6% and 8.3%, respectively, and for V2 the shrinkage had a moderate value of 28.7%. The correlation term of 0.98 between CL and V1 does not express a real correlation and is an artifact due to lack of information. However, its inclusion reduced the OFV, and it is well estimated, with a low standard error; therefore, it was decided that it should not be removed from the final model, although, as mentioned, it should not be interpreted as a real correlation. The equations describing the final model are as follows:

$$\mathrm{CL} = 0.0227\left(\frac{\mathrm{wt}}{1765}\right)^{0.75}\left(\frac{\mathrm{eCRCL}}{22}\right)^{0.672}$$

$$\mathrm{V1} = 0.283\left(\frac{\mathrm{wt}}{1765}\right)$$

$$Q = 0.151\left(\frac{\mathrm{wt}}{1765}\right)^{0.75}$$

$$\mathrm{V2} = 0.541\left(\frac{\mathrm{wt}}{1765}\right)$$

The goodness of fit of the model was assessed at all steps by diagnostic plots. Observed versus population predicted and individual predicted plots (Fig. S1) demonstrated satisfactory fit of the model to the data. In the prediction-corrected visual predictive check plots (pcVPC) (Fig. 1), the percentiles of the observed data lie within the confidence intervals (CI) of the corresponding percentiles of the model predictions, demonstrating that the model describes the data set well, including the observed variability. Also, the results from the nonparametric bootstrap procedure, together with the NONMEM estimates, are shown in Table 4. These include the mean estimates from 1,000 bootstrap runs, the relative standard errors calculated from the standard deviation of the nonparametric distribution of the bootstrap runs, and the corresponding 95% confidence intervals. The standard errors generally agree with the ones provided by NONMEM, while the parameter estimates lie within the confidence intervals, demonstrating the robustness of the model.

The PK parameters of area under the concentration-time curve over 24 h in the steady state (AUC_{24}) and half-life ($t_{1/2}$) can be calculated for this cohort of neonates from the final model, and were found to be 740.97 ± 320.61 mg/liter · h (mean ± standard deviation [SD]) and 29.75 ± 8.86 h, respectively. Of note, in order to calculate PK parameters for the steady state, no assumption was made that the steady state had been achieved. All calculations referring to the steady state have been done using the estimated PK parameters. This is one of the benefits of using a model-based approach,

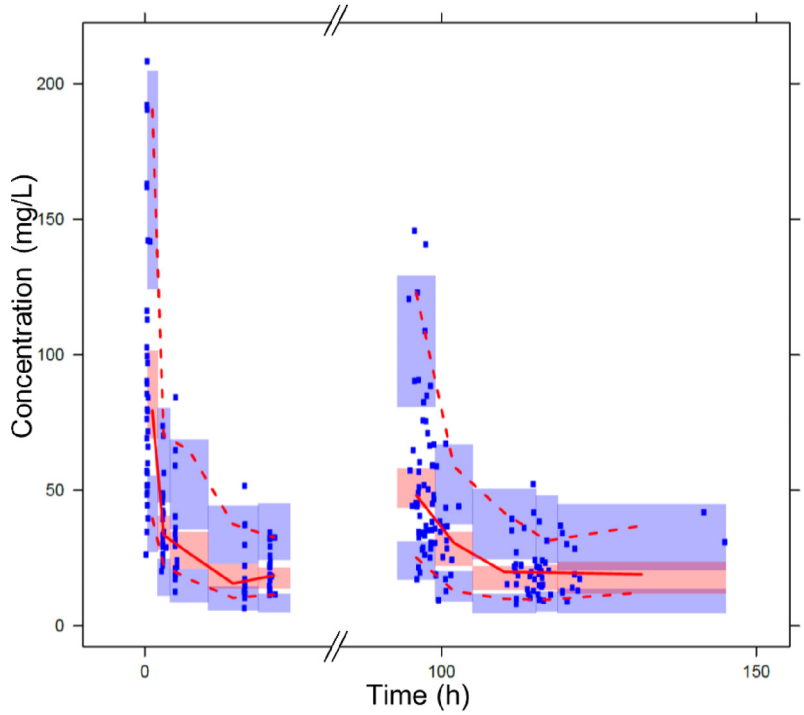

FIG 1 Prediction-corrected visual predictive check plots for the final model. Red solid line, median of the observations; red dashed lines, 5th and 95th percentiles of the observed data; pink band, 95% confidence intervals of the medians of the predictions; blue bands, 95% confidence intervals of the 5th (top band) and 95th (bottom band) percentiles of the predictions.

as it allows making predictions about the steady state without necessarily having achieved it. Having said that, due to the fact that a loading dose of 16 mg/kg was given to all patients, we anticipate that the steady state could have been achieved much earlier than the typical 5 to 6 half-lives.

Simulations. Monte Carlo (MC) simulations were used to determine the probability of target attainment (PTA) to achieve a target area under the concentration-time curve (AUC)/MIC of ≥400.The simulations were carried out with the intermediate model (model 3 in Table S3), which includes the effect of wt on CL and volumes but not the effect of eCRCL on CL, in order to avoid making assumptions about the distribution of eCRCL and its potential correlation with wt. This is in line with the main stratification strategy for dosing, which is done according to wt. The parameter estimates of this model are shown in Table S4 and are similar to the ones in the final model.

In Table 5, the PTA values for the 4 wt groups are shown for a range of MICs from 0.125 to 4 mg/liter and for a range of doses from 8 to 12 mg/kg. These are also shown graphically in Fig. 2. From these results, it can be concluded that for the first group, extremely low birth weight (ELBW) neonates (wt < 1 kg), for the maintenance dose of 8 mg/kg, only 68.5% of patients achieved the target of an AUC/MIC ratio of ≥400 at MIC = 1 mg/liter, while a higher maintenance dose of 11 mg/kg was needed for a PTA of 90%. For those with wt of 1 to <2 kg, the PTA for a maintenance dose of 8 mg/kg was 82.2%, while a dose of 9 mg/kg was needed to achieve 88.7%, and 10 mg/kg was needed to achieve 93%. For those with wt of ≥2 kg, the maintenance dose of 8 mg/kg was adequate and achieved PTA of 89.7% and 92.7% for weights of 2 to <3 kg and ≥3 kg, respectively. The results are adjusted accordingly for higher MIC values. Of note, for an MIC of 2 mg/liter, a doubling of the dose will be needed, i.e., one that produces a double AUC value, in order to achieve the same PTA value and retain a constant ratio of AUC/MIC.

TABLE 5 Probability of target attainment for the various weight groups, doses, and MIC values[a]

Group (wt) or dose (mg/kg)	Probability of target attainment (%) at MIC (mg/liter):					
	0.125	0.25	0.5	1	2	4
Group 1 (<1 kg)						
8	100	100	98.7	68.5	10.4	0.1
9	100	100	99.4	78.2	16.8	0.3
10	100	100	99.7	85.2	24.3	0.7
11	100	100	99.9	**90**	32.2	1.4
12	100	100	99.9	93.3	40.5	2.5
Group 2 (1 to <2 kg)						
8	100	100	99.6	82.2	20.4	0.5
9	100	100	99.8	88.7	29.9	1.2
10	100	100	99.9	**93**	39.9	2.3
Group 3 (2 to <3 kg)						
8	100	100	99.9	**89.7**	30.7	1.2
9	100	100	100	94	42.2	2.6
10	100	100	100	96.5	52.6	4.6
Group 4 (≥3 kg)						
8	100	100	99.9	**92.7**	37.8	2
9	100	100	100	96	49.3	3.9
10	100	100	100	97.8	60	6.8

[a]As calculated by MC simulations. Bold, underlined numbers indicate PTA values close to 90% for a MIC of 1 mg/liter and the corresponding recommended doses.

DISCUSSION

The results of our study suggest that the currently recommended teicoplanin doses are not appropriate for the entire neonatal population, leading some to receive subtherapeutic drug exposures. Despite their small size, neonates display huge interindividual variability in their physiology, and consequently in drug disposition (14); thus, not surprisingly, the extent of interpatient teicoplanin exposure variability in our population was significant. Based on MC simulations, preterm neonates weighing <2 kg are at greater risk of failing to attain therapeutic targets unless they are treated with higher doses.

To our knowledge, this is the first study that evaluated population PK of teicoplanin prospectively in a large number of preterm and term neonates ($n = 60$), utilizing a well implemented D-optimal design sampling scheme using prior information from a pediatric study in children 4 months to 12 years old (13). Optimal design, as part of the model-building process, is a useful adjunctive tool with increasing application in the last 10 years in population PK studies, where sparse designs are behooved due to ethical reasons, including in neonatal PK studies (15, 16). Using prior information, it opts for the best combination of design factors, such as the number and times of blood sampling and the number of patients that have to be enrolled, in this way minimizing blood loss and pain in the fragile neonatal population (17). The prospective character of the study, the predefined PK sampling schedule based on D-optimal design, and the number of subjects included strengthened the quality of the data. However, it should be noted that, regardless of the prior information, the model is developed without any assumptions, and all choices are validated; however, a better-informed design produces data with a higher information content that build a better model.

In the present study, a two-compartment model with linear elimination best described the data in accordance with previous pharmacokinetic studies in adults and children with malignant hematological disease (18–20), as well as in a recent popPK study in 18 neonates (12). Of the various covariates explored, wt was found to be a significant covariate on CL, V1, V2, and *Q*, following an allometric model, while eCRCL was also found to have an effect on CL. IIV estimates for CL, V1, and V2 of the final model were reduced from 56.2%, 65.1%, and 54.3% to 36.5%, 45.7%, and 51.4%,

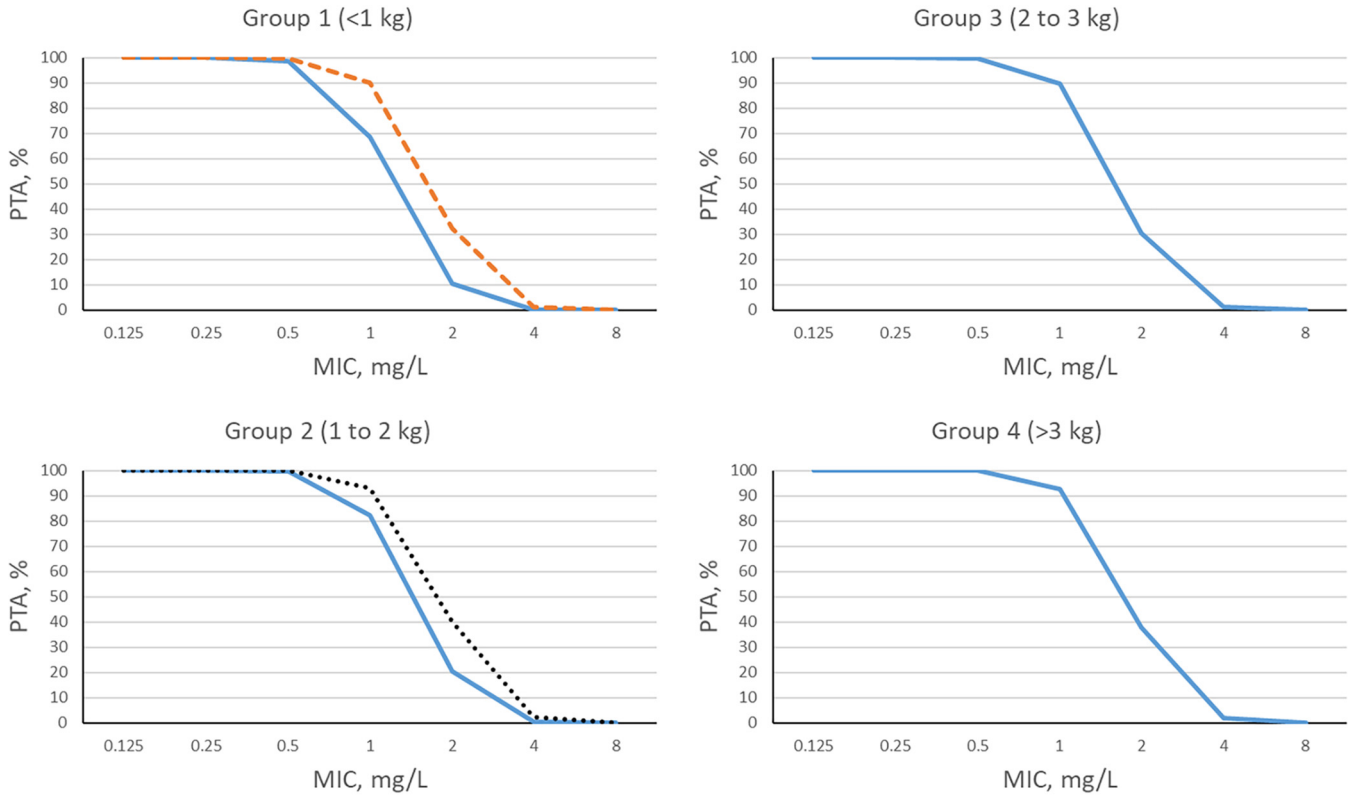

FIG 2 Probability of target attainment (PTA) for each weight group versus MIC values of *Staphylococcus* spp. Blue solid lines, dose 8 mg/kg; black dotted line in group 2, dose 10 mg/kg; red dashed line in group 1, dose 11 mg/kg.

respectively, indicating that wt and eCRCL explained a significant portion of the observed variability. Covariate analysis fitted the PK characteristics of teicoplanin well, and considering that this drug is mainly renally eliminated by glomerular filtration, it was anticipated that both renal function and size have an impact on dosing in neonates.

Ramos et al. found no relationship between teicoplanin clearance and estimated glomerular filtration rate (eGFR) or serum creatinine; these authors speculated that the absence of such a relationship was attributed either to the small sample size of their study or to poor estimates of eGFR in neonates using current nomograms (12). Our study involving a large number of subjects bypassed this problem and found that eCRCL explained a significant portion of the observed variability. Other covariates like GA, postmenstrual age (PMA), and postnatal age (PNA) failed to account for any portion of the observed variability, probably because both wt and renal function reflect growth and maturation.

In the last decade, the proposed dosing regimens for adults have been changed (augmentation of loading and maintenance doses and the number of loading doses depending on the site and the severity of the infection), as well as the recommended C_{trough} value for both adults and children (10). According to the SPC, teicoplanin trough levels of at least 15 mg/liter, measured by the fluorescence polarization immunoassay (FPIA) method, are proposed for most Gram-positive infections (complicated skin and soft tissue infections, pneumonia, and complicated urinary tract infections), but for the treatment of deep-seated infections (bone and joint infections) and infective endocarditis, trough levels of 20 mg/liter and 30 to 40 mg/liter, respectively, are recommended (10). Such modifications are parallel to growing evidence from studies, mainly in adults and to a lesser extent in children, that have doubted whether a standard dosing regimen can achieve optimal drug exposure in clinical practice and suggested that

higher doses are needed (20–22). In contrast, there are sparse data for the neonatal population, and no change of dosing has been proposed for children and neonates.

For glycopeptides, the most widely used PK/PD index associated with efficacy in clinical studies is AUC/MIC ratio, with the threshold of a total vancomycin AUC/MIC ratio of ≥400 being commonly used, although there are indications that higher thresholds of up to 600 may be needed (23, 24). Since Craig's report, teicoplanin exposure targets predictive of favorable clinical outcome are not well elucidated, and the optimal PK/PD targets remain uncertain (24). Studies in adults with multidrug-resistant *Staphylococcus aureus* (MRSA) infections have shown that an AUC_{24} value of 750 to 800 μg · h/ml increased the probability of treatment success, but neither studies could estimate AUC_{24}/MIC because exact MICs were not measured (25, 26). Interestingly, in the study of Hagihara et al. (25), teicoplanin trough levels were adequate in both treatment success and failure groups, but the AUC_{24} was significantly higher in the cured group, indicating what is already known about vancomycin, namely, that trough levels measured commonly in clinical practice are poorly indicative of AUC (27, 28). Matsumoto et al. found an AUC_{24}/MIC ratio of ≥900 associated with bacteriological response in adults with MRSA infections (29). Recently, a total AUC/MIC ratio of 610.4 for an MRSA strain (MIC = 0.5 mg/liter) was defined for efficacy in a hollow-fiber infection model and in a neutropenic murine thigh infection model (30). To our knowledge, the optimal AUC/MIC ratio of teicoplanin for treatment of CoNS infections has not been studied in neonates nor in adults.

In the present study, it was not feasible to explore any relationship between a PD index (e.g., AUC/MIC) and outcome. For the MC simulations, we used the target of an AUC/MIC ratio of ≥400, based on the assumption that CoNS species, predominant in neonatal LOS (1, 2), are less invasive and mainly cause bloodstream infections rather than deep-seated infections, and based on the results from an experimental study that found that a 2.5 to 3.0 times lower AUC/MIC ratio was needed to stop or kill methicillin-resistant *Staphylococcus epidermidis* than methicillin-susceptible *S. aureus* (31). The same target was recently used in a study for vancomycin in CoNS sepsis in neonates (32). According to our simulations, the currently recommended neonatal dosing regimen resulted in a high risk of underdosing, primarily in neonates with a wt of <2 kg. Only 68.5% of neonates weighing <1 kg achieved the target of an AUC/MIC ratio of ≥400 at a MIC of 1 mg/liter, while a higher maintenance dose of 11 mg/kg was needed for a PTA of 90%. Thus, inadequate empirical antimicrobial therapy is expected to result in increased infection-related morbidity and mortality. Similarly to Kuti et al. (33), we noticed that in a recent 16-month period in our NICU, 70% of CoNS isolated from the blood of neonates with LOS displayed teicoplanin MICs of ≥2 mg/liter (unpublished data). The increasing prevalence of staphylococcal species with increased MICs to glycopeptides (≥2 mg/liter) is quite worrisome and raises significant concerns for the management of neonatal sepsis (32, 34). Of note, for staphylococcal species with an MIC of 2 mg/liter, a significantly high proportion of the neonatal population is at risk for therapeutic failure. In such situations, a doubling of the dose that can correspondingly produce a doubled AUC value may be needed in order to achieve the same PTA values and retain a constant ratio of AUC/MIC; whether such high doses of teicoplanin are safe or an alternative agent should be given has to be studied.

The fact that no response data are available in this study cannot be considered a drawback, since a rational approach to establish efficacy for antibiotics is that efficacy studies are conducted in adults and extrapolated to neonates through PK. In addition, we could not explore the effects of nonmaturational factors related to underlying disease (sepsis and necrotizing enterocolitis [NEC]) and to its severity, comorbidities, or/and treatment interventions on the PK profile of teicoplanin, as our population was comprised of mainly hemodynamically stable, non-critically ill neonates with normal renal and liver function. Apart from the maturational changes in neonatal physiology, the PK profile of an antibiotic is also subject to factors related to the severity of sepsis or NEC, such as the hemodynamic condition of the patient, hypoalbuminemia, and treatment interventions that may alter drug distribution and elimination and conse-

quently blood concentrations of hydrophilic antibiotics like teicoplanin (35, 36). Children with hematological malignancy are at higher risk of underdosing due to higher teicoplanin clearance associated with higher CRCL; the altered PK profile was attributed to the high glomerular filtration secondary to hyperhydration as part of the malignancy therapeutic protocol (20). Further studies exploring the PK/PD of teicoplanin in critically ill neonates are needed.

The data in the present study are derived from a single institution's population, and before they become the basis of general dosing recommendations, they need to be validated in other institutions. The analytical methods used for determination of teicoplanin concentrations and serum creatinine levels vary among centers, significantly influencing the population PK parameters (7, 37). We also acknowledge that the PK/PD target used for MC simulations is not evidence based, and, as a consequence, the proposed dosing regimen based on these assumed targets may be questioned in the future if new evidence is presented.

In conclusion, an informative popPK model for neonates with LOS, based on high-quality data obtained prospectively, shows that teicoplanin PK is variable in neonates, with body wt having the most significant impact on the parameters, while eCRCL is also an important covariate on CL. Furthermore, our results indicate that the current teicoplanin dosing regimen is not suitable for the ELBW preterm neonates and those with wt of <2 kg. MC simulations suggest that stratification of doses according to wt minimizes the number of patients with suboptimal teicoplanin exposures. Neonates with a wt of <2 kg may need a higher maintenance dose than the 8 mg/kg currently recommended for pathogens with MIC values of ≤ 1 mg/liter, while for neonates with a wt of ≥ 2 kg, the recommended doses seem to be adequate. Augmentation of the maintenance dose up to 10 mg/kg and 11 mg/kg for preterm neonates with a wt of 1 to <2 kg and <1 kg, respectively, increases the probability of reaching the therapeutic targets early in therapy and minimizes the risk of therapeutic failure. A further prospective study to validate the proposed dosing regimen of teicoplanin in clinical practice in neonates is warranted.

MATERIALS AND METHODS

Study design and population. This was a prospective, open-label population PK study performed in a level 3 academic NICU between October 2013 and April 2016 using a D-optimal design approach. The study was approved by the Ethics Committees of Aristotle University of Thessaloniki and Hippokration General Hospital. Signed written informed consent was obtained from parents/guardians prior to study enrollment of the neonates. Term and preterm neonates with a gestational age (GA) of >25 weeks and a postnatal age (PNA) of >3 days or <60 days were enrolled in the study. Neonates that were receiving teicoplanin for sepsis either empirically or as targeted therapy and were likely to survive for >72 h were eligible for the study. The choice of teicoplanin as coverage against Gram-positive bacteria was at the discretion of the caring physician. Infants with known congenital malformations, perinatal asphyxia, acute kidney injury, and liver dysfunction were excluded from the study. Teicoplanin was administered intravenously over 30 min, with a loading dose of 16 mg/kg and a maintenance dose of 8 mg/kg/day (24 h after the administration of the loading dose). The duration of treatment until blood cultures were definitely negative was also at the discretion of the caring physician, with a minimum of 5 days.

Neonates enrolled in the study were divided in a number of sampling groups, determined by an optimal design methodology; within these groups, 4 blood samples were taken from each neonate. Additionally, in some randomly assigned neonates, one more sample was taken at 24 h after the 5th dose (C_{trough}), in coordination with the routine laboratory exams. Timing of blood sampling was coordinated as much as possible with that of the clinical routine, and the maximum amount of plasma for PK analysis was 300 μl. Demographic data, clinical characteristics, results of the laboratory investigation (i.e., kidney and liver function, sepsis workup), adverse reactions, and concomitant medications were prospectively recorded in all studied patients. The exact time of sampling for PK analysis, dosing regimen, and drug infusion time were recorded using specific documentation forms for each neonate.

Sample handling and assay for determination of teicoplanin concentrations. All blood samples were collected in heparinized tubes and centrifuged at $3,500 \times g$ for 10 min. Plasma samples were extracted and frozen within 1 h of collection at -20°C, and within a maximum of 24 h they were stored in aliquots at -80°C prior to analysis. All samples were stored for a maximum time period of 8 to 10 months until analysis. A previously developed and validated ultrahigh-pressure liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS, Waters, UK) method was used for the quantification of plasma teicoplanin (38). Selected reaction monitoring mode was applied for the detection and quantification of all six major components (A2-1, A2-2, A2-3, A2-4, A2-5, and A3-1) of teicoplanin. The limit of detection (LOD) was 8.5 ng/ml, and the limit of quantification (LOQ) was 25 ng/ml for total teicoplanin.

Accuracy and precision of the method were within the acceptable criteria of a relative standard deviation (RSD) of >85% and <15%, respectively, while the mean percent recovery for all isoforms was found to be 87%.

Optimal design. A sparse PK study was designed, using a D-optimal design approach with the PopDes MATLAB application script (39), using as prior information model and parameter estimates from a pediatric study in children from 4 months to 10 years old (13). The D-optimal design approach optimized the determinant of the population Fisher information matrix of a previously developed model, as prior information, in order to determine the optimal sampling times of a prospective PK study such that these carry the maximum information to estimate the population PK model parameters (17). Based on the prior information for teicoplanin use in children from Lukas et al. (13), a two-compartment model was considered with parameter values as follows: clearance (CL), 0.23 liters/h; central volume of distribution, 3.16 liters; rate constant from central to peripheral compartment, 0.23 h^{-1}; and rate constant from peripheral to central compartment, 0.04 h^{-1}. Furthermore, interindividual variability (IIV) for all parameters was assumed to be 30%, and a residual variability was assumed as a proportional error of 20%. A homogeneous distribution of current body weight (wt) ranging from 1 to 4 kg was considered, and CL and volume were scaled allometrically as a function of time with exponents of 0.75 and 1, respectively. Various scenarios of optimal designs were considered that included different groups of patients with different sampling times instead of a unique common design for all patients. One to 3 design groups were tested, and the number of subjects in each group was determined automatically during the optimization of the design. Also, practical constraints were introduced and explored, e.g., up to 4 samples per neonate and not more than 2 samples per neonate on the same day. The final design was evaluated by simulating a virtual clinical study of 50 subjects in NONMEM and also by estimating the parameter values in NONMEM in order to verify that these are indeed accurate and precise, i.e., that the estimates were close to the nominal values used in the simulation and the standard errors of the estimates were small. Robustness of the estimates was also confirmed by a bootstrap run.

PK modeling. The plasma teicoplanin concentrations were analyzed by a nonlinear mixed effects modeling approach in order to develop a population PK model using NONMEM software (version 7.2; Icon plc) with the first-order conditional estimation with interaction (FOCEI) method. Various structural modes, including 1, 2, and 3 disposition compartments, were tested, parameterized as clearances and volumes of distributions. Exponential IIV was included in the parameters, and residual error models of additive, proportional, and combined forms were tested.

The modeling choices during the development of the model were guided by goodness-of-fit plots, assessment of standard errors, and physical soundness of parameter values. Furthermore, the base model was evaluated by visual predictive check (VPC) plots and by the bootstrap method. VPC was run using Perl-speaks-NONMEM (PsN) scripts (https://uupharmacometrics.github.io/PsN/). Furthermore, for model evaluation, a nonparametric bootstrap procedure, as implemented in PsN, was performed for each of the candidate final models to calculate the confidence intervals and standard errors as a measure of the stability and precision of model parameter estimates.

Having developed a base population PK model, various covariates were tested to explain part of the observed variability of the PK parameters. The covariates considered were GA, PMA, PNA, wt, body surface area, and estimated creatinine clearance (eCRCL) calculated by the Schwartz formula ($k \times$ height/serum creatinine; the current height of each neonate was used, and $k = 0.33$ or 0.45 for preterm and term neonates, respectively) (40, 41). The functional form of covariate inclusion for parameters followed a centered power law.

For the effect of wt, the performance of fixed value allometric exponents, as described in Anderson and Holford (42), was assessed. This approach considers that CL is proportional to the wt raised to the power of three-fourths and volume scales proportionally to wt, and it is justified by physiological arguments.

For the adoption of a covariate in the final model, certain criteria must be fulfilled. The main statistical criterion is the likelihood ratio test, according to which the inclusion of a covariate introducing one more parameter to the model is statistically significant at a level of $\alpha = 0.001$. Furthermore, the random variability of the model with the covariate in question, as described by the corresponding ω parameter, must have a lower value compared to the respective value of the base model, i.e., the covariate must explain part of the variability. Also, the overall performance and robustness of the model as assessed by the goodness of fit plots, the VPC plot, and the bootstrap test, are taken into consideration.

Simulations. MC simulations were performed using the developed popPK model in MATLAB, generating a simulated population of 10,000 neonates in each of the following wt groups: group 1, wt <1 kg; group 2, wt 1 to <2 kg; group 3, wt 2 to <3 kg; group 4, wt ≥ 3 kg. The wt was considered to follow a homogenous distribution, with a range from 500 to 3,700 g, while the random IIV of CL was considered to follow the log-normal distribution, with parameter numbers as estimated in the popPK model. These were used to calculate CL values and, in turn, the area under the concentration-time curve over 24 h in the steady state (AUC_{24}) values from the formula AUC_{24} = dose/CL, where the dose was 8 mg/kg. For a range of MIC values from 0.125 to 4 mg/liter, the ratio of AUC_{24} divided by the MIC (AUC/MIC) was calculated for each of the virtual patients, and the probability of target attainment (PTA) was calculated as the percentage of the population with an AUC/MIC ratio of ≥400. Although the optimal PK/PD target of teicoplanin is not fully elucidated, we used an AUC/MIC ratio of ≥400 based on vancomycin experience; the most widely used PK/PD index is AUC/MIC, with the threshold of ≥400 being commonly used, although there are indications for higher thresholds of up to 600 (23, 24). Of note, both AUC_{24} values and the attainment target of 400 consider the total drug concentrations and not the free drug.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

ACKNOWLEDGMENTS

We thank the parents of the study subjects, who gave their permission to study teicoplanin PK in their infants. We also thank all personnel of the unit, who helped by referring neonates to the investigators for enrollment in the study and in numerous other ways.

No external funding was received for conducting the study.

REFERENCES

1. Cailes B, Kortsalioudaki C, Buttery J, Pattnayak S, Greenough A, Matthes J, Bedford Russell A, Kennea N, Heath PT, neonIN network. 2018. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Arch Dis Child Fetal Neonatal ed 103:F547–F553. https://doi.org/10.1136/archdischild-2017-313203.
2. Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK, Smith PB, Manzoni P, Jacqz-Aigrain E, Kaguelidou F, Cohen-Wolkowiez M. 2012. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev 88(Suppl 2):S69–S74. https://doi.org/10.1016/S0378-3782(12)70019-1.
3. Metsvaht T, Nellis G, Varendi H, Nunn AJ, Graham S, Rieutord A, Storme T, McElnay J, Mulla H, Turner MA, Lutsar I. 2015. High variability in the dosing of commonly used antibiotics revealed by a Europe-wide point prevalence study: implications for research and dissemination. BMC Pediatr 15:41. https://doi.org/10.1186/s12887-015-0359-y.
4. Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H, ARPEC project group. 2016. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. J Antimicrob Chemother 71:1106–1117. https://doi.org/10.1093/jac/dkv418.
5. Bugano DDG, Cavalcanti AB, Goncalves AR, de Almeida CS, Silva E. 2011. Cochrane meta-analysis: teicoplanin versus vancomycin for proven or suspected infection. Einstein (Sao Paulo) 9:265–282. https://doi.org/10.1590/S1679-45082011AO2020.
6. Rybak MJ. 2006. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 42(Suppl 1):S35–S39. https://doi.org/10.1086/491712.
7. Wilson AP. 2000. Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet 39:167–183. https://doi.org/10.2165/00003088-200039030-00001.
8. Svetitsky S, Leibovici L, Paul M. 2009. Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. Antimicrob Agents Chemother 53:4069–4079. https://doi.org/10.1128/AAC.00341-09.
9. Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DD, Silva E. 2010. Teicoplanin versus vancomycin for proven or suspected infection. Cochrane Database Syst Rev (6):CD007022. https://doi.org/10.1002/14651858.CD007022.pub2.
10. Sanofi. February 2018. Targocid 200mg powder for solution for injection/infusion or oral solution. Sanofi, Reading, UK.
11. Ramos-Martín V, Paulus S, Siner S, Scott E, Padmore K, Newland P, Drew RJ, Felton TW, Docobo-Pérez F, Pizer B, Pea F, Peak M, Turner MA, Beresford MW, Hope WW. 2014. Population pharmacokinetics of teicoplanin in children. Antimicrob Agents Chemother 58:6920–6927. https://doi.org/10.1128/AAC.03685-14.
12. Ramos-Martín V, Neely MN, McGowan P, Siner S, Padmore K, Peak M, Beresford MW, Turner MA, Paulus S, Hope WW. 2016. Population pharmacokinetics and pharmacodynamics of teicoplanin in neonates: making better use of C-reactive protein to deliver individualized therapy. J Antimicrob Chemother 71:3168–3178. https://doi.org/10.1093/jac/dkw295.
13. Lukas JC, Karikas G, Gazouli M, Kalabalikis P, Hatzis T, Macheras P. 2004. Pharmacokinetics of teicoplanin in an ICU population of children and infants. Pharm Res 21:2064–2071. https://doi.org/10.1023/b:pham.0000048198.56873.d8.
14. Allegaert K, Verbesselt R, Naulaers G, van den Anker JN, Rayyan M, Debeer A, de Hoon J. 2008. Developmental pharmacology: neonates are not just small adults. Acta Clin Belg 63:16–24. https://doi.org/10.1179/acb.2008.003.
15. Roberts JK, Stockmann C, Balch A, Yu T, Ward RM, Spigarelli MG, Sherwin C. 2015. Optimal design in pediatric pharmacokinetic and pharmacodynamic clinical studies. Paediatr Anaesth 25:222–230. https://doi.org/10.1111/pan.12575.
16. Aarons L, Ogungbenro K. 2010. Optimal design of pharmacokinetic studies. Basic Clin Pharmacol Toxicol 106:250–255. https://doi.org/10.1111/j.1742-7843.2009.00533.x.
17. Ogungbenro K, Dokoumetzidis A, Aarons L. 2009. Application of optimal design methodologies in clinical pharmacology experiments. Pharm Stat 8:239–252. https://doi.org/10.1002/pst.354.
18. Soy D, López E, Ribas J. 2006. Teicoplanin population pharmacokinetic analysis in hospitalized patients. Ther Drug Monit 28:737–743. https://doi.org/10.1097/01.ftd.0000249942.14145.ff.
19. Lortholary O, Tod M, Rizzo N, Padoin C, Biard O, Casassus P, Guillevin L, Petitjean O. 1996. Population pharmacokinetic study of teicoplanin in severely neutropenic patients. Antimicrob Agents Chemother 40:1242–1247. https://doi.org/10.1128/AAC.40.5.1242.
20. Zhao W, Zhang D, Storme T, Baruchel A, Declèves X, Jacqz-Aigrain E. 2015. Population pharmacokinetics and dosing optimization of teicoplanin in children with malignant haematological disease. Br J Clin Pharmacol 80:1197–1207. https://doi.org/10.1111/bcp.12710.
21. Ueda T, Takesue Y, Nakajima K, Ichki K, Wada Y, Tsuchida T, Takahashi Y, Ishihara M, Tatsumi S, Kimura T, Ikeuchi H, Uchino M. 2012. Evaluation of teicoplanin dosing designs to achieve a new target trough concentration. J Infect Chemother 18:296–302. https://doi.org/10.1007/s10156-011-0325-z.
22. Byrne CJ, Roberts JA, McWhinney B, Ryder SA, Fennell JP, O'Byrne P, Deasy E, Egan S, Desmond R, Enright H, D'Arcy DM, McHugh J. 2017. Population pharmacokinetics of teicoplanin and attainment of pharmacokinetic/pharmacodynamic targets in adult patients with haematological malignancy. Clin Microbiol Infect 23:674.e7–674.e13. https://doi.org/10.1016/j.cmi.2017.02.032.
23. Onufrak NJ, Forrest A, Gonzalez D. 2016. Pharmacokinetic and pharmacodynamic principles of anti-infective dosing. Clin Ther 38:1930–1947. https://doi.org/10.1016/j.clinthera.2016.06.015.
24. Craig WA. 2003. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 17:479–501. https://doi.org/10.1016/s0891-5520(03)00065-5.
25. Hagihara M, Umemura T, Kimura M, Mori T, Hasegawa T, Mikamo H. 2012. Exploration of optimal teicoplanin dosage based on pharmacokinetic parameters for the treatment of intensive care unit patients infected with methicillin-resistant *Staphylococcus aureus*. J Infect Chemother 18:10–16. https://doi.org/10.1007/s10156-011-0272-8.
26. Kanazawa N, Matsumoto K, Ikawa K, Fukamizu T, Shigemi A, Yaji K, Shimodozono Y, Morikawa N, Takeda Y, Yamada K. 2011. An initial dosing method for teicoplanin based on the area under the serum concentration time curve required for MRSA eradication. J Infect Chemother 17:297–300. https://doi.org/10.1007/s10156-010-0105-1.
27. Prybylski JP. 2015. Vancomycin trough concentration as a predictor of clinical outcomes in patients with *Staphylococcus aureus* bacteremia: a meta-analysis of observational studies. Pharmacotherapy 35:889–898. https://doi.org/10.1002/phar.1638.
28. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, Lodise TP. 2014. Are vancomycin trough concentrations adequate for optimal

dosing? Antimicrob Agents Chemother 58:309–316. https://doi.org/10.1128/AAC.01653-13.
29. Matsumoto K, Watanabe E, Kanazawa N, Fukamizu T, Shigemi A, Yokoyama Y, Ikawa K, Morikawa N, Takeda Y. 2016. Pharmacokinetic/pharmacodynamic analysis of teicoplanin in patients with MRSA infections. Clin Pharmacol Adv Appl 8:15–18. https://doi.org/10.2147/CPAA.S96143.
30. Ramos-Martín V, Johnson A, McEntee L, Farrington N, Padmore K, Cojutti P, Pea F, Neely MN, Hope WW. 2017. Pharmacodynamics of teicoplanin against MRSA. J Antimicrob Chemother 72:3382–3389. https://doi.org/10.1093/jac/dkx289.
31. Leiva ML, Imbett S, Gómez PJ, González M, Rodriguez AC, Agudelo M. 2014. Successful growth of *Staphylococcus epidermidis* in the neutropenic mouse thigh infection model (NMTIM) without the use of a foreign body, abstr A-1320. Abstr 54th Intersci Conf Antimicrob Agents Chemother, Washington, DC.
32. Padari H, Oselin K, Tasa T, Metsvaht T, Lõivukene K, Lutsar I. 2016. Coagulase negative staphylococcal sepsis in neonates: do we need to adapt vancomycin dose or target? BMC Pediatr 16:206. https://doi.org/10.1186/s12887-016-0753-0.
33. Kuti JL, Kiffer CRV, Mendes CMF, Nicolau DP. 2008. Pharmacodynamic comparison of linezolid, teicoplanin and vancomycin against clinical isolates of *Staphylococcus aureus* and coagulase-negative staphylococci collected from hospitals in Brazil. Clin Microbiol Infect 14:116–123. https://doi.org/10.1111/j.1469-0691.2007.01885.x.
34. Lutsar I, Metsvaht T. 2010. Understanding pharmacokinetics/pharmacodynamics in managing neonatal sepsis. Curr Opin Infect Dis 23:201–207. https://doi.org/10.1097/QCO.0b013e328337bb42.
35. Allegaert K, van den Anker J. 2019. Neonates are not just little children and need more finesse in dosing of antibiotics. Acta Clin Belg 74:157–163. https://doi.org/10.1080/17843286.2018.1473094.
36. Zuppa AF, Barrett JS. 2008. Pharmacokinetics and pharmacodynamics in the critically ill child. Pediatr Clin North Am 55:735–755, xii. https://doi.org/10.1016/j.pcl.2008.02.017.
37. Allegaert K, Kuppens M, Mekahli D, Levtchenko E, Vanstapel F, Vanhole C, van den Anker JN. 2012. Creatinine reference values in ELBW infants: impact of quantification by Jaffe or enzymatic method. J Matern Fetal Neonatal Med 25:1678–1681. https://doi.org/10.3109/14767058.2012.657277.
38. Begou O, Kontou A, Raikos N, Sarafidis K, Roilides E, Papadoyannis IN, Gika HG. 2017. An ultra-high pressure liquid chromatography-tandem mass spectrometry method for the quantification of teicoplanin in plasma of neonates. J Chromatogr B Analyt Technol Biomed Life Sci 1047:215–222. https://doi.org/10.1016/j.jchromb.2016.01.042.
39. Gueorguieva I, Ogungbenro K, Graham G, Glatt S, Aarons L. 2007. A program for individual and population optimal design for univariate and multivariate response pharmacokinetic-pharmacodynamic models. Comput Methods Programs Biomed 86:51–61. https://doi.org/10.1016/j.cmpb.2007.01.004.
40. Brion LP, Fleischman AR, McCarton C, Schwartz GJ. 1986. A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: noninvasive assessment of body composition and growth. J Pediatr 109:698–707. https://doi.org/10.1016/s0022-3476(86)80245-1.
41. Schwartz GJ, Feld LG, Langford DJ. 1984. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr 104:849–854. https://doi.org/10.1016/S0022-3476(84)80479-5.
42. Anderson BJ, Holford N. 2008. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 48:303–332. https://doi.org/10.1146/annurev.pharmtox.48.113006.094708.