



Beyond One-Size-Fits-All: Tailoring Teicoplanin Regimens for Normal Renal Function Patients Using Population Pharmacokinetics and Monte-Carlo Simulation

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Introduction/Objective

Teicoplanin, along with the glycopeptide antibiotic vancomycin, has an important role in the treatment of gram-positive bacterial infections, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [1,2]. Because of its long elimination half-life ranging from 83 to 182 h in patients with normal renal function, teicoplanin requires a loading dose to achieve therapeutic concentrations [2]. Based on the European Medicines Agency’s summary of the product characteristics (SmPC) for teicoplanin, adults and the elderly with normal renal function have recommended specific doses to effectively treat gram-positive infections [3]. For conditions such as complicated skin and soft tissue infections, pneumonia, and complicated urinary tract infections, a loading dose (LD) of 400 mg or 6 mg/kg every 12 h for three initial doses is recommended, followed by a daily maintenance dose (MD) of 6 mg/kg to achieve trough concentrations (C_{trough}) greater than 10 mg/L as determined by high-performance liquid chromatography (HPLC). For more severe conditions, such as endocarditis, a C_{trough} of 15–30 mg/L, an increased LD of 800 mg or 12 mg/kg every 12 h for the first three doses, followed by an MD of 12 mg/kg daily, is recommended. Despite the emphasis on achieving specific C_{trough} targets for therapeutic success, the pharmacokinetic/pharmacodynamic (PK/PD) relationship of teicoplanin suggests that the ratio of the area under the concentration-time curve (AUC) for 24 h to the minimum inhibitory concentration (MIC) may be a more appropriate marker to predict teicoplanin efficacy. As an antibiotic that exhibits time-dependent killing activity, this PK/PD index is important to correlate with drug efficacy [4]. Studies of patients infected with MRSA have concluded that an AUC/MIC of ≥610–900 is required for a sufficient bacteriological response [5–8].

Because of the complexity of calculating the AUC through multiple blood samplings, using C_{trough} as a surrogate marker for AUC is considered customary in clinical practice. However, the recently revised consensus guidelines for vancomycin, based on the opinions of experts in the field and several studies, have concluded that C_{trough} is not an adequate surrogate indicator for AUC [9]. The guidelines now recommend the use of Bayesian-derived AUC monitoring, using well-developed vancomycin population PK models integrated into Bayesian software. For teicoplanin, AUC may be a more accurate predictor of efficacy than C_{trough}, but a consensus on this matter has yet to be established. Therefore, developing a robust PK model for teicoplanin and creating Bayesian software would greatly assist in the precision dosing of teicoplanin.

When developing new drugs, the evaluation of tolerance and PK in healthy individuals, who are not affected by the confounding factors of the disease, is done to explore the basic characteristics of a drug. Similarly, calculating the standard PK parameters of a drug in population PK studies is not only helps to understand the population PK in patients through subsequent patient-focused research, but also for creating models with superior predictive power. The purpose of this study was to develop a population PK model for healthy adults and use it to predict the optimal dosage regimen in patients with normal renal function.

Methods

A 200 mg dose of teicoplanin in 100 mL of normal saline was administered intravenously to healthy subjects over 30 min. Venous blood samples (6 mL each) were collected into heparinized tubes at 33, 36, 45, and 90 min, and 4, 8, 48–120, and 168–240 h after starting the infusion. Plasma levels of teicoplanin were quantified by tandem mass spectrometry coupled with HPLC (HPLC-MS/MS). The PK analysis of teicoplanin was done using a nonlinear mixed-effects modeling technique with NONMEM software (version 7.5, ICON Clinical Research LLC, North Wales, PA, USA).

To develop dosage recommendations for teicoplanin in patients with normal renal function, we used Monte Carlo simulations based on the final PK model. Building upon this model, we generated PK parameters for 5,000 virtual patients to assess the therapeutic targets for teicoplanin. The analysis focused on two primary endpoints obtained from days 3 to 7 following the initiation of treatment: the C_{trough}, which was determined just before the next dose, and the ratio of the AUC from 0 to 24 h to the pathogen’s MIC, which was designated AUC/MIC. PK profiles were simulated following the administration of LDs of 6, 8, 10, 12, 14, and 16 mg at 12-h intervals for four doses, followed by MDs at 24-h intervals for five doses.

To evaluate the potential therapeutic efficacy of teicoplanin, we conducted an analysis. MIC values of 0.25, 0.5, 1, and 2 mg/L were randomly assigned to 5,000 virtual patients, reflecting the distribution of teicoplanin MICs for MRSA as reported by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The distribution of MIC values among the virtual patients was as follows: 0.25 mg/L for 5.6% (31/555), 0.5 mg/L for 40.4% (224/555), 1 mg/L for 43.1% (239/555), and 2 mg/L for 11.0% (61/555) of the cases. Based on these distributions, we calculated the PTA, in which the C_{trough} was at least 20 mg/L and, concurrently, the AUC/MIC ratio was at least 800.

Results

The demographic and clinical characteristics of the 12 healthy adult subjects (6 females, 6 males) are listed in Table 1.

Table 1. Patients Characteristics

Parameters	Mean (CV%)	Median (IQR)	
Demographic characteristics			
Age, years	34.8 (17.2%)	32.0 (30.0–40.3)	
Height, cm	165 (4.91%)	164 (158–169)	
Weight, kg	64.8 (19.9%)	67.9 (51.3–73.4)	
Body surface area, m ²	1.71 (11.3%)	1.77 (1.52–1.85)	
Body mass index (BSA), kg/m ²	23.6 (15.1%)	24.8 (20.6–25.5)	
Laboratory characteristics			
Protein, g/dL	7.52 (5.07%)	7.35 (7.30–7.70)	
Albumin, g/dL	4.96 (4.90%)	4.90 (4.80–5.03)	
Cystatin C, mg/dL	0.808 (14.6%)	0.760 (0.710–0.928)	
Creatinine, mg/dL	0.867 (15.2%)	0.875 (0.793–0.925)	
Blood urea nitrogen, mg/dL	11.2 (26.0%)	11.2 (10.1–12.0)	
Alanine aminotransferase, U/L	23.2 (79.7%)	19.5 (8.50–29.0)	
Aspartate aminotransferase, U/L	25.9 (41.3%)	22.5 (19.5–27.5)	
Gamma-glutamyl transferase, U/L	23.8 (46.6%)	22.5 (17.0–28.0)	
Renal functions			
CL _{CR} by Cockcroft-Gault (mL/min) ^a	102 (19.5%)	104 (94.3–113)	
eGFR by MDRD (mL/min/1.73 m ²) ^b	88.6 (13.4%)	89.4 (81.8–96.1)	
eGFR by CKD-EPI _{CR} (mL/min/1.73 m ²) ^c	104 (10.7%)	105 (97.7–115)	
eGFR by CKD-EPI _{CR,CYS} (mL/min/1.73 m ²) ^d	108 (11.6%)	108 (98.8–120)	
Adjusted eGFR by MDRD for BSA (mL/min) ^e	87.5 (16.3%)	89.7 (80.1–96.0)	
Adjusted eGFR by CKD-EPI _{CR} for BSA (mL/min) ^e	103 (15.5%)	105 (96.7–113)	
Adjusted eGFR by CKD-EPI _{CR,CYS} for BSA (mL/min) ^e	106 (11.8%)	105 (101–112)	

CV, coefficient of variation; IQR, interquartile range; CL_{CR}, creatinine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CR, creatinine; CYS, cystatin C; min, the minimum of (CR or CYS)/number and 1; max, the maximum of (CR or CYS)/number and 1.

^aCL_{CR} = (140 – Age) × weight/CR × 72 (×0.85 if female).

^beGFR = 175 × CR^{–1.54} × Age^{–0.203} × (0.742 if female)

^ceGFR (female) = 142 × min(CR/0.7,1)^{–0.241} × max(CR/0.7,1)^{–1.200} × 0.9938^{Age} × 1.012

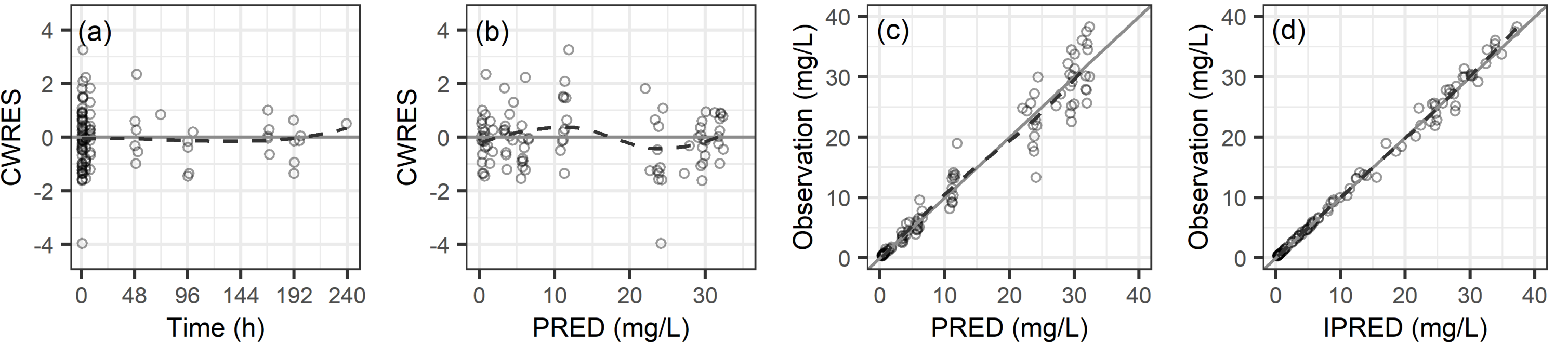
^deGFR (male) = 142 × min(CR/0.9,1)^{–0.302} × max(CR/0.9,1)^{–1.200} × 0.9938^{Age}

^eThe adjusted eGFR by MDRD and CKD-EPI equations are eGFR = eGFR (MDRD or CKD-EPI) × (BSA/1.73 m²).

Table 2. Parameter estimates and bootstrap medians (95% confidence intervals) of the final PK models

Parameter	Estimates	RSE(%)	Bootstrap median (95% CI)	
Structural model				
CL = θ ₁ × (CE/105.27) ⁰²				
θ ₁ (L/h)	0.693	2.97	0.693 (0.653–0.74)	
θ ₂	0.785	16.2	0.789 (0.422–1.16)	
V1 = θ ₃ (L)	3.96	8.41	3.97 (3.15–4.62)	
Q2 = θ ₄ (L/h)	4.45	11.6	4.45 (3.63–5.86)	
V2 = θ ₅ (L)	8.24	8.32	8.33 (7.07–9.85)	
Q3 = θ ₆ (L/h)	1.76	9.7	1.75 (1.44–2.13)	
V3 = θ ₇ × (WT/67.85) ⁰⁸				
θ ₇ (L)	69.8	8.74	69.7 (55.8–82.6)	
θ ₈	1.73	22.6	1.73 (0.67–2.44)	
Interindividual variability				
CL (%)	8.83 ^f			
V1 (%)	23.8 ^f			
Q2 (%)	32.7	20.2	30.7 (14.2–42.2)	
V2 (%)	23.9 ^f			
Q3 (%)	31.0	18.9	29.6 (16.7–41.4)	
V3 (%)	7.54 ^f			
Residual variability				
Proportional error (%)	6.33	13.1	6.22 (4.63–7.94)	

RSE, relative standard error; CI, confidence interval; CL, total clearance; V1, central volume of distribution; V2, the volume of distribution for the first peripheral compartment; Q2, intercompartmental clearance between V1 and V2; V3, the volume of distribution for the second peripheral compartment; Q3, intercompartmental clearance between V1 and V3; CE, estimated glomerular filtration rate calculated using the CKD-EPI equation based on creatinine levels, adjusted for body surface area; WT, weight; f, fixed.



Results (continued)

Figure 1. Diagnostic plots for the final PK model of teicoplanin: (a) conditional weighted residuals (CWRES) versus time, (b) CWRES versus population predicted concentration (PRED) (c) observed concentration versus PRED, and (d) observed concentration versus individual predicted concentration (IPRED). The dashed lines are smooth curves.

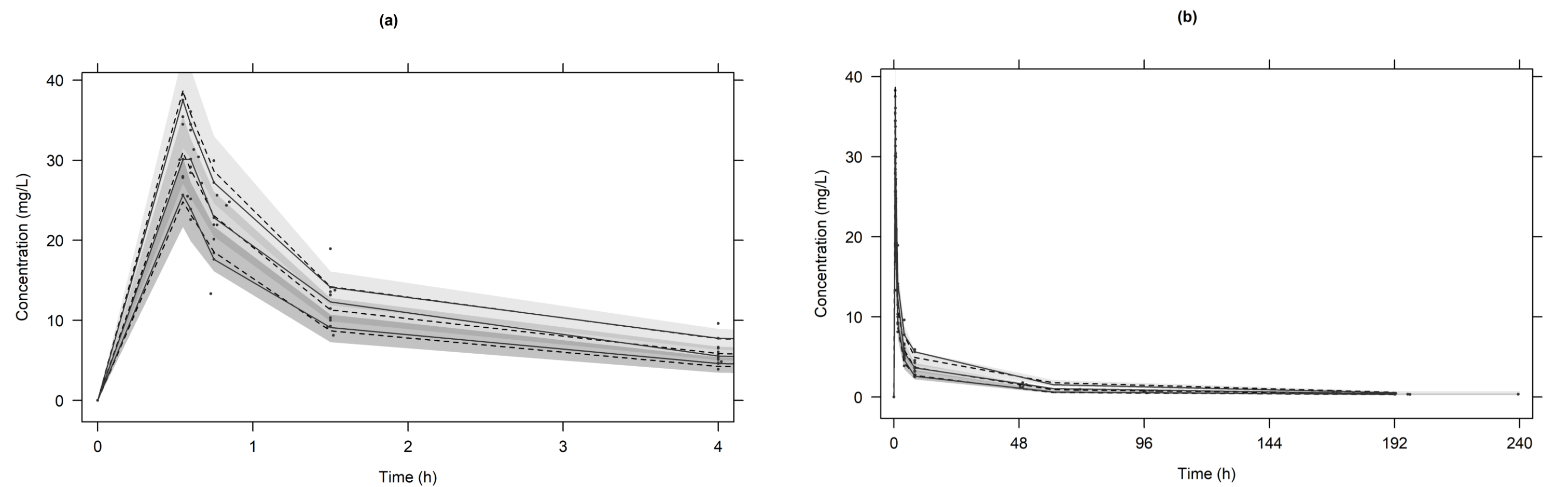


Figure 2. Visual predictive check from simulated concentrations of 1,000 virtual datasets of teicoplanin (a) 0 to 4 h, (b) 0 to 240 h: closed circles, observed concentrations; solid lines, 10th, 50th and 90th percentiles of observations; dashed lines, 10th, 50th and 90th percentiles of simulated concentrations; and shaded areas, 95% confidence intervals for the 10th, 50th, and 90th percentiles of simulated concentrations.

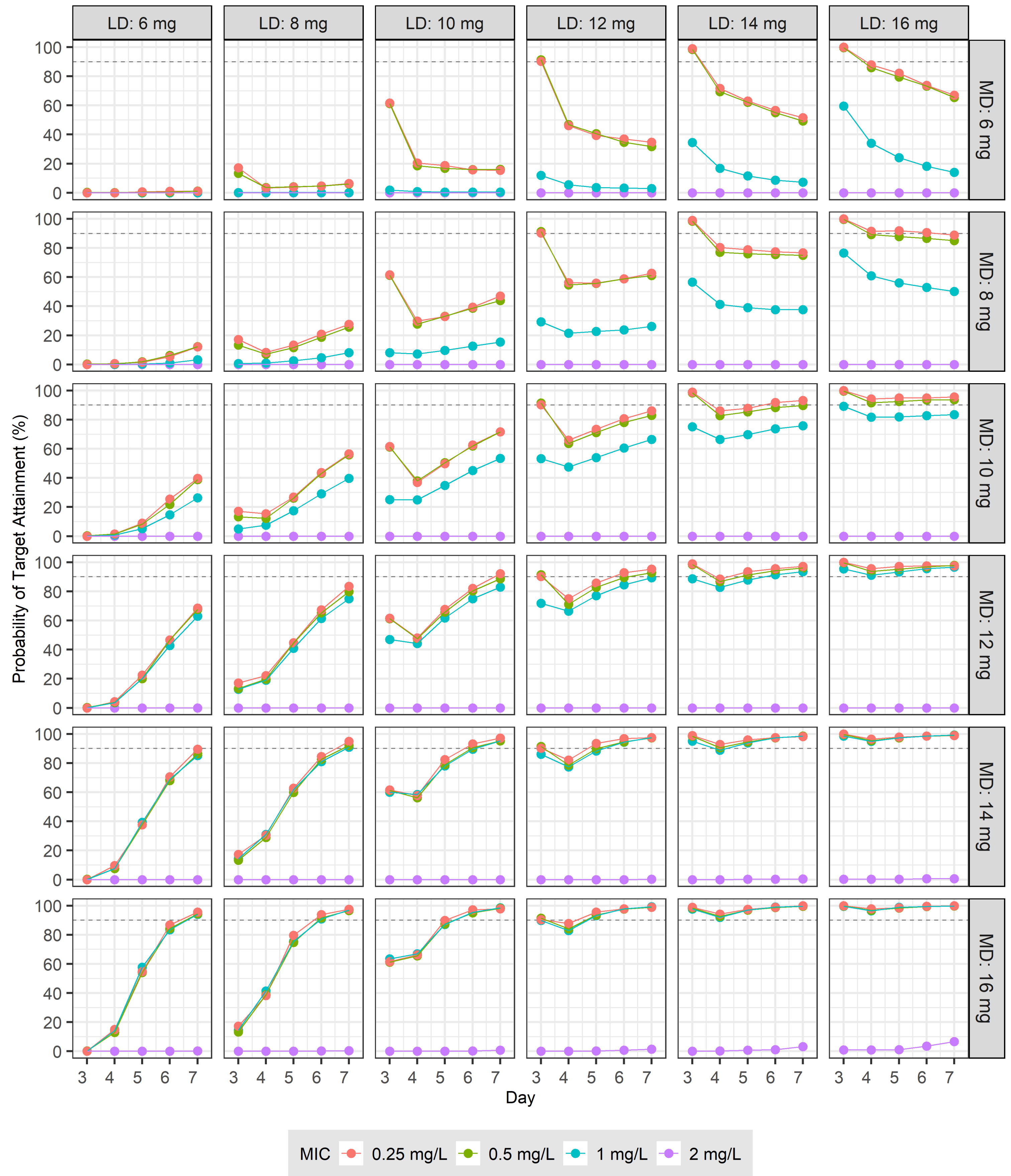


Figure 3. Probabilities of target attainment for trough concentrations >20 mg/L and AUC/MIC ≥800 in subjects with normal renal function across four MICs (0.25, 0.5, 1, and 2 mg/L): six loading doses (6, 8, 10, 12, 14, and 16 mg) were administered every 12 h four times, followed by six maintenance doses (6, 8, 10, 12, 14, and 16 mg) daily from days 3 to 7.

Conclusions

In conclusion, we established PK properties for teicoplanin in healthy subjects by applying a population approach. The concentration–time profile of teicoplanin is explained by a three-compartment model. Results from Monte-Carlo simulations suggest that, in patients with normal renal function, an increase in both LDs and MDs should be considered. Specifically, for pathogens with an MIC of 1 mg/L, we recommend administering an LD of 14 mg/kg every 12 h for four doses, followed by an MD of 16 mg/kg every 24 h. However, because of the long half-life of teicoplanin, in cases requiring long-term administration, it is necessary to perform TDM at appropriate times to prevent nephrotoxicity resulting from a high C_{trough}.

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