Use of Monte Carlo Simulation to Evaluate Vancomycin Dosing Regimens in Neonates
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Purpose
Vancomycin is considered to be a drug of choice to treat serious infection caused by methicillin-resistant Staphylococcus aureus in neonates. Several dosing regimens have been proposed, although it is unclear how often these regimens achieve target trough concentrations. This study aimed to develop the population PK of vancomycin and to simulate the probability of attaining target trough concentrations for neonates using several dosing regimens.

Methods
Data were collected for neonates (<28 days postnatal age) with one or more vancomycin serum concentrations obtained between 01/2006-09/2011. A population PK model was constructed using NONMEM 7.2 and was assessed using internal and external model evaluation methods. Stochastic simulations were performed using two pediatric dosing regimens based on post-menstrual age (PMA), postnatal age (PNA), and serum creatinine (SCR). The target trough concentration was defined as 15-20 mg/L. The p-value of 0.001 was considered as statistically significant.

Results
The PK model evaluated 960 vancomycin peak and trough concentrations from 198 neonates. The current weight (CWT) of these neonates was mean ± SD, 1.74 ± 1.1 kg and the mean PMA was 29.5 ± 5.5 weeks. A one-compartment model with first-order elimination was utilized. The final covariate model featured clearance (CL) = 0.03 • (CWT/2)0.757 • (1/SCR) • (PMAW-20)0.257 and volume of distribution (V) = 1.20 • (CWT/2). Inclusion of CWT as a covariate resulted in a 34.8% and 28.8% decrease in between-subject variability of CL and V (P<0.001), respectively. Predictive performance of the model was confirmed using the external dataset which included 128 vancomycin concentrations from 46 neonates. Approximately 19% and 14% (P<0.001) of simulated patients achieved the target trough concentration range for SCR-based and PMA- and PNA-based vancomycin dosing regimens, respectively.

Conclusion
The PK of vancomycin was described using a one-compartment model with first-order elimination. There was a statistically significant association with vancomycin CL and CWT, SCR and PMA. This suggests that the probability of achieving target trough concentrations is greatest for SCR-based vancomycin dosing regimens; however this method fails to achieve target troughs for a majority of neonates. Further study is warranted to develop a vancomycin dosing regimen that effectively reaches target trough concentrations for neonates.