Population Pharmacokinetics and Dosing Regimen Optimization of Intravenous Vancomycin in Infants
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Purpose
Efforts are currently underway to revise vancomycin dosing guidelines in neonates and infants, however, few studies have evaluated the pharmacokinetic (PK) characteristics of vancomycin in infants – a population which goes through rapid growth and maturation. This study aimed to investigate the PK properties of vancomycin in infants and develop optimal dosing regimens.

Methods
Patients (28 days-2 years) who received intravenous vancomycin and had ≥ 1 concentration(s) taken at an Intermountain Healthcare facility from 2006-2012 were included. Population PK modeling utilized NONMEM 7.2. Tested covariates included sex, age, gestational age (GA), postmenstrual age (PMA), birth weight (BW), current weight, height, serum creatinine concentration (SCR), and creatinine clearance (CrCL). Pharmacodynamic target achievement (area under the concentration-time curve for 24 hours/minimum inhibitory concentration, AUC24/MIC ≥ 400) was simulated in MATLAB (R2013b).

Results
This study included 184 infants who had 591 vancomycin concentrations obtained from 227 encounters. The mean patient age (SD) was 0.8 ± 0.5 years, GA 36 ± 4 weeks, PMA 78.8 ± 29.3 weeks, BW 2829 ± 939 g, weight 7.3 ± 2.9 kg, height 66 ± 12 cm, SCR 0.32 ± 0.26 mg/dL, CrCL by Schwartz formula 140.7 ± 89.6 mL/min/1.73 m², by modified Schwartz formula 105.6 ± 67.3 mL/min/1.73 m², by Schwartz-Lyon formula 95.4 ± 60.8 mL/min/1.73 m². A one-compartment model with first-order elimination fit the data best with a combined additive and proportional error model. Clearance (CL) was estimated at 0.8 L/h with a between-subject variability (BSV) of 22.4%. The volume of distribution (V) was estimated at 4.6 L with a BSV of 25.2%. Vancomycin CL was significantly influenced by weight (p<0.001) and CrCL by Schwartz-Lyon formula (p<0.001). Weight also influenced V (p<0.001). Monte-Carlo simulation was used to propose optimal vancomycin dosing regimens that achieved an AUC24/MIC ≥ 400 in 90% of cases.

Conclusion
Vancomycin PK in infants was well described by a one-compartment model with first-order elimination, with weight having a significant influence on CL and V and CrCL by Schwartz-Lyon formula on CL. Studies are underway to develop optimal vancomycin dosing regimens for infants.