Population Pharmacokinetic Modeling of Gentamicin in Children Diagnosed with Cancer
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Purpose
The aim of this study was to determine the pharmacokinetics (PK) of gentamicin in pediatric patients (2-12 years of age) and investigate the potential influences of cancer diagnosis among several other clinically relevant covariates through population modeling/simulation approaches.

Methods
The gentamicin concentration-time data and clinically relevant covariates were retrieved from the Enterprise Data Warehouse (EDW) maintained by Intermountain Healthcare (IH). Pediatric patients (2 to 12 years of age) from January 2006 to December 2014 received intravenous gentamicin (≥2 doses). Children with cancer (n=122) and those without cancer (n=135) but presenting similar demographic features were included in the analysis. A population PK model was developed using NONMEM 7.3.0 (ICON Development Solutions, Ellicott City, MD, USA). The clinically relevant covariates examined including body weight, height, sex, age, race, ethnicity, serum creatinine, creatinine clearance (calculated using Modified Schwartz method), and cancer diagnosis (binary, yes=1, no=0) were evaluated in a stepwise fashion to identify their potential influences on the model.

Results
A total of 310 observations from 257 pediatric patients were pooled for model development. The PK data were best described by a one-compartmental model with an additive error model structure. The estimated population plasma clearance (CL) (95% confidence interval) was 1.98 L/h (1.788-2.172 L/h), and the volume of distribution (V) was 5.38 L (4.418-6.342 L), with an inter-individual variability of 4.9% and 9.1% (CV %), respectively. Stepwise covariate search (forward addition p<0.05, backward elimination p<0.01) returned body weight (BW) and creatinine clearance (CLCR) as significant covariates. A power relationship was assumed relative to median BW and CLCR and expressed mathematically as below:

$$CL_i = 1.98 \times (BW/18)^{a_{CL}} \times (CLCR/159.5)^{\beta_{CL}} \times \exp(\eta_{CL})$$
$$V_i = 5.38 \times (BW/18)^{a_V} \times \exp(\eta_V)$$

where $CL_i$ and $V_i$ are the plasma clearance and volume distribution for the $i$th subject, respectively. $\eta$ is the random between subject variability. $a_{CL}$ (95% confidence interval), $\beta_{CL}$, and $a_V$ are the power exponents and were estimated to be 0.795 (0.548-1.042), 1.36 (1.251-1.469), and 0.817 (0.462-1.172), respectively. Diagnosis with cancer was not identified as a significant covariate.

Conclusion
The population PK of gentamicin in children was best described by a one-compartment model with first-order elimination. No significant differences in PK parameters were detected between children with cancer and those with no malignancies. Body weight and creatinine clearance had significant influences on gentamicin pharmacokinetics and should be considered when determining optimal dosing plans for young children.