

1 **External Evaluation of a Gentamicin Infant Population Pharmacokinetic**
2 **Model Using Data from a National Electronic Health Record Database**

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25 **ABSTRACT**

26 Gentamicin is a common antibiotic used in neonates and infants. A recently published population
27 pharmacokinetic (PK) model was developed using data from multiple studies, and the objective
28 of our analyses is to evaluate the feasibility of using a national electronic health record (EHR)
29 database to further externally evaluate this model. Our results suggest that with proper data
30 capture procedures, EHR data can serve as a potential data source for external evaluation of PK
31 models.

32 Gentamicin is one of the most commonly used antibiotics prescribed for treatment or prophylaxis
33 of Gram-negative infections in infants (1–3). Nephrotoxicity and ototoxicity are major adverse
34 reactions that are associated with supratherapeutic gentamicin concentrations (4). Due to its
35 narrow therapeutic index and wide pharmacokinetic (PK) variability, therapeutic drug
36 monitoring of gentamicin is required (5, 6). Target peak concentrations of gentamicin should
37 range from 5 to 10 mg/L, and trough levels should be <2 mg/L (7).

38 Gentamicin population PK models have been developed for infants in previous studies.
39 Both 2- and 3-compartment models were used to characterize gentamicin's disposition in infants
40 (8–12). Since gentamicin is almost entirely renally eliminated, age, weight, and serum creatinine
41 (SCR) concentration were commonly identified as important covariates on gentamicin clearance.
42 These publications either did not perform an external evaluation or performed an evaluation
43 using an external dataset consisting of 70 to ~160 subjects (7-11).

44 Unlike the traditional clinical trials that are challenging to perform in children due to the
45 ethical, logistical and financial factors, electronic health record (EHR) data allow researchers to
46 access large volumes of clinical data easily and efficiently (13). The large sample size and
47 widely distributed profiles in EHR data make it an ideal data source for evaluation of PK models.
48 In previous studies, EHR data had been used to develop PK models or assess the relationship
49 between drug exposure and safety (14, 15). However, to date we are not aware of any studies that
50 have used a national EHR database data to externally evaluate a population PK model. The
51 objective of this paper is to use gentamicin as a case study to explore the potential use of EHR
52 data in the evaluation of population PK models.

53 In this study, EHR data from 348 Pediatrix Medical Group neonatal intensive care units
54 from 1997 to 2014 was used to evaluate a previously reported gentamicin population PK model.

55 Information in the EHR included age, weight, sex, dose records, SCR concentrations, and
56 peak/trough plasma concentrations of gentamicin. The population PK model developed by
57 Germovsek et al. is a 3-compartment model with weight, postmenstrual and postnatal age, and
58 SCR concentration as covariates for clearance. This model was developed based on 1325
59 gentamicin serum concentrations from 205 infants, and evaluated using 483 gentamicin serum
60 measurements from 163 infants (8).

61 The following assumptions and criteria were used to extract relevant and reliable EHR
62 data: (1) only infants receiving intravenous (IV) injections were included; (2) the infusion time
63 was assumed to be 30 min; (3) only concentrations ranging from 4 to 20 mg/L (peaks) and 0.3 to
64 10 mg/L (trough) were included; (4) peak samples were assumed to be collected 1 hour after
65 dosing and trough samples 2 min before dosing; (5) observations collected from infants with a
66 SCR concentration >10 mg/dL were excluded; (6) infants with postnatal age (PNA) >60 days
67 and gestational age (GA) <23 weeks were excluded; (7) observations with doses >6 mg/kg/day
68 were excluded; (8) to avoid model misspecification caused by data entry error when there is a
69 regimen switch, only observations taken during the first dosing regimen were included; and (9)
70 an occasion was defined as a dose with subsequent gentamicin samples taken. These assumptions
71 and criteria were made based on common clinical practice and infant demographics in the model-
72 building dataset. A summary of demographics and dosing for the model-building dataset and
73 filtered EHR data is shown in **Table 1** (8).

74 To assess the predictive performance of the model, population predicted concentrations
75 versus observations plots for peak and trough concentrations were generated. Parameters were
76 fixed to the final estimates reported in the original publication. The relationship between relevant
77 covariates (body weight [WT, kg], measured serum creatinine concentration [MSCr, $\mu\text{mol/liter}$],

78 typical value of serum creatinine concentration [TSCr ($\mu\text{mol/liter}$) = - 2.849 * PMA (weeks) +
 79 166.48], postmenstrual age [PMA, weeks] and postnatal age [PNA, days]) and PK parameters
 80 are described as follows: $\text{CL (L/h)} = 6.2 \times \text{PMA}^{3.33} / (\text{PMA}^{3.33} + 55.4^{3.33}) \times (\text{WT} / 70)^{0.632} \times$
 81 $(\text{MSCr} / \text{TSCr})^{-0.13} \times (\text{PNA} / (1.70 + \text{PNA}))$; $\text{V}_1 (\text{L}) = 26.5 \times (\text{WT} / 70)$; $\text{V}_2 (\text{L}) = 21.2 \times (\text{WT} /$
 82 $70)$; $\text{V}_3 (\text{L}) = 147.9 \times (\text{WT} / 70)$; $\text{Q}_1 (\text{L/h}) = 2.2 \times (\text{WT} / 70)^{0.75}$; and $\text{Q}_2 (\text{L/h}) = 0.3 \times (\text{WT} /$
 83 $70)^{0.75}$ (CL: clearance; V: volume of distribution; Q: intercompartmental clearance). Analyses
 84 were performed using the NONMEM (version 7.3, Icon Development Solutions, Ellicott City,
 85 MD, USA). The first-order conditional estimation method with interaction was used. Data
 86 manipulation was performed in the software R (version 3.3.2) and RStudio (version 1.0.136).
 87 The packages xpose4 and lattice packages in R and RStudio were used for data visualization
 88 (16–18). Visual predictive checks (VPC) were performed based on 1000 simulations using Perl-
 89 speaks-NONMEM (version 4.6.0). The bias and precision of the model was evaluated by
 90 calculating the j th prediction error (PE_j) and relative prediction error (RPE_j), mean prediction
 91 error (MPE), and mean absolute predicted error (MAPE) (Equations 1-4).

$$92 \quad \text{PE}_j = (\text{PRED}_j - \text{OBSERVATION}_j) \quad \text{Eq. 1}$$

$$93 \quad \text{RPE}_j = \frac{\text{PE}_j \times 100}{\text{OBSERVATION}_j} \quad \text{Eq. 2}$$

$$94 \quad \text{MPE} = \text{Mean} \left(\frac{\text{PE}_j \times 100}{\text{OBSERVATION}_j} \right) \quad \text{Eq. 3}$$

$$95 \quad \text{MAPE} = \text{Mean} \left(\frac{|\text{PE}_j| \times 100}{\text{OBSERVATION}_j} \right) \quad \text{Eq. 4}$$

96 Filtered EHR data contained 6753 measurements with 2580 peak concentrations and
 97 4173 trough concentrations from 4519 infants. The EHR population has similar age range
 98 compared to the model-building dataset (**Table 1**). **Figure 1** shows box plot of prediction error
 99 and relative prediction error for peak and trough concentrations. In the VPC (**Figure 2**), 27.7%
 100 of observations were below and 8.2% were above the 80% prediction interval. There was a trend

101 towards gentamicin concentrations plateauing after 24 h (**Figure 2**), which may be related to
102 large variation in gentamicin trough concentrations due to timing of sample collection and
103 varying degrees of renal dysfunction in these infants. The median (2.5th to 97.5th percentile)
104 prediction errors were 3.43 (-6.20, 12.95) mg/L and 0.35 (-2.03, 1.78) mg/L for peak and trough,
105 respectively. The median (2.5th to 97.5th percentile) relative prediction errors (%) were 40.82 (-
106 49.72, 213.55) and 47.14 (-73.22, 344.92) for peak and trough concentrations, respectively
107 (negative values indicate under-prediction of concentrations). The mean prediction errors from
108 predictions of peak and trough concentrations were 51.0% and 71.0%, respectively. The
109 precision (measured by mean absolute predicted error) for peak and trough concentrations were
110 62.9% and 92.3%, respectively.

111 Our results demonstrate that the model developed by Germovsek et al. successfully
112 captured the central tendency of the gentamicin concentrations in the EHR database (**Figure 2**),
113 with some notable overprediction (i.e., the distribution of relative prediction errors was skewed
114 to the right) of peak and trough concentrations (**Figure 1**). Peak concentrations were predicted
115 with greater accuracy and precision compared to trough concentrations, which is consistent with
116 the findings from the original analysis. Overall, the model appears to have less accuracy and
117 precision when evaluated with the EHR data compared to the initial external database (8). This
118 may be explained by assumptions we made in modeling the EHR data, particularly the lack of
119 exact sampling times which may lead to misspecification. There are variations in clinical practice
120 for when peak concentrations are obtained, and if a significant number of samples were drawn at
121 1 hour after dosing rather than 30 minutes, this may lead to overprediction in gentamicin
122 concentrations. Additionally, differences in the gentamicin assay used across centers may
123 introduce measurement error, especially for trough concentrations falling near the lower limit of

124 quantification. Since therapeutic hypothermia is associated with alterations in gentamicin PK and
125 we cannot capture this from the current dataset, this may also explain some of the observed
126 misspecification (19). Therefore, it is likely that model misspecification we observed in our
127 analyses is related to the assumptions we made in developing our gentamicin EHR database for
128 external evaluation. Given that this model has performed well in previous external evaluation
129 (8), further study focused on clinical implementation and evaluation of this model's use in
130 facilitating dose individualization is justified.

131 While the use of EHR databases can significantly enhance the quantity of clinical data,
132 ensuring that data is of high quality is still crucially important. The major challenge we
133 encountered in performing population PK modeling of EHR data was the lack of accurate
134 documentation of sampling times and appropriate format of clinical data. This required us to
135 apply reasonable assumptions to estimate missing information as well as significant effort to
136 prepare analysis-ready datasets. As a result, the misspecification we identified may result from
137 either model error or data inaccuracy, which makes the evaluation of PK models more
138 challenging. To maximize the use of EHR in building and evaluating population PK models,
139 more studies are needed to identify efficient procedures for extracting high volumes of accurate
140 clinical data from EHR databases. In addition, the widespread use of EHR databases in model
141 evaluation could benefit from improvements to protocols for clinical data collection, particularly
142 timing of dosing and PK measurements.

143 In conclusion, a national EHR database was used to externally evaluate a published
144 population PK model for gentamicin in infants. Despite notable misspecifications, the model
145 captured the central tendency of the gentamicin concentrations in the EHR database.

146 Improvements to EHR data collection are still required to maximize the robustness of EHR
147 databases in population PK model evaluation.

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- 224

225 **Figure Legends**

226 **Figure 1.** Box plot of (A) prediction error (mg/L) and (B) relative prediction error (%) for peak
227 and trough concentrations. The bottom and top of the box are the 25th and 75th percentile and the
228 band in the middle of the box is the 50th percentile. The length of the box is the interquartile
229 range (IQR). Upper whisker = 75th percentile + 1.5*IQR; Lower whisker = 25th percentile -
230 1.5*IQR.

231 **Figure 2.** Visual predictive check plot of gentamicin concentrations versus time after last dose.
232 The shaded regions denote the 95% prediction interval around the 10th, 50th, and 90th percentiles
233 of simulated concentrations. The dashed lines represent the 10th, 50th, and 90th percentiles for the
234 observed data. The solid lines represent the 10th, 50th, and 90th percentiles for the predicted data.
235 Open circles are the observed values.

236 **Table 1.** Population demographics for model-building and EHR data.

	Participants (N)	Number of measurements	GA (weeks)*	PNA (days)*	WT (kg)*	Dose
Model- building dataset**	205	1325	34 (23.3 – 42.1)	5.4 (1 – 66)	2.12 (0.53 – 5.05)	Initial dose of 2-3 mg/kg (twice daily) or 4 mg/kg (every 24 hours)
EHR	4519	6753	29 (23 - 42)	1 (1 - 59)	1.26 (0.31 - 4.79)	3.50 (0.49 - 6.00) mg/kg/day

237 * Data were presented as median (range). GA: gestational age; PNA: postnatal age; WT: body weight.

238 ** Reference (8)



