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

Shufan Ge[1], Ryan J. Beechinor[1], Christoph P. Hornik[2,3], Joseph F. Standing[4], Kanecia Zimmerman[2,3], Michael Cohen-Wolkowiez[2,3], Matthew M. Laughon[5], Reese Clark[6], and Daniel Gonzalez[1]*

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA; [3]Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina, USA; [4] Inflammation, Infection and Rheumatology Section, Great Ormond Street Institute of Child Health, University College London, London, United Kingdom; [5] Department of Pediatrics, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [6] Pediatrix Medical Group, Inc., Sunrise, Florida

*Corresponding author: Daniel Gonzalez, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, CB #7569, Chapel Hill, NC 27599-7569, USA. Tel:+1-919-966-9984; Fax: 919-962-0644; E-mail: daniel.gonzalez@unc.edu.

Running title: Gentamicin Infant Population Pharmacokinetics

Key words: EHR, external evaluation, gentamicin, infant, and pharmacokinetics

Manuscript word count: 1528

Abstract word count: 74

Number of figures/tables: 2/1

Number of references: 19

ABSTRACT

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

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

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

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

In this study, EHR data from 348 Pediatrix Medical Group neonatal intensive care units 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, μmol/liter],

typical value of serum creatinine concentration [TSCr (μmol/liter) = - 2.849 * PMA (weeks) + 166.48], postmenstrual age [PMA, weeks] and postnatal age [PNA, days]) and PK parameters are described as follows: CL (L/h) = 6.2 × $PMA^{3.33}$ / ($PMA^{3.33}$ + $55.4^{3.33}$) × (WT / 70)$^{0.632}$ × (MSCr / TSCr)$^{-0.13}$ × (PNA / (1.70 + PNA)); V_1 (L) = 26.5 × (WT / 70); V_2 (L) = 21.2 × (WT / 70); V_3 (L) = 147.9 × (WT / 70); Q_1 (L/h) = 2.2 × (WT / 70) $^{0.75}$; and Q_2 (L/h) = 0.3 × (WT / 70)$^{0.75}$ (CL: clearance; V: volume of distribution; Q: intercompartmental clearance). Analyses were performed using the NONMEM (version 7.3, Icon Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation method with interaction was used. Data manipulation was performed in the software R (version 3.3.2) and RStudio (version 1.0.136). The packages xpose4 and lattice packages in R and RStudio were used for data visualization (16–18). Visual predictive checks (VPC) were performed based on 1000 simulations using Perl-speaks-NONMEM (version 4.6.0). The bias and precision of the model was evaluated by calculating the *j*th prediction error (PE_j) and relative prediction error (RPE_j), mean prediction error (MPE), and mean absolute predicted error (MAPE) (Equations 1-4).

$$PE_j = (PRED_j - OBSERVATION_j) \quad \text{Eq. 1}$$

$$RPE_j = \frac{PE_j \times 100}{OBSERVATION_j} \quad \text{Eq. 2}$$

$$MPE = \text{Mean}\left(\frac{PE_j \times 100}{OBSERVATION_j}\right) \quad \text{Eq. 3}$$

$$MAPE = \text{Mean}\left(\frac{|PE_j| \times 100}{OBSERVATION_j}\right) \quad \text{Eq. 4}$$

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

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

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

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

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

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

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

ACKNOWLEDGEMENTS

The authors wish to acknowledge Dr. Jaimit Parikh for his contribution towards dataset preparation.

DISCLOSURE OF FUNDING SOURCES

R.J.B. is supported by the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) under award T32GM086330. C.P.H. receives salary support for research from the National Institute of Child Health and Human Development (NICHD) (K23HD090239), the U.S. government for his work in pediatric and neonatal clinical pharmacology (Government Contract HHSN267200700051C, PI: Benjamin, under the Best Pharmaceuticals for Children Act), and industry for drug development in children. K.Z. receives support for research from NICHD (HHSN275201000003I and K23HD091398) and the Duke Clinical and Translational Science Awards (KL2TR001115). M.C-W. receives support for research from the NIH (1R01-HD076676-01A1), the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), the National Institute of Allergy and Infectious Disease (NIAID) (HHSN272201500006I and HHSN272201300017I), NICHD (HHSN275201000003I), the Food and Drug Administration (1U01FD004858-01), the Biomedical Advanced Research and Development Authority (BARDA) (HHSO100201300009C), the nonprofit organization Thrasher Research Fund (www.thrasherresearch.org), and from industry (CardioDx and Durata Therapeutics) for drug development in adults and children (www.dcri.duke.edu/research/coi.jsp). M.M.L. receives support from the US government for work in pediatric pharmacology and trials (FDA

169 R01FD005101, PI: Laughon; NHLBI 1R34HL124038, PI: Laughon; NICHD Pediatric Trials
170 Network Government Contract HHSN267200700051C, PI: Benjamin). D.G. receives support for
171 research from NICHD (K23HD083465). The remaining authors have no funding to disclose. The
172 content is solely the responsibility of the authors and does not necessarily represent the official
173 views of the NIH.

174 **References**

175 1. Chattopadhyay B. 2002. Newborns and gentamicin—how much and how often? J
176 Antimicrob Chemother 49:13–16.

177 2. Rocha MJ, Almeida a M, Afonso E, Martins V, Santos J, Leitão F, Falcão a C. 2000. The
178 kinetic profile of gentamicin in premature neonates. J Pharm Pharmacol 52:1091–7.

179 3. Glover ML, Shaffer CL, Rubino CM, Cuthrell C, Schoening S, Cole E, Potter D, Ransom
180 JL, Gal P. 2001. A multicenter evaluation of gentamicin therapy in the neonatal intensive
181 care unit. Pharmacotherapy 21:7–10.

182 4. Begg EJ, Barclay ML. 1995. Aminoglycosides--50 years on. Br J Clin Pharmacol 39:597–
183 603.

184 5. Touw DJ, Westerman EM, Sprij AJ. 2009. Therapeutic drug monitoring of
185 aminoglycosides in neonates. Clin Pharmacokinet 48:71-88.

186 6. Van Lent-Evers NAEM, Mathôt RAA, Geus WP, Van Hout BA, Vinks AATMM. 1999.
187 Impact of goal-oriented and model-based clinical pharmacokinetic dosing of
188 aminoglycosides on clinical outcome: A cost-effectiveness analysis. Ther Drug Monit
189 21:63–73.

190 7. Chambers H. 2006. The aminoglycosides, p. 1155–1171. *In* Goodman & Gilman's the
191 Pharmacological Basis of Therapeutics, 11th ed.

192 8. Germovsek E, Kent A, Metsvaht T, Lutsar I, Klein N, Turner MA, Sharland M, Nielsen
193 EI, Heath PT, Standing JF. 2016. Development and evaluation of a gentamicin
194 pharmacokinetic model that facilitates opportunistic gentamicin therapeutic drug
195 monitoring in neonates and infants. Antimicrob Agents Chemother 60:4869–4877.

196 9. Nielsen EI, Sandström M, Honore PH, Ewald U, Friberg LE. 2009. Developmental
197 pharmacokinetics of gentamicin in preterm and term neonates: Population modelling of a
198 prospective study. Clin Pharmacokinet 48:253–263.

199 10. García B, Barcia E, Pérez F, Molina IT. 2006. Population pharmacokinetics of gentamicin
200 in premature newborns. J Antimicrob Chemother 58:372–379.

201 11. Fuchs A, Guidi M, Giannoni E, Werner D, Buclin T, Widmer N, Csajka C. 2014.
202 Population pharmacokinetic study of gentamicin in a large cohort of premature and term
203 neonates. Br J Clin Pharmacol 78:1090–1101.

204 12. Medellín-Garibay SE, Rueda-Naharro A, Peña-Cabia S, Garcí B, Romano-Moreno S,
205 Barcia E. 2015. Population pharmacokinetics of gentamicin and dosing optimization for
206 infants. Antimicrob Agents Chemother 59:482–489.

207 13. The Necessity and Challenges of Clinical Research Involving Children, p. 58–92. *In*
208 Field, MJ, Behrman, RE (eds.), Ethical Conduct of Clinical Research Involving Children.

209 14. Zimmerman KO, Wu H, Greenberg R, Guptill JT, Hill K, Patel UD, Ku L, Gonzalez D,
210 Hornik C, Jiang W, Zheng N, Melloni C, Cohen-Wolkowiez M. 2016. Therapeutic Drug
211 Monitoring, Electronic Health Records, and Pharmacokinetic Modeling to Evaluate

Sirolimus Drug Exposure-Response Relationships in Renal Transplant Patients. Ther Drug Monit 38:600–606.

15. Salerno S, Hornik CP, Cohen-Wolkowiez M, Smith PB, Ku LC, Kelly MS, Clark R, Gonzalez D. 2017. Use of Population Pharmacokinetics and Electronic Health Records to Assess Piperacillin–Tazobactam Safety in Infants. Pediatr Infect Dis J 36:855–859.

16. Sarkar D, Andrews F. 2016. latticeExtra: extra graphical utilities based on lattice.

17. Sarkar D. 2008. Lattice multivariate data visualization with R. Springer, New York.

18. Jonsson EN, Karlsson MO. 1998. Xpose - An S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 58:51–64.

19. Mark LF, Solomon A, Northington FJ, Lee CKK. 2013. Gentamicin pharmacokinetics in neonates undergoing therapeutic hypothermia. Ther Drug Monit 35:217–222.

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)