

# Simulated Comparison of a Bayesian Clinical Decision Support System Versus Standard of Care For Achieving Gentamicin Pharmacokinetic Targets in Neonates

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**Background:** Gentamicin therapy in neonates is optimized through achieving specific peak and trough concentrations. The objective of this study was to compare the ability a Bayesian clinical decision support system (CDSS) with standard of care (SOC) in determining personalized gentamicin therapies for neonates, at regimen initiation and in response to measured drug concentrations.

**Methods:** This retrospective review and simulation compared target attainment among 4 arms: historical dosing according to SOC, via nomogram for initial dosing (SOC-initial) and via clinician judgment in response to measured concentrations (SOC-adjusted), and simulated dosing using the CDSS, incorporating a neonatal pharmacokinetic model for initial dosing (CDSS-initial) and incorporating maximum a posteriori-Bayesian analysis in response to measured concentrations (CDSS-adjusted). “True” patient pharmacokinetic parameters and peak and trough concentration predictions were calculated via the CDSS using the entirety of the patient dosing and concentration history. The primary outcome was pharmacokinetic target attainment of desired gentamicin peak and trough concentrations.

**Results:** The study included 564 gentamicin concentrations among 339 patients. Mean demographics were 35 weeks gestational age (52% premature births) and 2.44kg dosing weight. Mean PK parameters were 0.0533L/h/kg clearance, 0.458L/kg volume of distribution, and 8.66 hours half-life. Peak concentrations in the desired range were achieved in 96% of significantly more often in the CDSS-initial regimens and 94% of CDSS-adjusted regimens versus 86% of SOC-initial regimens and 66% of SOC-adjusted regimens. No difference was found in trough target attainment among study groups.

**Conclusions:** In simulation, a Bayesian CDSS showed superiority to SOC in achieving gentamicin pharmacokinetic exposure targets in neonates. Use of a CDSS may improve the safety and efficacy of gentamicin therapy for neonates.

**Key Words:** neonatal Pharmacokinetics Bayesian analysis, clinical decision support, precision medicine, machine learning  
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Each author of this manuscript has significantly participated to the study.

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Neonatal sepsis is a life-threatening condition that affects 1–6 newborns per 1000 births.<sup>1,2</sup> Gentamicin in conjunction with ampicillin is the first-line therapy against suspected pathogens—primarily Group B *Streptococcus*, *Escherichia coli* and *Listeria monocytogenes*.<sup>3,4</sup> The pharmacodynamic bactericidal properties of gentamicin for neonates are optimized at peak-to-minimum inhibitory concentration (peak:MIC) ratios of 8–10. However, dosing via extended dosing intervals (every 24–48 hours) to achieve absolute peak concentrations of 6–15 mg/L and trough concentrations of <2 mg/L is often used to minimize toxicity and optimize pharmacodynamic and pharmacokinetic effects.<sup>5</sup>

At the University of California at San Francisco Benioff Children’s Hospital (UCSF-BCH), the standard of care (SOC) for gentamicin therapy in neonates consists of an initial regimen guided by an institutional nomogram followed by dose regimen adjustments in response to measured gentamicin concentrations using judgment and external resources as warranted by the clinician, to achieve the target concentrations listed above. Studies on gentamicin dosing via nomogram report up to 93% of peaks and up to 39% of troughs outside of target ranges in the neonatal population.<sup>6,7</sup> Studies on adjustments to regimens in response to measured drug concentrations made purely via clinical judgment report up to 33% of peaks and 15% of troughs outside of target ranges.<sup>7–9</sup> Consequently, a meta-analysis reported gentamicin-induced nephrotoxicity in up to 27% of neonates and ototoxicity in 3% of neonates.<sup>10</sup>

The use of maximum a posteriori (MAP)-Bayesian-based dosing strategies incorporating published population pharmacokinetic (POP-PK) models and patient-specific pharmacokinetic (PS-PK) covariates have shown promise in aminoglycoside therapy, with the potential for improved target attainment and reduced adverse effects.<sup>11,12</sup> The Bayesian forecasting framework uses the parametric MAP estimation method to predict forecasted concentrations and optimal dosing regimens as well as in silico probabilities of achieving target concentrations in individual patients.

The aim of this study was to determine whether use of a clinical decision support system (CDSS) with MAP-Bayesian forecasting for initial dosing and dose-adjustments of gentamicin could improve pharmacokinetic target attainment in neonates when compared with the SOC of initial dosing by nomogram and subsequent adjustment by clinician judgment.

## MATERIALS AND METHODS

A retrospective observational study of gentamicin utilization in neonates at UCSF-BCH combined with in silico simulation of alternative dosing using the CDSS was approved by the UCSF Institutional Review Board (#17-23162) and conducted in accordance with UCSF’s Human Research Protection Program. The study consisted of 2 parts: (1) Initial dosing performed according to the SOC [SOC-initial] was compared with initial dosing using the CDSS determined by a population pharmacokinetic model (CDSS-initial) for achievement of therapeutic gentamicin peaks and troughs; (2) dose adjustments made by clinicians (SOC-adjusted) were compared with dose adjustments made in accordance with patient-specific pharmacokinetics using the CDSS tool (CDSS-adjusted).

Pharmacokinetic target attainment—defined as percent of gentamicin peak levels between 6 and 15 mg/L and percent of trough levels  $<2$  mg/L—was evaluated as the primary outcome.

## Data Collection

Patient demographics and medical conditions as well as treatment and laboratory information were extracted from the Epic electronic health record Clarity database (Epic Systems, Verona, WI). Data from patients' medication orders, auditory screening results using the ALGO brainstem evoked response test (Natus Medical Incorporated, Pleasanton, CA) and diagnosis list were collected to assess order indications, ototoxicity and nephrotoxicity, respectively. Bayesian dosing predictions and regimen simulations were performed on a model-informed precision dosing (MIPD) CDSS web application with quantitative pharmacology and machine learning capabilities (InsightRX, San Francisco, CA).

## Sample Population

The study included neonates hospitalized at UCSF-BCH between 2013 and 2017, who received at least 1 gentamicin intravenous dose and for whom at least 1 gentamicin concentration was obtained. Patients lacking gestational age (GA), weight (Wt), height (Ht) or serum creatinine (SCr) were excluded. Drug concentrations collected during infusion, concentrations drawn from regimens started prior to UCSF admission and patients with dosing intervals  $<24$  hours were also excluded.

## Regimen Selection

The regimen selection and prediction calculation process are detailed below and in Figure 1.

Part (1): Historical SOC-initial dosing regimens were selected by clinicians, primarily using an institutional nomogram based on guidelines set by Hitron et al and intended to achieve gentamicin peaks of 6–15 mg/L and gentamicin troughs  $<2$  mg/L.<sup>13,14</sup> Regimen selection could be at the discretion of the clinicians.

CDSS-initial dosing regimens were selected using a pharmacokinetic model derived by Fuchs et al.<sup>15</sup> Model-derived POP-PK

parameters were used to guide selection of an initial dosing regimen predicted to achieve a target peak concentration of 10 mg/L (selected as an integer midpoint of the 6–15 mg/L range) and a trough concentration of  $<2$  mg/L.

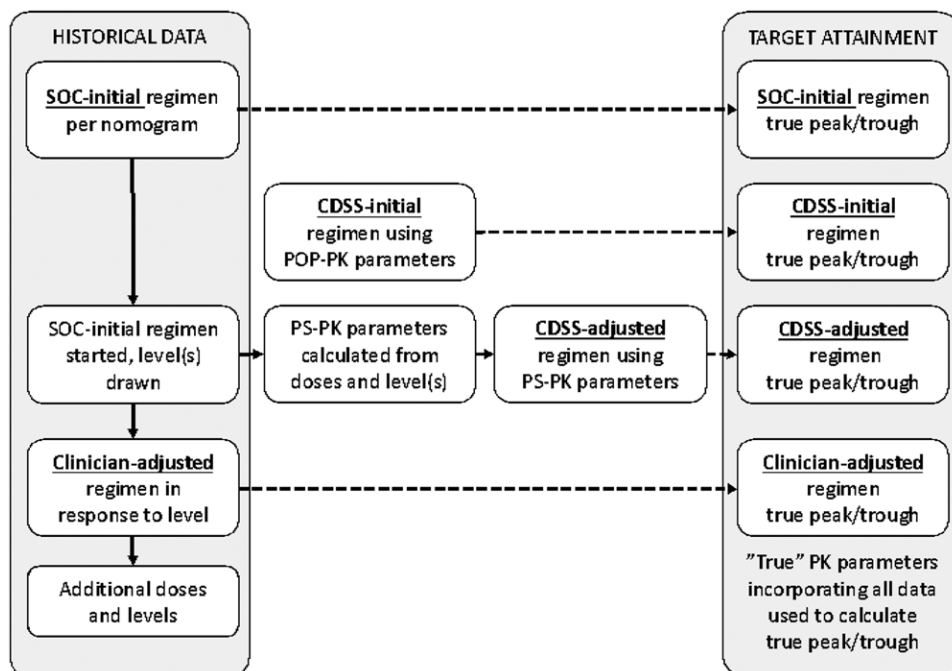
Part (2): In patients for whom multiple sets of concentrations (eg, multiple troughs or peaks over course of therapy) had been obtained, an assessment of CDSS-adjusted versus SOC-adjusted regimens was performed. In the CDSS-adjusted arm, historical drug administrations and a single pair of peak/trough concentrations or unpaired concentration were entered into the CDSS platform and used to calculate patient-specific pharmacokinetic (PS-PK) parameters. A dosing algorithm selected a regimen that would achieve a peak concentration of 10 mg/L (therapeutic peak range: 6–15 mg/L) and trough  $<2$  mg/L according to the PS-PK parameters. In the historical SOC-adjusted arm, regimens were selected by clinicians at their discretion in response to measured concentrations to achieve therapeutic pharmacokinetic targets, with use of external tools (eg, calculators, nomograms).

## Calculation of True Pharmacokinetic Parameters and Comparison of Dosing Regimens

The entirety of the dosing history with associated drug concentrations was entered into the CDSS to establish “true” pharmacokinetic parameters and associated “true” exposure predictions for the aforementioned regimens. “True” peak and trough predictions for these 4 regimens (SOC-initial, CDSS-initial, SOC-adjusted and CDSS-adjusted) were calculated according to the “true” pharmacokinetic parameters and compared for target attainment. For the purposes of this study, a peak was defined as the drug concentration exactly at the completion of infusion at steady-state, while a trough was defined as the drug concentration exactly 1 dosing interval after the initiation of infusion at steady-state.

## Statistical Analysis

The primary outcome was the percent of patients in each regimen group that achieved therapeutic pharmacokinetic targets (peak concentration 6–15 mg/L and trough concentration  $<2$  mg/L).



**FIGURE 1.** Methods. Illustration of the overall methodology for regimen selection and final predictions. SOC-initial and SOC-adjusted regimens were taken from historical records. CDSS-initial regimens were selected using POP-PK parameters as determined by the CDSS tool and the model of Fuchs et al.<sup>15</sup> CDSS-adjusted regimens were selected using PS-PK parameters as determined by the CDSS tool utilizing MAP-Bayesian analysis and the model of Fuchs et al.<sup>15</sup> Calculations of true peaks and troughs for all regimens were determined using the CDSS tool and “true” PK parameters incorporating all patient data.

Statistical significance was determined by the Exact McNemar test performed in the R statistical analysis software (version 3.4.0).

## RESULTS

### Summary of Patient Data

Queries of the electronic health record found 2041 neonates who received gentamicin dose(s). The exclusion criteria removed 1619 patients for no gentamicin concentrations, 24 patients for having concentrations collected after 30 post-natal days, 4 patients for having regimens <24 hours dosing intervals and 55 patients for missing covariates. The study population had a total of 624 drug concentrations. Among the concentration collections that deviated from their scheduled time, 37 troughs and 4 peaks were excluded for being drawn during infusion, and 19 concentrations were drawn from gentamicin regimens that were given prior to UCSF admission. A total of 339 patients receiving 1947 gentamicin doses and with 564 drug concentrations measured (185 peaks, 376 troughs and 3 random concentrations) were included in the final analysis.

Primary outcome analyses were based on proportional statistics and a normal approximation of a binomial distribution for a 1 group sample with dichotomous outcomes. With paired sampling, 95% confidence concentration, 5%  $\alpha$ , 20%  $\beta$ , 50% sample size proportion, and 5% standard deviation change, the 339 patients powered this study to detect an effect size of 0.8%.

### Summary of Pharmacokinetic Parameters

Summarized in Table 1, the study population included neonates who had premature births of <37 gestational weeks (52%) and low weight (<2.5 kg) births (43%). Calculated PK parameters from patient demographics were 0.0533 L/h/kg mean clearance, 0.458 L/kg mean volume of distribution, and 8.66 hours mean half-life. Neonatal sepsis was indicated for gentamicin use in 81% of the subjects. Septicemia was 14% of gentamicin indications. No gentamicin-induced toxicities were diagnosed during hospitalization. Twelve patients did not pass the ALGO test administered prior to discharge and were referred for follow-up audiology examination. In 2 neonates, gentamicin therapy was discontinued due to acute kidney injury or dysfunction.

### Comparison of Dosing Regimens

For gentamicin doses, the CDSS-initial and CDSS-adjusted regimens had an overall wider range of 7.8 mg/kg (2.2–10.0 mg/kg), compared with the narrower range of 4.4 mg/kg (2.5–6.9 mg/kg) in the SOC-initial and SOC-adjusted regimens (Fig. 2). In total, 567 concentrations following the initial regimen and 97 drug concentrations following the adjusted regimen were analyzed.

#### Part 1: SOC-initial Versus CDSS-initial

Predicted peak and trough concentrations are summarized in Figure 3 and Table 2. The mean simulated trough concentrations and percent in therapeutic range were 1.13 mg/L (92% in range) for SOC-initial and 1.0 mg/L (94% in range) for CDSS-initial (not statistically significant). The mean simulated peak concentrations and percent in therapeutic range were 10.28 (87% in range) for SOC-initial and 8.97 (96% in range) for CDSS-initial ( $P < 0.001$ ). The effect of comedications was also investigated. A significant difference in peak concentrations was observed between SOC-initial and CDSS-initial when patients were co-administered with diuretics or on HIE ( $P < 0.001$ ).

#### Part: 2: SOC-adjusted Versus CDSS-adjusted

The mean simulated trough concentrations and percent in therapeutic range were 1.14 mg/L (91%) for SOC-adjusted and

**TABLE 1.** Summary of Demographics

Parameter	$n_p = 339$
Post-natal age at first dose (days, mean)	1.85 (SD $\pm 3.58$ )
Gestational age (weeks, mean)	34.92 (SD $\pm 5.22$ )
Premature births (GA <37 weeks, n)	176 (51.92%)*
Low weight births (Wt <2.5 kg, n)	146 (43.07%)*
Weight around initial dosing (kg, mean)	2.44 (SD $\pm 1.13$ )
Height around initial dosing (cm, mean)	44.87 (SD $\pm 7.60$ )
Serum creatinine around initial dosing (mg/dL, mean)	0.79 (SD $\pm 0.25$ )
Females (n)	151 (44.54%)*
Clearance (L/h/kg, mean)	0.05 (SD $\pm 0.02$ )
Volume of distribution (L/kg, mean)	0.46 (SD $\pm 0.10$ )
Half-life (hours, mean)	8.66 (SD $\pm 2.75$ )
Drug concentrations from initial regimens (n)	467 (82.80%) <sup>†</sup>
Drug concentrations from adjusted regimens (n)	97 (17.20%) <sup>†</sup>

\*percent of study patients.

<sup>†</sup>percent of measured drug concentrations.

1.09 mg/L (97%) for CDSS-adjusted (not statistically significant). The mean simulated peak concentration and percent in therapeutic range were 8.92 (66%) for SOC-adjusted and 9.36 (94%) for CDSS-adjusted ( $P < 0.001$ ).

## DISCUSSION

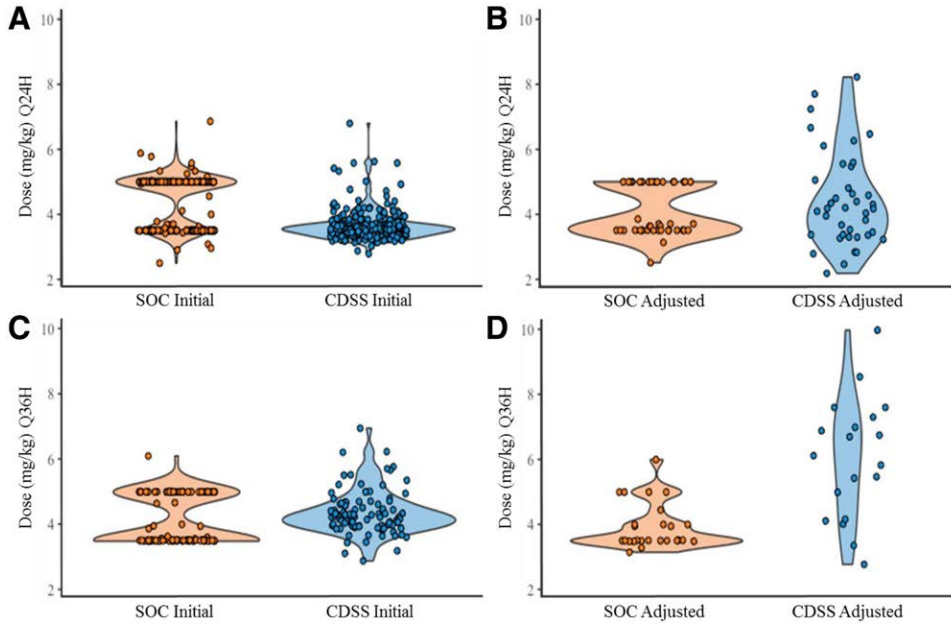
In our analysis, CDSS-guided regimens were significantly more effective in achieving peak targets than SOC, with both CDSS-initial and CDSS-adjusted regimens showing improvement over nomogram-derived SOC-initial dosing or clinician-guided SOC-adjusted regimens.

We propose 2 separate rationales for the differences seen in initial and adjusted dosing. In initial dosing, the lower rate of target peak attainment in the nomogram-derived group may be attributed to an inadequate nomogram. The institutional nomogram used in this study relies mostly on gestational age for dose selection, along with the presence of a few impactful disease states. The inclusion of additional covariates in the underlying pharmacokinetic model, such as post-natal age, weight, and renal function, may provide more granularity to patient pharmacokinetic predictions and thus improve the accuracy of exposure predictions.

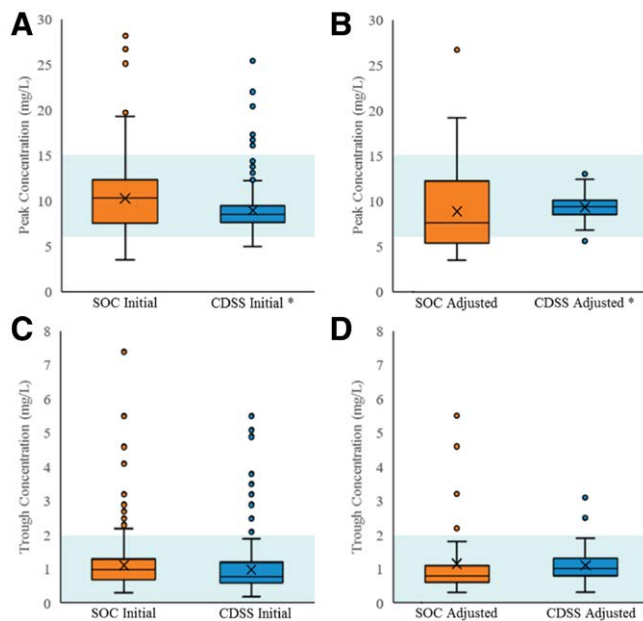
With regard to dosing adjustments in response to concentrations, we ascribe much of the disparity between arms to the markedly low target peak attainment in the SOC group: while peak target attainment in the CDSS group remained >90% in both initial and adjusted dosing, peak target attainment fell from 87% in SOC-initial dosing to 66% in SOC-adjusted dosing. In soliciting feedback from clinicians regarding our findings, we found that while clinicians were routinely willing to decrease the gentamicin dose or dosing frequency to avoid toxicity, few would consider increasing the gentamicin dose or frequency to ensure efficacy. It remains to be seen whether the use of a CDSS tool would impact this perception sufficiently to enact practice change.

Of note, the CDSS utilized a wider range of doses compared with the SOC-initial and SOC-adjusted regimens (Fig. 2). We would infer that the limitations in dose size selection in SOC—whether designated by a nomogram or perceived by cultural practice—may preclude a clinician’s ability to achieve pharmacokinetic targets across the diverse neonatal population.

We acknowledge limitations to the study design. The CDSS tool was used both as a simulated treatment arm, as well as a calculator for “true” pharmacokinetic parameters and predictions. In theory, a tool with high consistency but low accuracy could appear to perform well and create faulty results. Additionally, the predictions from the CDSS-initial arm are dependent upon the population



**FIGURE 2.** Distributions of CDSS and SOC dosing regimens. Illustration to show that predicted doses of the CDSS regimens had a greater overall variation than the observed doses from SOC regimens. In initial regimens that were administered every 24 hours (A), SOC dosing ranged from 2.5 to 6.9 mg/kg and CDSS dosing ranged from 2.8 to 6.8 mg/kg. In adjusted regimens that were administered every 24 hours (B), SOC dosing ranged from 2.5 to 5.0 mg/kg and CDSS dosing ranged from 2.2 to 8.2 mg/kg. In initial regimens that were administered every 36 hours (C), SOC dosing ranged from 3.5 to 6.1 mg/kg and CDSS dosing ranged from 2.9 to 7.0 mg/kg. In adjusted regimens that were administered every 36 hours (D), SOC dosing ranged from 3.1 to 6.0 mg/kg and CDSS-adjusted dosing ranged from 2.8 to 10.0 mg/kg. SOC had no initial or adjusted regimens with Q48H frequency. CDSS had 20 and 8 initial and adjusted regimens with Q48H frequency, respectively. [full color online](#)



**FIGURE 3.** Distributions of peak and trough concentrations for initial and adjusted regimens. Illustration of the primary outcomes of this simulation study. The areas at 6–15 mg/L (A and B) represent the therapeutic range for peak concentrations. The areas at <2 mg/L (C and D) represent the therapeutic range for trough concentrations. For peaks derived from initial regimens (A), 96% of CDSS regimens were within therapeutic concentrations while 86% of SOC regimens were within therapeutic concentrations. For peaks derived from adjusted regimens (B), 94% of CDSS regimens were within therapeutic concentrations while 66% of SOC regimens were within therapeutic concentrations. Troughs from initial (C) and adjusted (D) regimens were not significantly different for the CDSS and SOC dosing strategies. Statistical difference (\*) is  $P$ -value < 0.05 using the McNemar Test. [full color online](#)

**TABLE 2.** Predicted Outcomes From Bayesian Forecasting

Measures (n <sub>tdm</sub> = 564)		Initial regimens		Adjusted regimens	
		SOC (% in range)	CDSS (% in range)	SOC (% in range)	CDSS (% in range)
Concentrations (mg/L, mean) before infusion	Troughs	1.13 (92%)	1.00 (94%)	1.14 (91%)	1.09 (97%)
Concentrations (mg/L, mean) at 0 hour after infusion	Peaks	10.28 (87%)	8.97 (96%)*	8.92 (66%)	9.36 (94%)*
Concentrations (mg/L, mean) without concomitant DDIs (n <sub>0</sub> = 193)	Troughs	1.09 (94%)	0.90 (96%)	1.01 (96%)	1.06 (96%)
	Peaks	10.62 (91%)	8.72 (99%)*	9.21 (71%)	9.37 (93%)*
Concentrations (mg/L, mean) with concomitant dopamine use (n <sub>da</sub> = 122)	Troughs	1.24 (89%)	1.20 (90%)	1.26 (87%)	1.10 (97%)*
	Peaks	9.76 (81%)	9.54 (92%)*	8.74 (60%)	9.24 (95%)*
Concentrations (mg/L, mean) with concomitant diuretic use (n <sub>ts</sub> = 64)	Troughs	1.03 (92%)	0.99 (95%)	1.13 (89%)	1.10 (96%)
	Peaks	9.72 (77%)	8.99 (94%)*	8.67 (46%)	9.60 (96%)*
Concentrations (mg/L, mean) with concomitant NSAID use (n <sub>nsin</sub> = 4)	Troughs	1.03 (100%)	0.75 (100%)	1.30 (100%)	1.00 (100%)
	Peaks	7.43 (75%)	7.43 (75%)	6.80 (100%)	7.90 (100%)
Concentrations (mg/L, mean) while on ECMO (n <sub>ecmo</sub> = 7)	Troughs	1.14 (86%)	0.89 (100%)	0.60 (100%)	0.50 (100%)
	Peaks	12.21 (86%)	9.29 (100%)	9.60 (100%)	6.80 (100%)
Concentrations (mg/L, mean) while in HIE (n <sub>hie</sub> = 34)	Troughs	1.05 (91%)	1.11 (91%)	0.63 (100%)	0.93 (100%)
	Peaks	13.45 (85%)	10.24 (97%)*	13.91 (100%)	8.63 (100%)
Area-under-the-curve (mg/Lh)	AUC <sub>(0-24 hr)</sub>	76.74 (50%)*	67.70 (30%)*	71.33 (30%)*	73.94 (52%)*
Number of every 24 hours interval regimens	n <sub>Q24H</sub>	244	224	41	40
Number of every 36 hours interval regimens	n <sub>Q36H</sub>	95	95	26	19
Number of every 48 hours interval regimens	n <sub>Q48H</sub>	0	20	0	8
Number of trough concentrations ≥2 mg/L	n <sub>troughs</sub>	27	20	6	2
Number of peak concentrations >15 mg/L	n <sub>peaks</sub>	18	8	3	4
Number of peak concentrations <6 mg/L	n <sub>peaks</sub>	27	5	20	0

(% in range): for trough concentration, this is defined by <2 mg/L. For peak concentration, this is defined by concentration falling between 6 and 15 mg/L.  
\*p-value of <0.05.

pharmacokinetic model used. While the Fuchs et al POP-PK model was not validated on our data, it has been validated externally, and the higher target attainment by CDSS regimens supports the model's utility in the sample population.<sup>15</sup> However, caution should be taken in extrapolating our results to other pharmacokinetic models. Finally, the in silico portion of the study was performed under ideal conditions in a single institution; we encourage prospective validation of this study at other institutions to support or refute our findings in a real-world setting.

### CONCLUSIONS

Gentamicin regimens formulated by a CDSS and a validated pharmacokinetic model achieved target concentrations in neonates more often than regimens selected from an institutional nomogram and clinician adjustments in response to concentrations. Prospective studies are needed to further assess the application of the Bayesian CDSS in dosing gentamicin for neonates and to observe its effects on clinical, operational and financial outcomes.

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### REFERENCES

- Gerdes JS. Diagnosis and management of bacterial infections in the neonate. *Pediatr Clin North Am.* 2004;51:939–959, viii.

- Cohen-Wolkowicz M, Moran C, Benjamin DK, et al. Early and late onset sepsis in late preterm infants. *Pediatr Infect Dis J.* 2009;28:1052–1056.
- Fuchs A, Bielicki J, Mathur S, et al. Reviewing the WHO guidelines for antibiotic use for sepsis in neonates and children. *Paediatr Int Child Health.* 2018;38(sup1):S3–S15.
- Polin RA; Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics.* 2012;129:1006–1015.
- Stankowicz MS, Ibrahim J, Brown DL. Once-daily aminoglycoside dosing: an update on current literature. *Am J Health Syst Pharm.* 2015;72:1357–1364.
- Glover ML, Shaffer CL, Rubino CM, et al. A multicenter evaluation of gentamicin therapy in the neonatal intensive care unit. *Pharmacotherapy.* 2001;21:7–10.
- Touw DJ, Westerman EM, Sprij AJ. Therapeutic drug monitoring of aminoglycosides in neonates. *Clin Pharmacokinet.* 2009;48:71–88.
- Hoff DS, Wilcox RA, Tollefson LM, et al. Pharmacokinetic outcomes of a simplified, weight-based, extended-interval gentamicin dosing protocol in critically ill neonates. *Pharmacotherapy.* 2009;29:1297–1305.
- Antolik TL, Cunningham KJ, Alabsi S, et al. Empirical gentamicin dosing based on serum creatinine levels in premature and term neonates. *Am J Health Syst Pharm.* 2017;74:466–472.
- Musiime GM, Seale AC, Moxon SG, et al. Risk of gentamicin toxicity in neonates treated for possible severe bacterial infection in low- and middle-income countries: systematic review. *Trop Med Int Health.* 2015;20:1593–1606.
- Pons G, Tréluyer JM, Dimet J, et al. Potential benefit of bayesian forecasting for therapeutic drug monitoring in neonates. *Ther Drug Monit.* 2002;24:9–14.
- DiCenzo R, Forrest A, Shish JC, et al. A gentamicin pharmacokinetic population model and once-daily dosing algorithm for neonates. *Pharmacotherapy.* 2003;23:585–591.
- MacDougall C. Gentamicin and Tobramycin Dosing in Neonates. Infectious Diseases Management Program at UCSF; 2013. Available at: <https://idmp.ucsf.edu/gentamicin-and-tobramycin-dosing-neonates>. Accessed March 1, 2019.
- Hitron AE, Sun Y, Scarpace SB. Accuracy of empiric gentamicin dosing guidelines in neonates. *J Pediatr Pharmacol Ther.* 2010;15:264–273.
- Fuchs A, Guidi M, Giannoni E, et al. Population pharmacokinetic study of gentamicin in a large cohort of premature and term neonates. *Br J Clin Pharmacol.* 2014;78:1090–1101.