JPPT | Single-Center Retrospective Study

Targeting Lower Serum Trough Concentrations: A New Gentamicin Dosing Strategy for Suspected Neonatal Early-Onset Sepsis

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OBJECTIVE Neonatal gentamicin dosing algorithms are not designed to achieve serum trough concentrations ≤1 mcg/mL. The purpose of our study was to evaluate a new gentamicin algorithm based on serum creatinine (SCr) and gestational age (GA) designed to achieve serum gentamicin trough concentrations ≤1 mcg/mL.

METHODS A retrospective cohort study was conducted in a level IIIB neonatal intensive care unit. The incidence of elevated serum gentamicin troughs for this study was compared with the center's previously published results to evaluate the proposed dosing algorithm. Patients were included if gentamicin was administered within the first 7 days of life and a serum gentamicin trough concentration and a baseline SCr concentration were obtained. Patients were further subdivided into groups based on GA for data analysis: ≤30 weeks (group 1), 30–34 weeks (group 2), and ≥35 weeks (group 3). The SCr was considered mildly elevated (0.81–0.99 mg/dL) or elevated (≥1 mg/dL). The respective outcomes between the post-algorithm and control groups were examined using intention-to-treat analysis and Bayesian modeling to calculate rate differences.

RESULTS Of the 2377 patients evaluated, 366 met the inclusion criteria. Significantly lower percentages of elevated serum gentamicin troughs were noted in groups 2 and 3 subsequent to the implementation of the dosing algorithm with 16% and 15% lower rate differences, respectively. Regardless of GA, there were significantly fewer elevated serum troughs in the post-implementation groups than in the control with mildly elevated and elevated SCr $p < 0.001$.

CONCLUSIONS Using a dosing algorithm based on SCr significantly reduced the number of elevated serum trough rates in neonates with a GA greater than 30 weeks.

ABBREVIATIONS CI, credible interval; GA, gestational age; NICU, neonatal intensive care unit; SCr, serum creatinine

KEYWORDS algorithm; creatinine; early-onset sepsis; gentamicin; gestational age; neonatal; neonate; nomogram

J Pediatr Pharmacol Ther 2023;28(1):71–77

DOI: 10.5863/1551-6776-28.1.71

Introduction

Neonatal sepsis is one of the leading causes of morbidity and mortality among term and preterm neonates. The American Academy of Pediatrics, the Canadian Paediatric Society, Fetus and Newborn Committee, and the National Institute for Health and Care Excellence guidelines recommend initial empiric treatment with a β-lactam and an aminoglycoside, such as gentamicin, for suspected or confirmed early-onset neonatal sepsis.[1–3] The combination of ampicillin and gentamicin target the 2 most common pathogens for early-onset neonatal sepsis, *Streptococcus agalactiae* (group B streptococcus) and *Escherichia coli*, as well as have synergistic activity against group B streptococcus and *Listeria monocytogenes*.[2,3] Many of the clinical signs of sepsis are nonspecific and observed with other noninfectious conditions in the neonate. This makes the diagnosis of neonatal early-onset sepsis difficult, leading to the empiric use of antibiotics until infection can be excluded as a diagnosis.

The pharmacokinetic and pharmacodynamic properties of aminoglycosides favor extended-interval dosing regimens in neonates. Once-daily dosing regimens with gentamicin in neonates have been widely studied and are preferred to multiple-dose-per-day regimens because of their potential for greater efficacy through the achievement of higher peak concentrations, adequate clearance of sepsis, and the ability to achieve serum gentamicin trough concentrations of ≤2 mcg/mL.[2,4–8] Dosing regimens typically include adjustments to the dosing interval accounting for gestational age (GA), with longer

Table 1. Empiric Gentamicin Dosing Interval by Postmenstrual Age

GA of Neonate, wk	Chronologic Age, days	Dosing Interval, hr
<30	0–7	q48
30–34	0–7	q36
≥35	0–7	q24

GA, gestational age

Table 2. Gentamicin Dosing Interval by Gestational Age (GA) and Serum Creatinine (SCr)

GA of Neonate, wk	SCr, mg/dL	Dosing Interval, hr
<30	Any	q48
30–34	<1	q36
	≥1	q48
≥35	<0.81	q24
	≥0.81	q36

intervals for lower GA.[4,5] An elevated serum gentamicin trough concentration raises the concern for potential risk of nephrotoxicity,[9] whereas low peak serum concentrations have been associated with reduced efficacy.[4,5] Previous studies support target serum gentamicin peak concentrations greater than 5 mcg/mL and trough concentrations of less than 1 to 2 mcg/mL for neonates.[5–10] The standard of practice at our institution has been to use once-daily dosing with a target serum gentamicin trough concentration of ≤1 mcg/mL, because of the lack of correlation between lower serum gentamicin troughs and poor outcomes, as well as the potential to decrease nephrotoxicity.[9] However, most published dosing algorithms have used a goal serum trough concentration of ≤2 mcg/mL.[6–8]

In 2017, our institution published an article describing the effect of serum creatinine (SCr) on serum gentamicin concentrations within the first 7 days of life.[11] The study found that mildly elevated (0.81–0.99 mg/dL) and elevated (≥1 mg/dL) SCr concentrations were significantly associated with the presence of an elevated serum gentamicin trough, defined as >1 mcg/mL, in neonates with a GA of ≥30 weeks, $p < 0.001$. The findings indicated that baseline SCr values in the first 24 hours of life may play an important role in identifying neonates at risk for elevated serum gentamicin trough concentrations at ≥30 weeks GA.[11] A dosing algorithm was developed based on GA, the initial SCr value obtained 12 to 24 hours after birth, and gentamicin pharmacokinetics to achieve a higher attainment of serum gentamicin trough concentrations of ≤1 mcg/mL.[11] The purpose of this study was to determine what effect the change in the gentamicin dosing protocol may have had on the rate of elevated serum gentamicin trough concentrations and to provide the data, if positive, to support the dosing algorithm based on GA and SCr values in the neonatal intensive care unit (NICU).

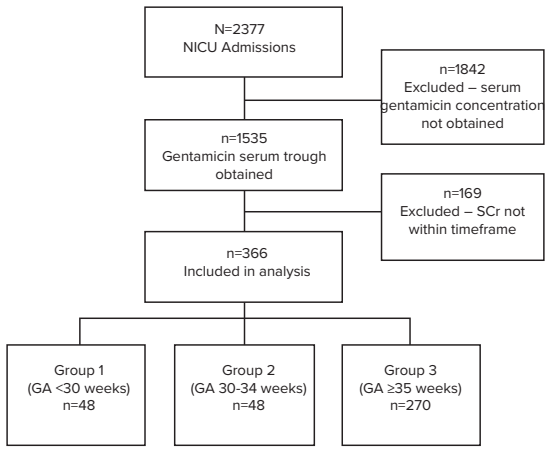
Materials and Methods

A single-center, retrospective cohort study was conducted in a stand-alone, teaching children's hospital. Data were extracted and collected from Epic (Epic Systems Corporation, Verona, WI) medical record for all neonates admitted to the NICU January 1, 2015–December 31, 2017. Patients were included if gentamicin was administered to neonates within the first 7 days of life, and a serum gentamicin trough concentration and a baseline SCr measured within the first 12 to 24 hours of life were obtained. The time frame for obtaining the baseline SCr was based on the original study conducted by Antolik et al.[11] Patients were excluded if they failed to meet the inclusion criteria, received gentamicin for less than 48 hours, or had a serum gentamicin trough concentration obtained more than 60 minutes prior to the next due trough time. Serum gentamicin peak concentrations were not evaluated as part of this study. Additionally, data were collected on demographic characteristics, gentamicin dose and frequency, and dosing algorithm concordance.

The standard gentamicin dose in our NICU is 4 mg/kg, regardless of GA. Empiric dosing frequency is ordered according to the patient's calculated postmenstrual age (Table 1). After the SCr value is obtained at 12 to 24 hours of life, the dosing intervals are adjusted empirically and continued for their 5- to 7-day course in accordance with the proposed dosing strategy (Table 2). Values for SCr were stratified into multiple categories, with a normal value being ≤0.8 mg/dL, mildly elevated at 0.81 to 0.99 mg/dL, and elevated at ≥1 mg/dL. Neonates were further stratified by GA to account for kidney maturation with GA intervals of < 30 weeks (group 1), 30 to 34 weeks (group 2), and ≥35 weeks (group 3). The target serum gentamicin trough concentration was defined as ≤1 mcg/mL and any concentration ≥1.1 mcg/mL was considered to be an elevated serum trough value. The serum trough was drawn within 60 minutes prior to the administration of the third dose, except for patients in group 1 who received a random serum trough value at 48 hours after the first dose because of delayed and unpredictable renal clearance.

The incidence of elevated serum troughs for this study was compared with previously published results from our center for GA and SCr.[11] The results from the Antolik et al[11] publication served as the control group for the our analysis because these study results led to the implementation of the current dosing algorithm. Descriptive statistics were performed by calculating the rate of patients with elevated and target serum gentamicin trough concentrations based on GA and SCr values.

Figure 1. Study enrollment.



GA, gestational age; NICU, neonatal intensive care unit; SCr, serum creatinine.

The respective outcomes between the post-algorithm and control groups were examined using intent-to-treat modeling, which presumed the algorithm was appropriately facilitated for neonates based on GA and SCr values. Study estimates were based on differences in proportions using a Bayesian model with flat beta priors and 100,000 Monte Carlo samples to calculate the rate differences from posterior distributions (the analytic code for this analysis is outlined in the Supplemental Table). The α value was set at 0.05 and estimates are reported with 95% credible intervals (CIs).

Results

All patients admitted to the NICU within the first 7 days of life who received gentamicin beyond 48 hours with a serum gentamicin trough concentration during the study period were evaluated. In total, 2377 patients were evaluated and 2011 were excluded for not meeting the inclusion criteria, resulting in a study sample of 366 patients (Figure 1). This was an intention-to-treat analysis; therefore, patients were included regardless of compliance with the dosing algorithm. The mean ± SD GA was 36 ± 5 weeks with 36% of the population male.

Patient GA, SCr concentration, and elevated serum gentamicin trough concentration rates between the control group and post-dosing algorithm group are presented in Tables 3 and 4, revealing lower percentages of elevated serum troughs in patients subsequent to the implementation of the dosing algorithm. Regardless of GA, there were significantly fewer elevated serum troughs in the post-implementation groups than in the control in neonates with mildly elevated SCr and elevated SCr, $p < 0.001$ (Table 3). Posterior probabilities were examined to evaluate the changes in the rate of supratherapeutic troughs in neonates after implementation of the dosing algorithm to further quantify the difference in elevated serum troughs, stratified by GA and SCr (Figure 2). The average elevated serum trough was 1.4 mcg/mL with a median value of 1.3 mcg/mL, ranging from 1.1 to 4 mcg/mL, with 6 patients recording a serum trough value ≥2 mcg/mL.

Group 1. There was no change in the dosing algorithm for this GA group. The average and median GA was 25 weeks, ranging from 23 to 29 weeks' gestation. Data were collected and analyzed for comparison against the original study. The difference in elevated serum trough incidence between the post-algorithm and control groups was not a statistically significantly difference at −13% (95% CI, −31 to 4).

Group 2. The average and median GA for group 2 was 32 weeks, ranging from 30 to 34 weeks' gestation.

Table 3. Elevated Rates of Serum Gentamicin Concentration by Gestational Age (GA) and Serum Creatinine (SCr) Before and After the Implementation of a Gentamicin Dosing Protocol

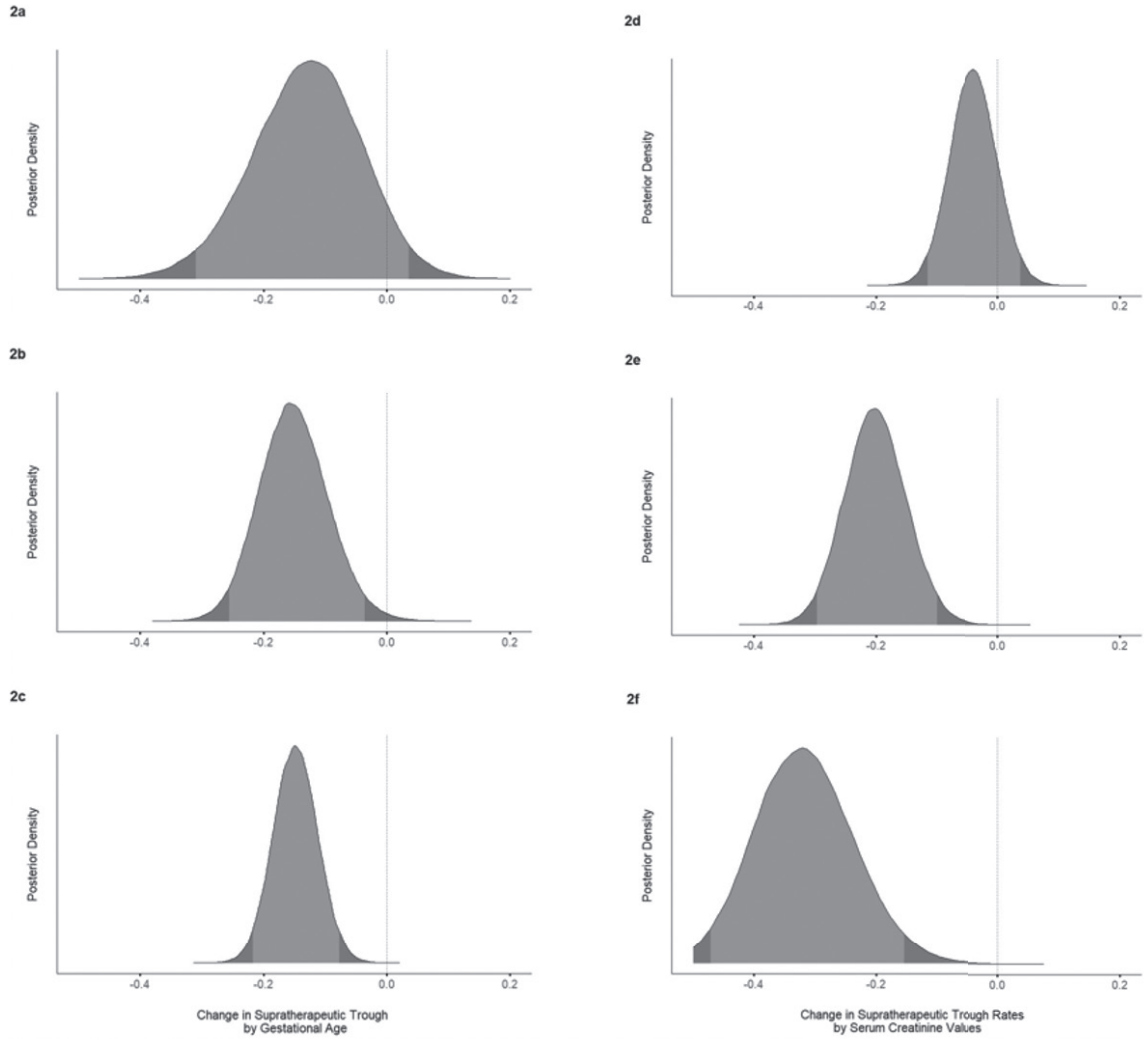
	Elevated Rates of Serum Gentamicin Concentration*		
	Controls,[11] n/group total (%), N = 507	Post-implementation, n/group total (%), N = 366	GA Rate Difference (95% CI)†
GA, wk			
<30	7/30 (23)	5/48 (10)	-13% (-31 to 4%)
30–34	23/102 (23)	3/48 (6)	-16% (-26 to -4%)
≥35	145/375 (39)	64/270 (24)	-15% (-22 to -8%)
SCr, mg/dL			
<0.81	53/236 (23)	36/196 (18)	-4% (-12 to 4%)
0.81–0.99	78/195 (40)	23/118 (20)	-20% (-30 to -10%)
≥1	44/76 (58)	13/52 (25)	-33% (-47 to -16%)

CI, credible interval

* Cells contain counts of patients with an elevated rate of serum gentamicin concentrations, which are further broken down by GA and SCr subgroups, comparing the number of patients in the control group with the post-algorithm implementation group, resulting in a calculated rate difference of elevated serum gentamicin concentrations.

† Based on Bayesian analysis using 100,000 Monte Carlo simulations and non-informative priors.

Figure 2. Posterior probabilities of changes in the rate of supratherapeutic troughs in neonates after implementation of a dosing algorithm. (a) Gestational age (GA) <30 wk. (b) GA 30–34 wk. (c) GA ≥35 wk. (d) Serum creatinine (SCr) value <0.81 mg/dL. (e) SCr 0.81–0.99 mg/dL (f) SCr ≥1.



CI 95%; 100%

For neonates in group 2, the difference in incidence of elevated serum gentamicin trough concentrations between the post-algorithm and control groups was −16% (95% CI, −26 to −4), with 94% having a serum trough gentamicin concentration <1 mcg/mL with the new dosing algorithm, which was a statistically significant improvement from controls, p = 0.02. However, when examining SCr and elevated serum trough rates controlling for GA, a significant difference was not observed for either dosing interval according to the dosing algorithm based on SCr <1 or SCr ≥1 (Table 4). Notably, only 3 patients had an elevated serum trough overall and 14 patients within this group did not follow the dosing algorithm, including all 3 patients with an elevated serum trough.

Group 3. For neonates within group 3, the average GA was 38.5 weeks with a median of 39 weeks, ranging from 35 to 41 weeks' gestation. There was a statistically significant difference of −15% (95% CI, −22 to −8) in the incidence of elevated serum trough values compared with the control with the new dosing algorithm, p < 0.001. Notably, 21 patients in group 3 had an incorrect dosing interval per the protocol and if excluded, the difference in elevated serum troughs would be −21%. Of the 114 patients with an SCr ≥0.81, 60 did not follow the dosing algorithm (Figure 3). Elevated serum troughs were more common in patients not in concordance with the dosing algorithm (63%) compared with those in compliance (12.5%; Figure 3).

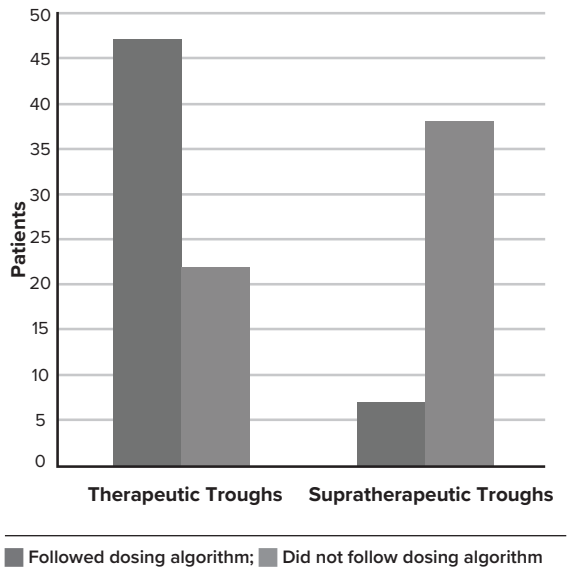
Table 4. Odds of Elevated Serum Gentamicin Trough Concentrations According to Gestational Age (GA) and Serum Creatinine (SCr) After Dosing Algorithm Implementation*

GA, wk	SCr, mg/dL	n	OR	95% CI	p value
<30	Any	48	2.62	0.75–9.18	0.13
30–34	0.81–0.99	20	13.3	0.75–236.45	0.08
	≥1	11	1.56	0.31–7.87	0.59
≥35	<0.81	156	1.14	0.69–1.87	0.62
	≥0.81	114	3.30	1.98–5.50	<0.001

CI, confidence interval

* Odds ratio was calculated based on the number of patients exposed to the dosing algorithm with an elevated serum gentamicin concentration compared with the number of patients with an elevated serum gentamicin concentration prior to the dosing algorithm implementation using a 95% CI.

Figure 3. Concordance in dosing with the dosing algorithm for group 3 and resultant serum gentamicin concentrations.



Discussion

Gentamicin pharmacokinetics have been widely studied in neonates to understand the variability in serum trough concentration and gentamicin clearance. Postnatal age, patent ductus arteriosus, neonatal sepsis, total body cooling, and elevations in baseline SCr have all been implicated as factors that can potentially alter gentamicin disposition in neonates.[12–17] The results of this study have further demonstrated the effect an elevated SCr concentration at birth has on gentamicin clearance in neonates, particularly at ≥35 weeks' gestation, and there may be a need for the development of new dosing algorithms to target a goal serum trough ≤1 mcg/mL.

Glomerular filtration is primarily responsible for aminoglycoside clearance in neonates, which is dependent on both gestational and postnatal age.[18] A neonate's glomerular filtration rate increases rapidly within the first 1 to 2 weeks of life, which makes SCr a difficult measurement to assess a neonate's renal function.[5] Nephrogenesis is complete by 36 weeks' gestation for full-term neonates, but it can continue to develop for more than a month of postnatal life in preterm babies. Neonatal serum creatinine concentrations can be reflective of maternal creatinine concentrations at birth[19]; however, some literature has indicated there may be an SCr concentration that correlates with a higher likelihood of decreased aminoglycoside clearance.[11,20] Additionally, aminoglycoside nephrotoxicity occurs because of the accumulation of gentamicin in the proximal renal tubule, leading to structural damage and nonoliguric renal failure.[5] Thus, it is reasonable to speculate a baseline SCr concentration at birth may predict an elevated serum gentamicin trough concentration. The pharmacokinetics of gentamicin lend it to allow for extension of the dosing interval without affecting efficacy because of concentration dependence and post-antibiotic effect.

Our previous study was a large, retrospective review evaluating gentamicin dosing and the effect of an initial SCr drawn 12 to 24 hours after delivery on elevated serum gentamicin trough concentrations.[11] The results of this study drew similarities with other published studies by Stach et al[20] and DeHoog et al,[19] including correlation of elevated serum gentamicin trough values related to SCr and a low percentage of patients achieving the target serum trough goal based on current dosing algorithms.

The study by Stach et al[20] indicated elevated SCr values in neonates may provide insight into identifying patients at higher risk of developing elevated serum gentamicin trough concentrations. The study found neonates with an SCr greater than 0.8 mg/dL were up to 25.6 times more likely to have an elevated serum gentamicin trough concentration that exceeded 2 mcg/mL. DeHoog et al[19] found current published algorithms were not designed to target the lower serum trough value of ≤1 mcg/mL, but rather to achieve a target serum trough <2 mcg/mL. For sites aiming for lower serum trough goals of ≤1 mcg/mL among neonates, a lower target attainment rate may occur with the use of standard algorithms due to a higher

percentage of serum trough values returning above the target goal of 1 mcg/mL.

Our current study explored the efficacy of the gentamicin algorithm based on SCr that was proposed in our previous study[11] to determine if empirically adjusting the gentamicin dosing interval based on the SCr resulted in a lower incidence of elevated serum troughs. There was a large number of patients that were non-compliant with the dosing algorithm because of the reported difficulty prescribers had making adjustments based on the different SCr values for individual GA groups. Additionally, the use of standard neonatal drug references does not address dosing adjustment according to SCr. Although we were not able to validate the dosing algorithm externally, based on the statistically significant difference in elevated serum trough rates from group 3 with an SCr ≥0.81 and the posterior density curves indicating GA and SCr as associated with a change in the rate of supratherapeutic serum trough concentrations, we believe adjusting the gentamicin dosing interval based on the SCr is an appropriate intervention to decrease gentamicin toxicity to NICU babies in the first 7 days of life.

For patients within group 2 and an SCr ≥1, we found conflicting results compared with the control group. Antolik et al[11] found a significantly higher rate of elevated serum troughs in patients with an SCr ≥1, with an odds ratio of 4.08 (95% CI, 1.01–16.6; p = 0.049) with a nominal sample size of 19 patients, whereas the validation study failed to find a statistically significant difference based on 11 patients when stratified by GA (p = 0.59).[11] Despite the low sample size and poor concordance with the dosing algorithm by providers, the posterior probability shown in Figure 2 indicates there is a strong probability that GA and SCr concentrations do affect the rate of supratherapeutic serum gentamicin troughs and should be further explored. The conflicting results could be attributed to a low number of patients or possibly a type 1 error. Also noteworthy, of the 11 patients within this cohort, only 3 had the correct dosing interval per the algorithm, further nullifying these results if the protocol was efficacious.

Primary strengths of this study included having a relatively large number of patients with a small set of exclusion criteria. However, this study was not without limitations. There was a small number of patients within the individual SCr and GA groupings, which made finding statistical differences challenging. In addition, not all patients were eligible for study inclusion at our institution, making risk for selection bias higher if there was a systematic or differential causes associated with the clinical collection of inclusion criteria variables and the study outcome. The SCr timing of 12 to 24 hours was based on the original study findings by Antolik et al[11]; however, additional study is required to further validate the timing of SCr concentrations and ensure correlation of SCr with gentamicin concentrations. Also, study results were based on an intention-to-treat design making results more representative of protocol effectiveness than efficacy. It was also assumed that there was exchangeability in patients between the control and post-algorithm groups with no historical biases present at the facility during this time period. Lastly, with all single-center retrospective studies, results will need to be replicated at other institutions to demonstrate external validity.

The present study was able to internally validate the current dosing algorithm for neonates with a GA ≥35 weeks and an SCr ≥0.81 mg/dL; it provided additional data to support extending the dosing interval by 12 hours in these patients. The dosing interval adjustment for neonates 30 to 34 weeks of GA and SCr ≥1 was unable to be internally validated because of a low number of patients in this group and a lack of compliance with the suggested dosing algorithm.

Conclusion

These findings support the use of SCr as a laboratory marker that can aid in the adjustment of gentamicin dosing in neonates ≥35 weeks' gestation. This study also provides evidence advocating a need for better dosing algorithms to align with a goal serum trough value of ≤1 mcg/mL per primary references like *Neofax*[21] and the *Lexicomp Pediatric Dosage Handbook*.[22] Additional research is needed in the neonatal population with a higher patient population and inclusion of patients at other institutions to bolster external validity and further demonstrate that neonates with elevated SCr values should have gentamicin dosing intervals extended to decrease the incidence of elevated serum trough values and potentially decrease the risk of nephrotoxicity and ototoxicity.

Article Information

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Disclosures. The authors have nothing to disclose.

Ethical Approval and Informed Consent. The institution's review board approved the study with a waiver of consent.

Acknowledgment. *Drs. Kayser and Cunningham are co-first authors and attest that they contributed equally to the work.

Submitted. November 10, 2020

Accepted. June 9, 2021

Supplemental Material. DOI: 10.5863/1551-6776-28.1.71.S

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