JPPT | Retrospective Cohort Study

Comparison of Amikacin Pharmacokinetics in Neonates With and Without Congenital Heart Disease

Amy L. Nguyen, PharmD; Peter N. Johnson, PharmD; Stephen B. Neely, MPH; Kaitlin M. Hughes, PharmD; Kris C. Sekar, MD; Robert C. Welliver, Sr, MD; and Jamie L. Miller, PharmD

OBJECTIVES The primary objective was to compare the volume of distribution (Vd), clearance (CL), elimination rate (K_e), and half-life (t½) of amikacin in neonates with cyanotic defects, acyanotic defects, and controls, adjusted for gestational and postnatal age. Secondary objectives were to compare the incidence of acute kidney injury (AKI) between controls and the congenital heart disease (CHD) group and to identify potential risk factors.

METHODS This retrospective cohort study included neonates receiving amikacin from January 1, 2013 to August 31, 2016. Patients were excluded if concentrations were not appropriately obtained or if AKI or renal anomalies were identified prior to amikacin initiation. Congenital heart disease was classified as acyanotic or cyanotic. Patients with CHD were matched 1:1 with non-CHD controls according to postmenstrual age. Bivariate analyses were performed using Wilcoxon-Mann-Whitney test, Pearson χ^2 tests, or Fisher exact as appropriate with a p value <0.05. Regression analyses included logistic and analysis of covariance.

RESULTS Fifty-four patients with CHD were matched with 54 controls. Median (IQR) postnatal age (days) at amikacin initiation significantly differed between CHD and controls, 3.0 (1.0–16.0) versus 1.0 (1.0–3.0), p = 0.016. After adjusting for gestational and postnatal age, there was no difference in the mean (95% CI) Vd (L/kg) and CL (L/kg/hr) between CHD and controls, 0.47 (0.44–0.50) versus 0.46 (0.43–0.49), p = 0.548 and 0.05 (0.05–0.05) versus 0.05 (0.05–0.05), p = 0.481, respectively. There was no difference in K_e or t½ between groups. There was no difference in AKI between the CHD and controls, 18.5% versus 9.3%, p = 0.16.

CONCLUSIONS Clinicians should consider using standard amikacin dosing for neonates with CHD and monitor renal function, since they may have greater AKI risk factors.

ABBREVIATIONS AKI, acute kidney injury; ANCOVA, analysis of covariance; CHD, congenital heart disease; CL, clearance; ICD, International Classification of Diseases; K_e, elimination rate; NICU, neonatal intensive care unit; PMA, postmenstrual age; PNA, postnatal age; SCr, serum creatinine; t½, half-life; Vd, volume of distribution

KEYWORDS acute kidney injury; amikacin; congenital heart disease; neonates; pharmacokinetics

J Pediatr Pharmacol Ther 2021;26(4):372–378

DOI: 10.5863/1551-6776-26.4.372

Introduction

Aminoglycosides are commonly used in combination with ampicillin or vancomycin, as empiric antibiotic therapy for early or late-onset neonatal sepsis, respectively.[1] When comparing neonates to children and adults, they have a higher volume of distribution (Vd) and delayed renal elimination of aminoglycosides. In addition, these pharmacokinetic properties can also vary greatly when comparing preterm, late preterm, and term neonates.[2,3] Patients with congenital heart disease (CHD) may have further alteration of Vd secondary to development of edema and delayed renal elimination secondary to impaired cardiac output and decreased renal perfusion.[4]

Although most NICUs are using gentamicin or tobramycin as their aminoglycoside of choice for treatment of early or late-onset sepsis, there has been an change in resistance patterns of *Escherichia coli* to gentamicin and tobramycin.[5-7] Due to the increased resistance rates for this organism, some institutions have opted to change their first-line aminoglycoside to amikacin for empiric treatment of early and late-onset sepsis.[8] There are a limited number of studies that have evaluated dosing and pharmacokinetics of amikacin in the neonatal population and some of these were published between the 1980s and 1990s.[8-18] However, the NICU patient demographics have changed dramatically over the last 30 to 40 years with a lower viable gestational age, improved respiratory support strategies, and development of medical and surgical treatment of neonates with CHD.[19,20] A more recent study compared published dosing recommendations to the institution's modified dosing protocol and noted greater attainment of goal peak concentrations

with the modified dosing.[8] However, previous studies have not specifically evaluated the effect of CHD on amikacin pharmacokinetics and dosing requirements. The purpose of this study was to compare amikacin pharmacokinetics in neonates with and without CHD, with the goal of optimizing initial dose selection of amikacin in neonates with CHD.

Methods

Study Design. This was an institutional review board-approved, retrospective review conducted at an academic medical center with a level IV, 96-bed NICU. Patients receiving amikacin in the NICU from January 1, 2013 through August 31, 2016 were screened using the institution's pharmacy database, Meditech (Medical Information Technology, Inc, Westwood, MA). They were included in the CHD group if they had cyanotic or acyanotic CHD; if surgery was required, patients were only included if their amikacin course occurred in the presurgical period. For each patient with CHD, a control patient was matched 1:1 according to postmenstrual age (PMA) during the same year of admission. Patients were included if they had an amikacin peak and trough concentration drawn appropriately, defined as a peak concentration obtained 30 minutes after completion of the infusion and amikacin trough concentration 30 to 60 minutes before the next scheduled dose. For concentrations not meeting the above criteria, peak and trough concentrations were extrapolated by the appropriate pharmacokinetic equation and were excluded only if the calculated Vd was ± 30% of the expected population Vd estimates 0.4 to 0.6 L/kg.[8] Patients were excluded if they 1) had amikacin serum concentrations obtained prior to the third dose; 2) had acute kidney injury (AKI), defined as a reduction in urine output to < 0.5 mL/kg/hr for more than 8 hours, an absolute increase in serum creatinine (SCr) by 0.3 mg/dL, or an increase in SCr greater than 50% from baseline prior to receiving amikacin therapy;[21] 3) received extracorporeal membrane oxygenation; 4) had congenital renal anomalies (e.g., hydronephrosis, multicystic kidney disease, renal agenesis); or 5) had undetectable serum trough concentrations <0.8 mg/L.

Study Objectives and Data Collection. Demographic data including postnatal age (PNA), PMA, and weight at time of amikacin administration were recorded. For those with CHD, the presence of a cyanotic or acyanotic defect was noted based on *International Classification of Diseases* (ICD)-9[22] or ICD-10[23] codes and/or documentation in the medical record. Concomitant nephrotoxic agents (i.e., acyclovir, amphotericin, contrast, furosemide, ibuprofen, indomethacin, and vancomycin) and inotrope or vasopressor therapy received during amikacin therapy were noted. For those with positive cultures, microbiology results were recorded. Renal function markers, including SCr and urine output, were collected during amikacin therapy. The amikacin regimen, including dose and times of administration were collected. The Supplemental Table includes the dosing protocol used at the study institution.[8] For each patient, pharmacokinetic data were calculated from amikacin concentrations using published pharmacokinetic equations, including elimination rate constant (K_e), half-life (t½), Vd, and clearance (CL).[24]

The primary objective of this study was to compare the Vd, CL, K_e, and t½ of amikacin in neonates with cyanotic defects, acyanotic defects, and controls, adjusted for gestational and PNA. The secondary objective was to compare the incidence of AKI during amikacin treatment up to 24 hours following discontinuation between controls and the CHD group. An additional analysis was to identify potential risk factors associated with the development of AKI.

Statistical Methods. Descriptive statistics were computed for all demographic and clinical variables. Subjects with and without CHD were categorized and comparisons between these groups were of primary interest. Categorical variables, such as AKI and nephrotoxic agents, were compared between groups using asymptotic or exact Pearson χ^2 or Fisher exact tests. Interval and continuous variables such as Vd and CL were assessed for normality using the Shapiro-Wilk test (not reported) and compared between groups using Wilcoxon-Mann-Whitney tests. Logistic regression was used to determine the odds (95% CI) of AKI occurrence, controlling for PNA, use of inotropes/vasopressors, presence and number of nephrotoxins, and CHD status. Analysis of covariance (ANCOVA) was used to determine difference in CHD status least square means on pharmacokinetic variables after adjusting for gestational age and PNA. Subjects with CHD were further categorized as cyanotic or acyanotic, and similar descriptions and comparisons of categorical and continuous variables were made on this smaller subset of study participants. Tests of significance are 2-tailed and a 0.05 significance level was used. SAS STAT software for Windows version 9.4 (SAS Institute Cary, NC) was used for all analyses.

Results

Patient Demographics. Sixty patients with CHD met inclusion and exclusion criteria. The Vd for all of these patients were within ± 30% of the expected population Vd estimates; however, six with acyanotic CHD were excluded because a control patient could not be matched based on PMA during the admission year. Therefore, 54 patients with CHD who were awaiting surgical correction were matched with 54 controls according to PMA. Table 1 contains a comparison of demographics between patients with and without CHD. No significant differences were noted in gestational age and PMA; however, patients in the control group were significantly younger based on median PNA, 1.0 (IQR, 1.0–3.0) versus 3.0 (1.0–16.0) days, p = 0.016. In addition, the

Table 1. CHD Versus Non-CHD Demographics

Variable	CHD (n = 54)	Non-CHD (n = 54)	p value
Age, median (IQR)			
Gestational, wk	36.1 (33.4–39.0)	37.1 (33.2–39.1)	0.37
Postnatal, days	3.0 (1.0–16.0)	1.0 (1.0–3)	0.016
Postmenstrual, wk	37.0 (33.1–39.0)	37.3 (34.0–39.3)	0.72
Weight, median (IQR), kg	3.0 (2.0–3.5)	2.7 (1.8–3.4)	0.54
Length, median (IQR), cm	48.0 (40.0–51.0)	47.5 (42.5–50.5)	0.71
Sex, n (%), male	36 (66.7)	34 (63.0)	0.69
Reason for admission, n (%)			
Prematurity	14 (25.9)	15 (27.8)	<0.001
Respiratory distress	13 (24.1)	17 (31.5)	
Surgical	1 (1.9)	12 (22.2)	
Infectious	0	5 (9.3)	
Cardiac	21 (38.9)	0	
Other	5 (9.3)	5 (9.3)	
Positive culture, n (%)	11 (20.4)	1 (1.9)	0.002
Baseline SCr, median (IQR), mg/dL*	0.46 (0.32–0.7)	0.6 (0.42–0.8)	0.13
Baseline UOP, median (IQR), mL/kg/day†	3.4 (2.8–4.7)	3.0 (2.3–4.2)	0.10

CHD, congenital heart disease; SCr, serum creatinine; UOP, urine output

* Data unavailable for 1 control patient.

† Data unavailable for 1 control patient.

primary reason for NICU admission differed between groups, with cardiac (38.9%), prematurity (25.9%), and respiratory (24.1%) reasons being predominant in the CHD group and respiratory (31.5%), prematurity (27.8%), and surgical (22.2%) in the non-CHD group, $p < 0.001$. A significantly greater number of patients with CHD had positive cultures compared with the non-CHD group, 20.4% versus 1.8% ($p = 0.002$), respectively.

Of those with CHD, 33 (61.1%) had acyanotic CHD and 21 (38.9%) had cyanotic CHD. Table 2 provides an overview of the type of defects, and Table 3 compares demographics between groups. The cyanotic patients with CHD appeared to be older in both median gestational age and PMA compared with acyanotic patients, 38.9 (IQR, 36.1–39.3) weeks versus 34.9 (IQR, 27.0–37.4) weeks, $p < 0.05$ and 39.0 (IQR, 37.1–39.3) weeks versus 35.0 (IQR, 30.0–38.0) weeks, $p < 0.05$, respectively.

Pharmacokinetic Analysis. Table 4 contains a comparison of pharmacokinetic parameters between patients with and without CHD, as well as comparisons

Table 2. Types of Acyanotic and Cyanotic Defects

Variable	Number (%)
Cyanotic defects (n = 21)	
Transposition of the great arteries	4 (19.0)
Tetralogy of Fallot	4 (19.0)
Coarctation of the aorta	3 (14.3)
Single ventricle physiology	3 (14.3)
Total anomalous pulmonary venous return	3 (14.3)
Interrupted aortic arch	2 (9.5)
Atrioventricular canal defect	1 (4.8)
Truncus arteriosus	1 (4.8)
Acyanotic defects (n = 33)	
Ventricular septal defect	10 (30.3)
Ventricular hypertrophy	8 (24.2)
Atrial septal defect	6 (18.2)
Aortic valve dysfunction and pulmonary stenosis	2 (6.1)
Mitral valve regurgitation	2 (6.1)
Ventricular septal/atrial septal defects	2 (6.1)
Bicuspid aortic valve	1 (3.0)
Mesocardia	1 (3.0)
Ebstein anomaly	1 (3.0)

Table 3. Comparison of Acyanotic Versus Cyanotic Congenital Heart Disease Demographics

Variable	Acyanotic (n = 33)	Cyanotic (n = 21)	p value
Sex, n (%), male	23 (69.7)	13 (61.9)	0.55
Age, median (IQR)			
Gestational, wk	34.9 (27.0–37.4)	38.9 (36.1–39.3)	<0.05
Postnatal, days	3.0 (1.0–8.0)	4.0 (1.0–18.0)	0.44
Postmenstrual, wk	35.0 (30.0–38.0)	39.0 (37.1–39.3)	<0.05
Weight, median (IQR), kg	2.7 (1.2–3.3)	3.2 (2.5–3.5)	0.059
Length, median (IQR), cm	46.0 (39.0–50.0)	50.0 (48.0–53.0)	0.033
Positive culture, n (%)	8 (24.2)	3 (14.3)	0.50

between patients with acyanotic, cyanotic, and no CHD. Because there was a significant difference in PNA between groups, an ANCOVA was performed to control for this variable. Using the ANCOVA analyses, there was no difference in pharmacokinetic variables between groups after adjusting for gestational age and PNA.

AKI Occurrences. A total of 10 (18.5%) patients with CHD and five (9.3%) control patients developed AKI; this was not statistically different between groups. Table 5 contains a comparison of AKI occurrences and nephrotoxins between those with and without CHD. There were more patients in the CHD group that received a nephrotoxic medication compared with the non-CHD group, 34 (63.0%) versus 18 (33.3%), respectively, p = 0.0021. In addition, statistical differences were noted in the number of nephrotoxins that were concomitantly administered during use of amikacin (Table 5). A greater number of patients in the CHD group versus non-CHD group received vancomycin (42.6% versus 14.8%, p = 0.001) and furosemide (44.4% versus 9.5%, p < 0.001) concomitantly with amikacin. In addition, more patients in the CHD group received inotropes and/or vasopressors for cardiovascular support, 35.2% versus 14.8%, p = 0.015. In the regression analysis, use of inotropes and/or vasopressors was associated with a 4.5-times greater risk for development of AKI in CHD and non-CHD patients, OR 4.5 (95% CI, 1.43–13.8). Other factors such as PNA, acyanotic CHD, cyanotic CHD, and concomitant nephrotoxins were not associated with development of AKI.

Discussion

This is the first study to evaluate pharmacokinetic parameters and incidence of AKI with amikacin in neonates with and without CHD. Although amikacin is not commonly used first-line in many NICUs, use may increase in the future as a result of changing resistance patterns for gentamicin and tobramycin. Therefore, it is important to evaluate amikacin pharmacokinetic differences in infants with CHD because concerns for altered pharmacokinetic parameters for gentamicin have been noted in this population.[25,26] Overall, we found no statistical difference in amikacin pharmacokinetic parameters between neonates with and without CHD. However, we did find neonates with CHD had a higher rate of AKI than those without CHD, though not statistically significant.

In the 2 previous studies that have evaluated gentamicin dosing in neonates and children with CHD, no comparator group was included.[25,26] Rather, they assessed potential differences in gentamicin pharmacokinetics in 42 patients with CHD, including 14 infants

Table 4. CHD Versus Non-CHD Comparison of Pharmacokinetics

Variables*	CHD (n = 54)	Type of CHD		No Defect (n = 54)	p value†	
		Acyanotic (n = 33)	Cyanotic (n = 21)		CHD vs No Defect	Acyanotic vs Cyanotic vs No Defect
K_e, hr^{-1}	0.11 (0.10–0.11)	0.11 (0.10–0.12)	0.11 (0.10–0.12)	0.11 (0.10–0.11)	0.763	0.730
t½, hr	6.9 (6.4–7.3)	6.8 (6.2–7.4)	7.2 (6.5–7.9)	6.9 (6.4–7.3)	0.783	0.691
Vd, L/kg	0.47 (0.44–0.50)	0.48 (0.44–0.52)	0.46 (0.41–0.51)	0.46 (0.43–0.49)	0.548	0.753
CL, L/hr	0.05 (0.05–0.05)	0.05 (0.05– 0.06)	0.05 (0.04–0.05)	0.05 (0.05–0.05)	0.481	0.360

CHD, congenital heart disease; CL, clearance, K_e, elimination rate; t½, half-life; Vd, volume of distribution

* Mean (95% CI) are least squares means produced from the analysis of covariance model and are adjusted for gestational age and postnatal age.

† Analysis of covariance.

Table 5. CHD Versus Non-CHD Comparison of Concomitant Nephrotoxins and AKI Occurrences

Variable	CHD (n = 54)	Non-CHD (n = 54)	p value
AKI, n (%)	10 (18.5)	5 (9.3)	0.16
Concomitant nephrotoxins, n (%)			
0	20 (37.0)	36 (66.7)	<0.001
1	17 (31.5)	16 (29.6)	
2	15 (27.8)	2 (3.7)	
3	2 (3.7)	0 (0)	
Type of nephrotoxin, n (%)			
Ibuprofen/indomethacin	3 (5.5)	4 (7.4)	1
Acyclovir	2 (3.7)	2 (3.7)	1
Vancomycin	23 (42.6)	8 (14.8)	0.001
Furosemide	24 (44.4)	5 (9.3)	<0.001
Contrast	1 (1.9)	1 (1.9)	1
Vasopressors or Inotropes, n (%)	19 (35.2)	8 (14.8)	0.015

AKI, acute kidney injury; CHD, congenital heart disease

and 4 neonates.[25] They compared their values to previous population estimates and found similar values to patients without CHD. However, due to the small number of infants and neonates, the authors stated that definitive conclusions could not be made, and they were unable to control for other confounding variables. In our study, we attempted to control for confounding variables by including a control group of neonates without CHD that were matched to the patients with CHD by PMA, because this is one of the primary determinants for selection of dose and dosing interval. However, despite attempts to match patients, there were differences noted in PNA. Those in the CHD group were older, and this has implications on other variables that were assessed. For example, the reason that amikacin was initiated, and the antibiotics selected for empiric treatment would be different between groups. Because the median (IQR) age for the non-CHD group was 1 day (1–3), a majority of these were likely initiated on ampicillin and amikacin for rule out early-onset sepsis. Whereas the median (IQR) age for the CHD group was 3 days (1–16), and many of these were likely initiated on vancomycin and amikacin for late-onset sepsis. This is supported by the greater percentage of patients with CHD with culture positive sepsis and a greater number receiving vancomycin versus the non-CHD group. It is also not surprising due to pathophysiology that a greater percentage of the CHD group required use of furosemide and inotropes/vasopressors.

In this study, there were no pharmacokinetic differences noted between those with and without CHD for K_e, t½, Vd, or CL when adjusting for gestational age and PNA. Significant renal maturation occurs in the first week of life and can affect amikacin K_e, t½, and CL; therefore, it was important to control for PNA because there was a statistical difference noted between groups.[27] Also, no pharmacokinetic differences were noted when specifically looking at those patients with acyanotic or cyanotic CHD versus those without CHD. These pharmacokinetic differences were explored because previous studies have noted that children with more hemodynamically significant CHD have a higher Vd due to congestive heart failure and delayed renal CL.[4] The K_e, t½, Vd, and CL noted in this study is similar to previously reported pharmacokinetic parameters for amikacin in neonates.[8,13]

Nearly 20% of patients with CHD in this study developed AKI; however, this was not statistically different when compared with those without CHD. It was also noted that nearly two-thirds of patients with CHD also received another nephrotoxic agent during administration of amikacin, and half of these received more than 1 nephrotoxic agent concomitantly. Most commonly, these nephrotoxic agents were furosemide and vancomycin; this is not surprising given the frequent use of furosemide for diuresis in patients with CHD. Also, as stated previously, the empiric use of vancomycin with an aminoglycoside for late-onset sepsis is common practice. In their evaluation of gentamicin use in patients with CHD, Moffett et al[25] noted that 56% of their patients received at least 1 other nephrotoxic agent, with a majority of these receiving furosemide. However, this study did not include data regarding incidence of AKI in the patients with CHD receiving gentamicin, so it is difficult to compare our findings. A previous study assessing AKI in neonates receiving amikacin found an overall rate of 7.7%, which is similar to our control group. Previous studies have noted that children with CHD have higher rates of AKI versus children without CHD.[28]

There were several limitations to our study. First, due to the retrospective design, we were unable to determine the causality of AKI. Second, in September 2016, there was a change from an off-site laboratory to an on-site facility and a different assay method was used

for the analysis of the amikacin concentrations. With this change in the assay, the lower limit for detectability for the amikacin trough differed from the off-site to the on-site laboratory facilities, 0.8 to 2.5 mg/L, respectfully. With this higher threshold, many CHD and control patients had trough concentrations < 2.5 mg/L, and pharmacokinetic calculations were unable to be performed. Therefore, the decision was made to include only those with samples obtained prior to the laboratory change in September 2016. Although this resulted in a smaller sample size than expected, we believe that if we did not exclude those samples post-laboratory changes, the data would be skewed because those with faster CL would have undetectable trough concentrations < 2.5 mg/L. This is further supported by the fact that using the same dosing strategy as in the present study, Hughes et al[8] found a mean amikacin trough of 2 mg/L. Third, an attempt was made to compare pharmacokinetic parameters between patients with acyanotic and cyanotic CHD because it has been noted that children with more hemodynamically significant CHD may have altered pharmacokinetic parameters that affect dosing.[4] However, subdividing the CHD group resulted in even smaller samples sizes, 33 in the acyanotic and 21 in the cyanotic group. A post hoc power analysis was conducted and determined that we would have needed 330 and 1645 patients in the CHD and non-CHD groups to detect a difference between Vd and CL, respectively. If any differences exist between CHD and non-CHD patients, they may be clinically negligible. Last, we note that the CHD group had a higher number of positive cultures. Unfortunately, we are unable to explain these findings, but we feel that this does not impact our pharmacokinetic and AKI analysis.

At this time, we would recommend using the dosing strategy listed in the Supplemental Table for a majority of patients with CHD. Based on our previous study evaluating this dosing strategy, a mean peak and trough concentration of approximately 28 and 2 mg/L, respectively, would be achieved.[8] The exceptions would be for neonates who have not established adequate urine output (i.e., <1 mL/kg/hr), those neonates undergoing repair with cardiopulmonary bypass, and also those neonates with significant hemodynamic instability requiring a significant number of inotropes or vasopressors. For all of these neonates, clinicians may need to choose an extended dosing interval listed in the Supplemental Table and monitor trough concentrations more vigilantly to adjust the dosing interval if needed and avoid development of AKI.

Conclusions

There was no statistically significant difference in pharmacokinetic parameters and AKI between CHD and non-CHD groups. Although the incidence of AKI was slightly greater in the CHD group, this difference may have been due to the greater use of nephrotoxic agents and vasopressors/inotropes in those with CHD. Clinicians may consider using standard dosing of amikacin for neonates with CHD, with careful monitoring for AKI in those receiving concomitant nephrotoxic agents.

Article Information

Affiliations. Phoenix Children's Hospital, Department of Pharmacy (ALN), Phoenix, AZ; University of Oklahoma College of Pharmacy (PNJ, SBN, JLM), Oklahoma City, OK; Riley Hospital for Children at Indiana University Health (KMH), Indianapolis, IN; University of Oklahoma College of Medicine (KCS, RCW), Oklahoma City, OK.

Correspondence. Jamie L. Miller, PharmD; jamie-miller@ouhsc.edu

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by our institution review board. Given the nature of this study, informed consent, assent, and parental permissions were not required.

Submitted. May 1, 2020

Accepted. June 17, 2020

Supplemental Material. DOI: 10.5863/1551-6776-26.4.372.S

References

1. Puopolo KM, Benitz WE, Zaoutis TE; The American Academy of Pediatrics Committee on Fetus and Newborn and Committee on Infectious Diseases. Management of neonates born at ≥ 35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018;142(6):e20182894. doi: 10.1542/peds.2018-2894
2. Kenyon CF, Knoppert DC, Lee SK, et al. Amikacin pharmacokinetics and suggested dosage modifications for the preterm infant. *Antimicrob Agents Chemother*. 1990;34(2):265–268.
3. Treluyer JM, Merle Y, Tonnelier S, et al. Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. *Antimicrob Agents Chemother*. 2002;46(5):1381–1387.
4. Marlowe KF, Chicella MF, Claridge TE, Pittman SW. An assessment of vancomycin pharmacokinetic variability in pediatric cardiology patients. *J Pediatr Pharmacol Ther*. 2003;8(2):132–137.
5. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group b streptococcal and E. coli disease continues. *Pediatrics*. 2011;127(5):817–826.
6. Friedman S, Shah V, Ohlsson A, Matlow AG. Neonatal Escherichia coli infections: concerns regarding resistance to current therapy. *Acta Paediatr*. 2000;89(6):686–689.

7. Alarcon A, Pena P, Salas S, et al. Neonatal early onset Escherichia coli sepsis: trends in incidence and antimicrobial resistance in the era of intrapartum antimicrobial prophylaxis. *Pediatr Infect Dis J*. 2004;23(4):295–299.
8. Hughes KM, Johnson PN, Anderson MP, et al. Comparison of amikacin pharmacokinetics in neonates following implementation of a new dosage protocol. *J Pediatr Pharmacol Ther*. 2017;22(1):33–40.
9. Guadalupe Vasquez-Mendoza G, Vargas-Origel A, Del Carmen Ramos-Jimenez A, et al. Efficacy and renal toxicity of one daily dose of amikacin versus conventional dosage regime. *Am J Perinatol*. 2007;24(2):141–146.
10. Abdel-Hady E, El Hamamsy M, Hedaya M, Awad H. The efficacy and toxicity of two dosing-regimens of amikacin in neonates with sepsis. *J Clin Pharm Ther*. 2011;36(1):45–52.
11. Langhendries JP, Battisti O, Bertrand JM, et al. Once-a-day administration of amikacin in neonates: assessment of nephrotoxicity and ototoxicity. *Dev Pharmacol Ther*. 1993;20(3–4):220–230.
12. Allegaert K, Scheers I, Cossey V, Anderson BJ. Covariates of amikacin clearance in neonates: the impact of postnatal age on predictability. *Drug Metab Lett*. 2008;2(4):286–289.
13. An SH, Kim JY, Gwak HS. Outcomes of a new dosage regimen of amikacin based on pharmacokinetic parameters of Korean neonates. *Am J Health Syst Pharm*. 2014;71(2):122–127.
14. Padovani EM, Pistolesi C, Fanos V, et al. Pharmacokinetics of amikacin in neonates. *Dev Pharmacol Ther*. 1993;20(3–4):167–173.
15. Sardemann H, Colding H, Hendel J, et al. Kinetics and dose calculations of amikacin in the newborn. *Clin Pharmacol Ther*. 1976;20(1):59–66.
16. Assel BM, Parini R, Rusconi F, Cavanna G. Influence of intrauterine maturation on the pharmacokinetics of amikacin in the neonatal period. *Pediatr Res*. 1982;16(10):810–815.
17. Smits A, De Cock RF, Allergaert K, et al. Prospective evaluation of a model-based regimen for amikacin in preterm and term neonates in clinical practice. *Antimicrob Agents Chemother*. 2015;59(10):6344–6351.
18. Illamola SM, Colom H, van Hasselt JG. Evaluating renal function and age as predictors of amikacin clearance in neonates: model-based analysis and optimal dosing strategies. *Br J Clin Pharmacol*. 2016;82(3):793–805.
19. Lussky RC, Cifunetes RF, Siddappa AM. A history of neonatal medicine—past accomplishments, lessons learned, and future challenges: part II—the 1990s, the New Millennium, future challenges. *J Pediatr Pharmacol Ther*. 2005;19(3):143–158.
20. Tsintoni A, Dimitriou G, Karatza AA. Nutrition of neonates with congenital heart disease: existing evidence, conflicts, and concerns. *J Matern Fetal Neonatal Med*. 2020;33(14):2487–2492.
21. Duzova A, Bakkaloglu A, Kalyoncu M, et al. Etiology and outcome of acute kidney injury in children. *Pediatr Nephrol*. 2010;25(8):1453–1461.
22. World Health Organization. *International Classification of Diseases, Ninth Revision*. 1978. Accessed March 2020. On-line version available at https://apps.who.int/iris/handle/10665/39473.
23. World Health Organization. *International Classification of Diseases, Tenth Revision*. 2010. Accessed March 2020. Available at https://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf
24. UK Healthcare University of Kentucky. Clinical pharmacokinetics service & anticoagulation guidelines pharmacy services. Accessed April 22, 2020. https://ukhealthcare.uky.edu/sites/default/files/clinical-pks-anticoagulation-manual.pdf
25. Moffett BS, Bork SJD, Mott AR. Gentamicin dosing for pediatric patients with congenital heart disease. *Pediatr Cardiol*. 2010;31(6):761–765.
26. Moffett BS, Rossano JW. Use of a 4-mg/kg/24-hour empiric aminoglycoside dosing in preoperative neonates with congenital heart disease. *Ann Pharmacother*. 2012;46(9):1193–1197.
27. Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. *J Pediatr Pharmacol Ther*. 2014;19(4):262–276.
28. Benefield EC, Hagemann TM, Allen HC, et al. Vancomycin dosing and pharmacokinetics in postoperative pediatric cardiothoracic surgery patients. *J Pediatr Pharmacol Ther*. 2016;21(1):66–74.