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Evaluation of Gentamicin Exposure in the Neonatal Intensive Care Unit and Hearing Function at Discharge

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Abstract

Objective—To characterize the association between gentamicin dosing, duration of treatment, and ototoxicity in hospitalized infants.

Study design—This retrospective cohort study conducted at 330 neonatal intensive care units (2002–2014) included inborn infants exposed to gentamicin with available hearing screen results, and excluded infants with incomplete dosing data and major congenital anomalies. Our primary outcome was the final hearing screen result performed during hospitalization: abnormal (failed or referred for further testing in one or both ears) or normal (bilateral passed). The 4 measures of gentamicin exposure were highest daily dose, average daily dose, cumulative dose, and cumulative duration of exposure. We fitted separate multivariable logistic regression models adjusted for demographics, comorbidities, and other clinical events.

Results—A total of 84 808 infants met inclusion/exclusion criteria; median (25th, 75th percentile) gestational age and birth weight were 35 weeks (33, 38) and 2480 g (1890, 3184), respectively. Failed hearing screens occurred in 3238 (3.8%) infants; failed screens were more likely in infants of lower gestational age and birth weight, who had longer hospital lengths of stay, higher rates of morbidities, and were small for gestational age. Median highest daily dose, average daily dose, and cumulative dose were 4.0 mg/kg/day (3.0, 4.0), 3.8 mg/kg/day (3.0, 4.0), and 12.1 mg/kg (9.1, 20.5), respectively. Median cumulative duration of exposure was 3 days (3, 6). In adjusted analysis, gentamicin dose and duration of therapy were not associated with hearing screen failure.

Conclusions—Gentamicin dosing and duration of treatment were not associated with increased odds of failed hearing screen at the time of discharge from initial neonatal intensive care unit stay.

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In infants who spend more than 5 days in the neonatal intensive care unit (NICU), the risk of hearing loss increases 10-fold to 2%–4%.^{1,2} In very low birth weight (VLBW, <1500 g birth weight) infants, the reported incidence of sensorineural hearing loss varies between 0.4% and 5%.^{3–6} The variability likely is due to differences in therapeutic interventions such as mechanical ventilation, oxygen supplementation, ototoxic drugs, patent ductus arteriosus ligation, and medical conditions (respiratory failure, low Apgar scores, acidosis, hypotension, hyponatremia), as well as environmental factors including noise.⁷ Hearing loss in infancy often is irreversible, affecting not only the development of speech and language, but also cognitive, intellectual, cultural, and social child development.⁸

Gentamicin is the most commonly used aminoglycoside, and the second most commonly used drug in hospitalized infants.⁹ Aminoglycoside ototoxicity in older children and adults manifests as irreversible bilateral sensorineural hearing loss beginning at high frequencies (cochleotoxicity).^{10–12} The ototoxicity may be exacerbated when gentamicin is used for prolonged duration,^{13,14} multiple courses,¹⁵ concomitantly with other ototoxic drugs such as diuretics,¹⁶ in a noisy NICU environment,⁷ during hypoxia,¹⁷ or in some individuals with a genetic predisposition for developing hearing loss.¹⁸ Adult, child, and infant data that show an association between gentamicin use and ototoxicity^{16,19–24} come from small observational or retrospective studies, so larger, more robust analyses are needed during the neonatal period. In this study, we investigated the effect of gentamicin dose and duration of therapy on hearing screen results at the time of initial discharge in a large multicenter cohort of hospitalized infants.

Methods

We obtained data from the Pediatrix Medical Group Clinical Data Warehouse that prospectively captures clinical information entered into an electronic health record by clinicians at 330 NICUs in the US.²⁵ This study was approved by the Duke University institutional review board.

We included all inborn infants discharged home between 2002 and 2014, without major congenital anomalies, who had available hearing screen results at the time of discharge and who received gentamicin via intravenous or intramuscular administration route in the first 120 days after birth. We excluded infants with missing hearing screen results, and those with incomplete gentamicin dosing data.

We collected the following infant characteristics: sex, birth weight, daily weight, daily length, gestational age at birth, post-natal age, and postmenstrual age at the time of first gentamicin exposure; concomitant treatment with furosemide, ethacrynic acid, bumetanide, tobramycin, vancomycin, and inotropes (dobutamine, dopamine, epinephrine, norepinephrine, milrinone); presence of a patent ductus arteriosus (PDA), hypoxic ischemic encephalopathy (HIE), intraventricular hemorrhage (IVH) grade 3 or 4, necrotizing enterocolitis (NEC) on or before hearing screen day, or bronchopulmonary dysplasia (BPD) diagnosed at any time during the hospitalization; clinical and laboratory events prior to the hearing screen including any positive blood or cerebrospinal fluid culture; any laboratory

evidence of infection because of cytomegalovirus (CMV), *Toxoplasma gondii*, rubella, and herpes simplex or other viruses; and any total serum bilirubin measurement ≥ 15 mg/dL.

We extracted data on all courses of gentamicin treatment including daily dose (mg/kg/day), cumulative dose (mg/kg), and duration of exposure (days) during the first 120 days of hospitalization. We calculated days of exposure as the total number of calendar days during which an infant was exposed to gentamicin prior to the day of hearing screen.

Definitions

We defined a normal hearing screen as bilateral “pass” result, and abnormal hearing screen if the outcome was either “fail” or “refer” (for retesting/formal testing) in one or both ears. If multiple hearing screens were performed, then the result of the final recorded hearing screen was included in the analysis. We preferentially retained a normal over an abnormal test result if the test outcomes on the same day conflicted (220 infants, 0.3% of our sample). We defined small for gestational age as a birth weight below the tenth percentile for gestational age, based on Olsen growth curves.²⁶ We defined BPD based on gestational age: infants <32 weeks of gestational age were classified as having BPD if they received supplemental oxygen or respiratory support (nasal cannula, continuous positive airway pressure, or mechanical ventilation) after a corrected gestational age of 36^{0/7} weeks; infants ≥ 32 weeks of gestational age at birth were classified as having BPD if they received supplemental oxygen or respiratory support (nasal cannula, continuous positive airway pressure, or mechanical ventilation) continuously from a postnatal age of 28–34 days.²⁷ CMV infection was defined as a diagnosis of, acquired, or congenital CMV infection, or detection of CMV by culture or polymerase chain reaction. We defined other infections as any diagnosis of congenital rubella, toxoplasmosis, syphilis, and congenital or perinatal neonatal herpes. We defined sepsis as a positive blood culture, and meningitis as a positive cerebrospinal fluid culture. We identified exposures to inotrope medications (dobutamine, dopamine, epinephrine, norepinephrine, milrinone) and other ototoxic drugs (furosemide, ethacrynic acid, bumetanide, tobramycin, vancomycin). We examined the incidence of in-hospital outcomes including sepsis and meningitis, IVH grade III or IV, NEC, and PDA.

Statistical Analyses

The unit of observation for this analysis was an infant exposed. We summarized the distribution of continuous variables and categorical variables using medians (25th and 75th percentiles) and counts (%), respectively. We noted any missing values, but excluded them from these calculations. We compared distribution of study variables between infants with and without ototoxicity using Wilcoxon rank-sum, χ^2 , or Fisher exact tests, as appropriate.

To evaluate the association between gentamicin dose (daily and cumulative), duration of therapy, and hearing screen failure, we constructed separate mixed multivariable logistic regression models. The outcome variable for all models was the presence or absence of failed hearing screen (binary variable). We fit 4 models to separately evaluate 4 main predictor variables of interest: (1) highest daily gentamicin dose (mg/kg/day) received during hospitalization; (2) cumulative gentamicin dose (mg/kg) received during hospitalization; (3) average daily dose of gentamicin received during hospitalization (mg/kg/

day); and (4) cumulative duration of gentamicin exposure (calendar days). We report ORs with 95% CIs for the main predictors of interest from each model. In all 4 models, we adjusted for site variation using random effects, and included the following covariates as fixed effects: gestational age group, small for gestational age, male, prenatal steroids, PDA, HIE, IVH, NEC, BPD, positive blood or cerebrospinal fluid cultures, CMV and other infections (toxoplasma gondii, other viruses, rubella, cytomegalovirus, and herpes simplex infections), bilirubin ≥ 15 mg/dL, inotropes, and other ototoxic medications.

Statistical analysis was performed using Stata v 14.2 (Stata Corp, College Station, Texas).

Results

We included 84 808 infants with hearing screen results available and exposed to gentamicin in the analyses (Figure 1); 3238 of 84 808 (3.8%) infants exposed to gentamicin failed their hearing screen. In this cohort, 12 593 of 84 808 (15%) were VLBW infants. The proportion of VLBW infants was higher in the group who failed hearing screens (29%) compared with the group who passed (14%) (Table I).

Comorbidities including BPD and PDA were more common among infants who failed hearing screen than among those who passed (Table II). The incidence of HIE was low in our cohort ($<1\%$). Culture-proven infections (blood or cerebro-spinal fluid), CMV, and other congenital infections (rubella, syphilis, and toxoplasmosis) or congenital/perinatal herpes were more common among infants with failed hearing screens, as were hyperbilirubinemia (total bilirubin or unconjugated plasma bilirubin level >15 mg/dL), use of inotropes, and use of other potentially ototoxic drugs. Of the 84 808 infants exposed to gentamicin, 7125 (8.4%) also received vancomycin at some point during their hospitalization prior to the hearing screen; among these infants, 647 (9.1%) failed their hearing screen.

The median (25th, 75th percentile) highest daily dose, average daily dose, and cumulative dose received during hospitalization were 4.0 mg/kg/day (3.0, 4.0), 3.8 mg/kg/day (3.0, 4.0), and 12.1 mg/kg (9.1, 20.5), respectively. The median (25th, 75th percentile) cumulative duration of exposure was 3 days (3, 6). The median values of the average and cumulative daily dose were statistically different in the failed hearing screen group (3.85 and 12.08 for infants who passed vs 3.79 and 15.26 for infants who failed). The highest daily dose did not differ between groups (3.96 and 3.98, $P = .21$) (Figure 2). The median (25th, 75th percentile) duration of therapy was 4 (3, 7) days for infants who failed and 3 (3, 6) for those who passed ($P < .001$).

On adjusted analysis, there was no association between any of the 4 gentamicin exposure variables evaluated and failed hearing screening tests (Table III). Similar results were obtained when we repeated the regressions in the subgroup of VLBW infants, with the exception of cumulative dose, which was statistically significant, but clinically trivial.

Discussion

The association between gentamicin exposure and hearing deficit in infants remains controversial. Our results indicate that gentamicin administration within the observed doses

and durations of exposure is not associated with hearing screen failure at the time of discharge from initial NICU stay. We did not include in this analysis infants with incomplete gentamicin dosage data.

Most of the infants in our study were born at late preterm or term, and 15% were VLBW. Higher proportions of infants who failed their hearing screen were born <28 weeks (20% in failed vs 7% in passed), which is consistent with previous findings that preterm and low birth weight infants are at higher risk for ototoxicity.^{28,29} Though rates of sensorineural hearing loss in the general population are low (0.2%–0.3%),¹ the hearing screen fail/refer rate in our study falls within the range of reported rates in NICU infants (2%–4%).^{1,6,30}

The current view is that aminoglycoside toxicity is associated with the death of inner ear hair cells 1–2 days after exposure, and spiral ganglion cell loss occurs 3–15 days postexposure.^{31,32} The auditory ganglion is spared; however, the ototoxic effect of gentamicin is not completely understood, and the risk for toxicity may be affected by dose, potentiating medications, genetic susceptibility, and other environmental factors.

In a case-control study of VLBW infants analyzing gentamicin exposure in those who developed sensorineural hearing loss, there was no difference between cases and controls in the proportion of infants exposed to gentamicin, in the duration of gentamicin treatment, in the total cumulative dose, in maximum observed peak and 12-hour gentamicin levels, and in individual estimates of gentamicin PK measures (cumulative area under the concentration-time curve, gentamicin clearance, maximum predicted trough level).³³ In the case-control study, the median duration of gentamicin treatment was 3 days, both in the study group and the control group, which was 1 day less than our population. In a prospective, longitudinal study of 81 infants (term and near-term), the association of aminoglycosides with sensorineural hearing loss was evaluated over 4 years; there was no significant relationship between sensorineural hearing loss and cumulative aminoglycoside dose (>28 mg/kg), average dose per day (>4 mg/kg/day), and duration used (>7 days).² Similarly, a large (n = 2347), single-center, retrospective audit of hearing screening results in infants found no increased risk of ototoxicity with gentamicin treatment, especially compared with high rates of ototoxicity associated with vancomycin.²⁴

Other studies report an association between gentamicin treatment and ototoxicity in infants. In contrast to our findings, a prospective study of 91 infants found an increased risk of referral following distortion product otoacoustic emission screening in infants receiving >4 days of intravenous gentamicin treatment.²² In a pediatric cohort of 79 children receiving daily gentamicin, irreversible ototoxicity (ie, persisting abnormality 3 months after gentamicin exposure) was common with an incidence of 1.88% in the overall cohort and 3.1% in the subgroup of oncology patients.³⁴ The children experiencing toxicity (2 patients with hearing loss) were undergoing treatment for malignancies and had received ototoxic medicines before gentamicin.

Our study had several strengths. We used data from the Pediatrix' BabySteps database, which allowed us to identify a large and representative sample from across the US. The BabySteps database contains information on more than 1 million infants. Our cohort of more

than 84 000 infants exposed to gentamicin who had available hearing screen results is the largest to date. Our study was able to control for site variation, given the use of data from more than 300 NICUs across the country with diverse infant management practices. We were able to consider several comorbidities and concomitant medications, providing a more accurate picture of risk factors for failing a hearing screen. Finally, we were able to include information on specific dosing measures, such as course duration and maximum daily dose, as well as timing of clinical and laboratory events of interest, which other retrospective analyses have not.

Our study had a number of limitations, most of which relate to the retrospective observational design. Only one-half of the infants in this database had hearing screen data available and none had postdischarge follow-up data. Given our definition of an abnormal (failed or referred) hearing screen, we can only draw conclusions about the effects of gentamicin on in-hospital failed hearing screen. We cannot exclude a risk for long-term sensorineural hearing loss. With differences in hearing impairment between pre- and full-term infants being negligible by the time individuals reach 14 years of age,⁵ it would be ideal to investigate whether hearing screen failure in gentamicin-treated infants can persist long term, independent of infants' gestational age status. Our study did not differentiate between different forms of hearing screen (otoacoustic emission vs auditory brainstem response) with different sensitivity and accuracy levels, the methodology used to perform the test, or the training of the person performing the hearing test. Gentamicin levels (peak or trough) were not available for all the infants included in our study, and were not included in the analysis. We could not exclude the possibility of un-measured confounding variables (eg, noise level or genetic predisposition). Gentamicin administration was recorded at a daily level, and timestamps of when a dose is administered were not available.

Further research regarding gentamicin use and ototoxicity in infants is needed. Even though we found no association between dose measures and hearing screen failure, studies suggest that long course or high-dose gentamicin may be responsible for increased ototoxicity.^{22,33} A significant limitation of our study was the absence of follow-up data; though studies suggest that early screening is a good predictor of long-term hearing outcomes,²⁸ future studies of similar size with long-term follow-up information on former NICU patients will allow for more conclusive results regarding the association between gentamicin and sensorineural hearing loss. In addition, few studies in the current literature have characterized neonatal risk of vestibulotoxicity, a well-documented side effect of gentamicin in adults³⁵ that is difficult to evaluate in infants. Future studies with more follow-up data on former NICU patients may be able to answer this question.

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Glossary

BPD	Bronchopulmonary dysplasia
CMV	Cytomegalovirus
HIE	Hypoxic ischemic encephalopathy
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
VLBW	Very low birth weight

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Figure 1.

Patient flow diagram. This figure displays the final study population, from the initial cohort through exclusions.

Figure 2.

Median (25th, 75th percentiles) of gentamicin exposure variables, by hearing test result. The horizontal line in the middle of each box indicates the median, while the top and bottom borders of the box mark IQR (ie, 25th-75th percentile). The ends of the whiskers mark 1.5 times the IQR. The outside values were excluded from this graph. The gentamicin exposure variables: *Avg*, average daily dose (mg/kg/day); *Max*, highest daily dose (max mg/kg/day); *Total*, cumulative dose (mg/kg).

Table I.

Cohort characteristics by hearing screen test results

Cohort characteristics	Passed n = 81 570 (%)	Failed n = 3238 (%)	P value
Gestational age (wk)			<.001
<25	1251 (2)	224 (7)	
26–28	4275 (5)	433 (13)	
29–32	13 161 (16)	500 (15)	
33–36	30 074 (37)	890 (27)	
37	32 809 (40)	1191 (37)	
Birth weight (g)			<.001
<1000	3837 (5)	524 (16)	
1000–1499	7825 (10)	407 (13)	
1500–2499	28 180 (35)	904 (28)	
2500–3499	29 862 (37)	1037 (32)	
3500	11 866 (15)	366 (11)	
Male	46 474 (57)	1910(59)	.023
Small for gestational age	7139 (9)	422 (13)	<.001
Antenatal corticosteroids	24 974 (31)	1181 (36)	<.001
Hospital length of stay (d) median (25th, 75th percentiles)	11 (7, 24)	16(8, 53)	<.001

Table II.

Summary of comorbidities and clinical results by hearing screen test results

	Passed n = 81 570 (%)	Failed n = 3238 (%)	P value
BPD *	2830 (4)	404 (13)	<.001
NEC	892 (1)	61 (2)	<.001
HIE	189 (<1)	36 (1)	<.001
Grade III or IVIVH	672 (1)	86 (3)	<.001
PDA	8021 (10)	613(19)	<.001
Positive CSF culture	134 (<1)	11 (<1)	.018
Positive blood culture	3421 (4)	321 (10)	<.001
CMV	240 (<1)	49 (2)	<.001
Other TORCH	198 (<1)	37 (1)	<.001
Bilirubin >15 mg/dL	4318(5)	209 (6)	.004
Inotropes †	3594 (4)	385 (12)	<.001
Other ototoxic drugs ‡	11 227 (14)	931 (29)	<.001

CSF, cerebrospinal fluid; TORCH, toxoplasma gondii, other viruses, rubella, CMV, and herpes simplex.

* Diagnosed during the hospital stay.

† Dobutamine, dopamine, epinephrine, norepinephrine, milrinone.

‡ Tobramycin, vancomycin, furosemide, bumetanide.

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Table III.

aOR with 95% CI for abnormal hearing screen result

Gentamicin exposure variables	All infants exposed to gentamicin		VLBW infants	
	OR (CI)	P value	OR (CI)	P value
Average daily dose (mg/kg/d)	1.01 (0.98, 1.05)	.46	1.02 (0.97, 1.07)	.54
Cumulative dose (mg/kg)	1.00 (1.00, 1.00)	.07	1.00 (1.00, 1.01)	.03
Highest daily dose (mg/kg/d)	1.02 (0.99, 1.05)	.20	1.03 (0.99, 1.07)	.13
Duration of exposure (d)	1.01 (1.00, 1.02)	.10	1.01 (0.99, 1.02)	.26

All ratios adjusted for site variation using random effects, and included the following covariates as fixed effects: gestational age group, small for gestational age, male, prenatal steroids, PDA, HIE, IVH, NEC, BPD, positive blood or CSF cultures, CMV and other TORCH infections, bilirubin > 15 mg/dL, inotropes (dobutamine, dopamine, epinephrine, norepinephrine, milrinone) and other ototoxic medications (furosemide, ethacrynic acid, bumetanide, tobramycin, vancomycin).