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Effect of Sepsis and Systemic Inflammatory Response Syndrome on Neonatal Hearing Screening Outcomes following Gentamicin Exposure

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Abstract

Rationale—Hearing loss in neonatal intensive care unit (NICU) graduates range from 2–15% compared to 0.3% in full-term births, and the etiology of this discrepancy remains unknown. The majority of NICU admissions receive potentially ototoxic aminoglycoside therapy, such as gentamicin, for presumed sepsis. Endotoxemia and inflammation are associated with increased cochlear uptake of aminoglycosides and potentiated ototoxicity in mice. We tested the hypothesis that sepsis or systemic inflammatory response syndrome (SIRS) and intravenous gentamicin exposure increases the risk of hearing loss in NICU admissions.

Methods—The Institutional Review Board at Oregon Health & Science University (OHSU) approved this study design. Two hundred and eight infants met initial criteria, and written, informed consent were obtained from parents or guardians of 103 subjects ultimately enrolled in this study. Prospective data from 91 of the enrolled subjects at OHSU Doernbecher Children's Hospital Neonatal Care Center were processed. Distortion product otoacoustic emissions (DPOAEs; *f*2 frequency range: 2,063 to 10,031 Hz) were obtained prior to discharge to assess auditory performance. To pass the DPOAE screen, normal responses in >6 of 10 frequencies in both ears were required; otherwise the subject was considered a "referral" for a diagnostic hearing

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evaluation after discharge. Cumulative dosing data and diagnosis of neonatal sepsis or SIRS were obtained from OHSU's electronic health record system, and the data processed to obtain risk ratios.

Results—Using these DPOAE screening criteria, 36 (39.5%) subjects would be referred. Seventy-four (81%) subjects had intravenous gentamicin exposure. Twenty (22%) had ≥4 days of gentamicin, and 71 (78%) had <4 days. The risk ratio (RR) of referral with ≥4 days of gentamicin was 1.92 (p=0.01). Eighteen subjects had sepsis or met neonatal SIRS criteria, 9 of whom had ≥5 days of gentamicin and a DPOAE referral risk ratio of 2.12 (p=0.02) compared to all other subjects. Combining subjects with either vancomycin or furosemide overlap with gentamicin treatment yielded an almost significant risk ratio (RR = 1.77, p=0.05) compared to the rest of the cohort.

Conclusions—We report an increased risk of referral with DPOAE screening for those receiving ≥4 days of intravenous gentamicin administration that may contribute to the greater prevalence of hearing loss in NICU graduates. We propose an expanded prospective study to gather a larger cohort of subjects, identifying those with sepsis or neonatal SIRS, to increase the statistical power of this study design. Subsequent studies also need to obtain follow-up diagnostic audiological data to verify whether the outcomes of DPOAE screening, in addition to the standard AABR screen, is a reliable predictor of permanent hearing loss following gentamicin exposure in the NICU.

Keywords

sepsis; SIRS; gentamicin; aminoglycosides; ototoxicity; DPOAE; pediatrics

1.1 Introduction

Hearing loss in patients discharged from neonatal intensive care units (NICUs) range between 2–15% of admissions, compared to a 0.2–0.3% rate of congenital hearing loss in full-term births [1]. Risk factors for hearing loss in the NICU include illnesses or conditions requiring more than 48 hours of NICU admission, genetic predisposition, family history of childhood sensorineural hearing loss, hyperbilirubinemia exceeding 30mg/dl (requiring exchange transfusion), persistent pulmonary hypertension requiring mechanical ventilation, meningitis, seizures, in-utero infections (cytomegalovirus, herpes simplex, toxoplasmosis, rubella, syphilis) and TSH abnormalities, among others [2–4]. Bacteremia (sepsis), prolonged duration of therapy, and other drug administration factors have also been proposed as risk factors for ototoxicity in adult populations [3, 5]. Exposure to intravenous aminoglycoside antibiotics like gentamicin in the NICU may contribute up to 25% of this unexplained rate of hearing loss [5]. Experimental models of systemic inflammation show increased cochlear uptake of gentamicin into the cochlea and exacerbation of ototoxicity [6, 7]. This ototoxic synergy between gentamicin exposure and systemic inflammation may also contribute to the higher rates of hearing loss observed in NICU subjects.

This investigation is part of a larger study to measure noise exposure levels in the NICU and to determine the relationship between noise exposure, intravenous gentamicin exposure, and hearing screening outcomes [8]. Here, we describe a sub-analysis performed to identify the

inflammation status of enrolled NICU subjects in relation to their prospectively-acquired DPOAE outcomes, and total days of gentamicin exposure. A retrospective chart review was conducted to identify the number of NICU graduates diagnosed with sepsis or systemic inflammatory response syndrome (SIRS) who also received intravenous gentamicin treatments [9, 10].

Objective screening methods used to identify subjects with increased risk for hearing loss included a distortion product otoacoustic emissions (DPOAE) test in addition to the standard automated auditory brainstem response (AABR) hearing screen shortly before discharge. The AABR is currently the primary screening tool for infants in the NICU, whereas healthy infants are screened either with AABR or with DPOAEs [11]. The AABR reflects neural activity from the infant's auditory pathway has adequate neural integrity from the inner ear (cochlea) to upper brainstem (medial geniculate body) in response to transient sounds or clicks [4, 12, 13], and can detect infants at risk for auditory neuropathy spectrum disorder (ANSD). ANSD is characterized by normal outer hair cell function and abnormal, absent, or non-synchronous auditory nerve function [11]. Computerized AABR testing reduces human error, and manpower costs, in hearing screening [4]. Infants who 'refer' on this test are often re-screened before a diagnostic hearing evaluation is recommended.

DPOAEs, on the other hand, are frequency-specific byproducts of normal cochlear function when stimulated with two simultaneous tones close in frequency and level. DPOAEs are measured using an ear-level microphone and provide information about cochlear outer hair cell function, which is the primary site of cochlear damage for initial noise-induced hearing loss and aminoglycoside-induced ototoxicity in adult populations [9, 14]. DPOAE responses are influenced by hearing loss at the eliciting stimulus frequencies, ($f1$ and $f2$, where $f1<f2$), emission frequency ($2f1$-$f2$) and higher frequencies coded by more basal cochlear regions [15]. This makes DPOAE responses a valuable screening tool for detecting the onset of ototoxicity that first appears at higher frequency (basal) cochlear locations. The current study used clinical DPOAE tests in addition to the standard AABR to screen for potential hearing loss in a cohort of NICU subjects, most of whom were dosed with intravenous gentamicin at least once during admission.

2.1 Materials and Methods

Enrollment and Inclusion Criteria

The Institutional Review Board at Oregon Health & Science University (OHSU) approved this study design (eIRB protocol #8434). The admission notes of 252 premature (gestational age <37 weeks) infants to the NICU between August 2012 and October 2013 were screened. Two hundred and eight infants met initial criteria, and written, informed consent were obtained from parents or guardians of 103 subjects ultimately enrolled in this study. Forty-four patients were excluded prior to enrollment. Exclusion criteria included diagnosis of congenital hearing loss, or other known causes of hearing loss, including infections such as herpes simplex, rubella, syphilis, cytomegalovirus, or meningitis. Patients with known craniofacial or otologic abnormalities such as midfacial hypoplasia, microtia or aural atresia, were also excluded. For this study, prospective DPOAE and gentamicin dosing data were successfully collected on 93 infants. Two subjects were excluded due to preexisting

conditions associated with hearing loss (one with intraventricular hemorrhage, and another with congenital hydrocephalus), leaving a total subject cohort of 91.

Subject demographics and characteristics are shown in Table 1. Intravenous gentamicin medication exposure was obtained from OHSUs electronic health record system (EPIC). To identify subjects with sepsis or meeting criteria for neonatal SIRS (i.e., signs of systemic inflammation), Table 2, a chart review of subject vital signs, blood culture results and progress notes was performed in EPIC. Only subjects that met sepsis or SIRS criteria on the same day as receiving a dose of gentamicin were included in the inflammation group. Since gentamicin also binds to albumin and other serum proteins (17–27% protein-bound), and elevated serum calcium levels can weaken this association increasing free gentamicin levels, standard laboratory measures (including white blood cell count, albumin levels and calcium levels) for each subject were also obtained and examined [16].

Audiologic Outcome Measurements

Ninety-one NICU subjects who met the inclusion criteria were tested with DPOAE equipment at discharge between August 2012 and October 2013. DPOAE testing was performed with the Bio-logic Scout Sport (Natus Medical Incorporated, Mundelein, IL), with decibel levels of 65dB/55dB, and an $f2/f1$ ratio of 1.22. Ten $f2$ frequencies were used per ear: 2063, 2531, 2953, 3563, 4172, 4969, 5953, 7031, 8391, and 10,031 Hz. A normal DPOAE value was defined as a distortion product (DP) >0 with a difference between DP and noise floor (NF) >6. Reduced and absent OAEs for any given frequency were defined as “abnormal.” A reduced value was defined as a DP <0 with a DP-NF >6. An absent value was defined as a DP-NF <6. To pass the DPOAE screen, normal responses in more than 6 out of 10 frequencies in both ears were required; otherwise the subject was considered a “referral” for potential hearing loss evaluation after discharge.

Subjects admitted to the NICU were also screened with AABR tests prior to discharge from the hospital by OHSU Audiology staff using already-established institutional hearing screening protocols. The Natus ALGO 5 AABR hearing screener was used to complete a physiologic screen of the auditory pathway. Screening involved placing 3 sensors (forehead, nape of neck, and shoulder) and a set of earphones over the ears. Soft click stimuli (35 dB nHL) were presented through the earphones at a rate of 37 clicks/second. During the test, sound traveled through the outer ear and middle ear and into the cochlea, where it was converted into an electrical signal that travels along the auditory nerve and generates identifiable brainwaves that were processed and analyzed by the ALGO screener. Each ear was analyzed separately. A statistical detection algorithm was used to determine if brainwave responses matched normative data. Subjects were categorized as a ‘pass’ if responses were within the normative data, otherwise they were categorized as a ‘refer’. The subjects screened with AABR were of at least 34 weeks corrected gestational age, and close to discharge from the hospital. If a subject did not pass the initial screening, a second screening was completed at a later time and prior to discharge. If a subject received a second ‘refer’, the subject was referred for diagnostic audiologic testing. Diagnostic audiologic evaluations post-discharge from the NICU were assessed by chart review in EPIC. Statistical

analysis was performed using Stata version 13.1, using the “cs” command for cohort risk-ratio calculations.

3.1 Results

Thirty-six (39.5%) of the 91 subjects in this cohort would have been referred for follow-up diagnostic audiology testing based on our DPOAE screening criteria, including 23 (25%) with combined low frequency (2063 Hz – 3563 Hz) and high frequency (4172 Hz to 10031 Hz) referrals. Thirteen (14%) subjects would be referred only on the high frequency range and not the low frequency range. This is compared with 6 subjects (6.32%) that were referred based on standard clinical AABR screening criteria. Five of these 6 (83%) referred both on AABR and on DPOAE screening, while one referred on AABR, but passed the DPOAE screen. Therefore, the DPOAE screen identified an additional 7 subjects with potential high frequency hearing loss, frequently associated with initial onset of ototoxicity, that were not identified with the standard AABR screen [17, 18]. Among the 91 subjects, 74 (81%) had intravenous gentamicin exposure at least once during their NICU admission. Twenty (22%) had ≥4 days of gentamicin, and 71 (78%) had <4 days, including 17 (18.7%) with zero gentamicin dosing. The risk ratio (RR) of a DPOAE referral with ≥4 days of gentamicin, regardless of inflammation status, was 1.92 (p=0.01, 95% CI: 1.22, 3.03).

Eighteen (20%) out of 91 subjects showed clinical evidence of systemic inflammation (7 with sepsis; 11 with neonatal SIRS). Nine of these 18 received ≥5 days of gentamicin, with a DPOAE referral risk ratio of 2.12 compared to all subjects receiving <5 days of gentamicin (p=0.02, 95% CI: 1.35, 3.34). The risk ratio of a DPOAE referral in sepsis/SIRS subjects at the lower threshold of ≥4 days of gentamicin (11/18) compared to the rest of the subject cohort trended towards statistical significance (RR = 1.70, p=0.09, 95% CI: 1.00, 2.88). Twenty (22%) subjects had gentamicin treatment overlapping with other known synergistic ototoxic agents – vancomycin or furosemide – the risk ratio, when comparing this group to the rest of the cohort, also trended towards significance (RR = 1.77, p=0.050, 95% CI: 1.08, 2.88; Table 3).

At 18 months after discharge of the last enrolled subject, less than one-third of subjects had retrievable follow-up diagnostic audiometric data available for review. This insufficient follow-up data could not be used to draw any analytical conclusions on the relationship between gentamicin exposure and subsequent performance on DPOAE testing by providing corroborative diagnostic audiometric analysis.

Blood panel measures including white blood cell count, albumin levels and calcium levels were reviewed to categorize states of inflammation as well as characterize the pharmacokinetics of gentamicin dosing. The average white blood cell count per day per patient was a largely incomplete data set, and did not yield usable data for analysis. The average albumin value on the days subjects with sepsis/SIRS received gentamicin was 2.17, whereas the remaining subjects had an average of 2.43. The average calcium for subjects with sepsis/SIRS on days gentamicin was administered was 8.91, whereas the other 73 subjects had an average of 8.11. However, there was no significant relationship between these lab values, gentamicin exposure and referral on DPOAE or AABR screening.

4.1 Discussion

Previous studies have reported that ototoxicity from aminoglycoside antibiotics ranges between 2% to 25%, and that the rate of hearing loss in the NICU setting ranges between 2–15%, compared to 0.3% in full-term births [1, 5]. A substantial part of this differential prevalence of hearing loss between NICU graduates and full-term births may be associated with intravenous gentamicin administration due to clinical observation of sepsis and/or SIRS, as well as potential ototoxic synergy of aminoglycoside treatment with concomitant vancomycin, and/or loop diuretics [7, 19–23]. Some of the risk for this increased prevalence of hearing loss may also be due to systemic inflammation secondary to bacterial infection (sepsis, necrotizing enterocolitis, gastroschisis, among other etiologies), and subsequent lysis of bacteria, over and above the ototoxic properties of aminoglycoside antibiotics.

Lipopolysaccharide (LPS), an endotoxin in the outer membrane of gram-negative bacteria, is released into the serum following bacterial cell lysis, leading to a robust immune response, activation of macrophages and subsequent release of pro-inflammatory cytokines [6, 7]. Prior studies have shown that LPS potentiates the ototoxicity of aminoglycosides and loop diuretics, leading to extensive high frequency hearing loss [7, 22]. Markers of inflammation and LPS increase cochlear uptake of aminoglycosides, particularly into the highly-vascularized stria vascularis, potentially due to dysregulation of the integrity of the blood-labyrinth barrier [7, 24, 25]. Increased aminoglycoside trafficking across the stria vascularis will lead to greater clearance into endolymph and uptake by cochlear hair cells across their apical membrane and greater ototoxicity and sensory hair cell loss [7, 26–28].

Our data show that subjects who receive 4 or more days of gentamicin treatment, i.e. longer than the standard broad-spectrum rule-out sepsis treatment of gentamicin plus ampicillin of 2–3 days (while blood culture results are pending for narrowing of antibiotic therapy) are at an increased risk for hearing loss. Subjects with identified sepsis, as well as those with SIRS, are at even higher risk for hearing loss following gentamicin exposure compared to those without signs of inflammation. Subjects with inflammation tend to receive longer treatments of gentamicin as they are sicker, and receive more gentamicin treatment to eradicate the infection. Thus, NICU patients, especially those with sepsis/SIRS, are at higher risk for ototoxicity after receiving intravenous gentamicin treatment. It is crucial for NICU providers to carefully consider the duration of exposure to gentamicin and the consequent risk of hearing loss in their patients. A swift change to non-ototoxic antibiotic therapy should be a priority once the causative organism has been identified via positive blood culture or other means of bacterial species identification. There was also a trend towards significance when gentamicin treatment overlapped with other ototoxic medications such as furosemide and/or vancomycin in the NICU population, despite their low percentage within this small cohort, making this population very vulnerable for potential hearing loss.

Another study of young adults showed that DPOAEs in the 4–8 kHz range are affected by UHF (ultra-high frequency) hearing loss in the 11.2–20 kHz range, and concluded that this may be due either to outer hair cell damage not yet detected by pure-tone thresholds, or to damaged basal cochlear (high frequency) outer hair cells that then dysregulate more apical (lower frequency) cochlear functions [29]. Further, DPOAEs have been shown to

successfully detect high-frequency ototoxicity (at 8, 9, and 10 kHz) following streptomycin administration in adult human subjects [30]. Other studies have investigated DPOAEs combined with AABR as a method for detecting potential hearing loss in the neonatal population, with mixed results [31, 32]. In spite of these mixed results, it has been shown that DPOAE is a more sensitive test than AABR for early detection of gentamicin ototoxicity, and that two-stage screening protocols using both DPOAE and AABR yield lower false-positive rates with specificity >94% [4, 33].

Prior studies have examined the factors that can lead to a “false referral” using DPOAE equipment [34, 35]. Some of these factors include middle-ear fluid collection/infection, probes too thick to fit the size of the subject’s external meatus, and improper seal of the probe with the external meatus. Several studies have found that DPOAE false-positive rates are higher in the lower frequency ranges compared to high frequency ranges [11, 34, 36]. Another study examining a cohort of 350 randomly selected NICU babies and non-hospitalized healthy babies found a 0.003% false negative rate and a 0.028% false positive rate of DPOAE referrals, when comparing TEOAEs (transient evoked otoacoustic emissions) to DPOAEs [35]. Based on this study, it is unlikely that our referral criteria resulted from false-positive DPOAE referrals.

The major limitation of this study is the lack of follow-up diagnostic audiology, with data only available from less than one-third of subjects. This lack of follow-up data is partly a consequence of study design. Funding for parents to attend follow-up appointments, and other necessary preparations were not incorporated into this pilot study design. The lack of data may also be due to parent inability to access care, lack of need for follow-up due to normal initial AABR screen, subjects living or moving out of state and follow-up audiology data not incorporated in this state’s Early Hearing Detection and Intervention database, or other unknown factors. This issue has so far prevented the longitudinal study of these subjects to better determine the long-term hearing outcomes of subjects exposed to gentamicin after discharge from the NICU. However, our data suggest that DPOAE screening in the NICU setting, in addition to the already-performed AABR, is useful to screen patients for high-frequency hearing loss due to ototoxicity that might otherwise be missed by the standard AABR hearing screen alone.

5.1 Conclusions

This study reports an association between neonates receiving ≥4 days of intravenous gentamicin and an increased referral rate on DPOAE screening. This could contribute to the increased hearing loss rates observed in the NICU setting. Subjects with sepsis or SIRS (i.e., inflammation) are at higher risk of hearing loss. We propose an expanded study to gather a larger cohort of subjects, including those with sepsis and neonatal SIRS, to increase the statistical power of these observations. In addition, subsequent studies need to obtain reliable follow-up diagnostic audiological data to further verify whether the DPOAE screening data, in addition to the use of the standard AABR screen, is a reliable predictor of permanent hearing loss due to cumulative gentamicin dosing in the NICU.

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Table 1
Subject demographics and other pertinent characteristics

Ninety-one subjects were enrolled; 7 subjects were septic, and 11 met SIRS criteria. No subjects had hyperbilirubinemia ≥ 30mg/dl, though 73% received phototherapy. No subjects had meningitis or seizures. Only 3% had any kind of TSH abnormality. Only gentamicin exposure and sepsis/SIRS status were used for analysis with DPOAE referral.

	Range [Lower limit, Upper	Mean	Number
Gestational age (weeks)	[24.14, 36.9]	33 (2.96)	
Gender: male/female			54 (59%) /
Length of stay in NICU (days)	[3, 215]	34.7	
Race:			
White/Caucasian			70 (77%)
Hispanic/Latino/Pacific Islander			21 (23%)
Birth weight (kg)	[0.61, 3.255]	1.87	
Birth weight < 1.5kg			25 (27%)
APGAR Score (1 min):			
≤6			40 (44%)
≥7			51 (56%)
APGAR Score (5 min):			
≤6			21 (23%)
≥7			70 (77%)
Hyperbilirubinemia			73 (80%)
>30mg/dl			0 (0%)
Required phototherapy			67 (73%)
Required exchange transfusion			0 (0%)
Subjects with signs of			18 (20%)
Sepsis			7 (8%)
Meet SIRS criteria			11 (12%)
Gentamicin exposure			74 (81%)
<4days			71 (78%)
≥4 days			20 (22%)
Vancomycin exposure			16 (18%)
Loop diuretic exposure			13 (14%)
Meningitis			0 (0%)
Seizures			0 (0%)
TSH Abnormality			3 (3%)

Table 2

Pediatric SIRS criteria used to identify subjects with SIRS by electronic health record review. Only subjects meeting SIRS criteria on the same day as receiving intravenous gentamicin were considered for this analysis. If a subject met SIRS criteria, but did not receive gentamicin on that day, the subject was not categorized as a SIRS plus gentamicin subject in this analysis. Adapted from Goldstein et al. [10].

AGE GROUP	TACHYCARDIA	BRADYCARDIA	RESPIRATORY RATE (BREATHS/MIN)	LEUKOCYTE COUNT LEUKOCYTES $X10^3/MM^3$	SYSTOLIC BLOOD PRESSURE, MM HG
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 yr	>180	<90	>34	>17.5 or <5	<100
2–5 yrs	>140	N/A	>22	>15.5 or <6	<94
6–12 yrs	>130	N/A	>18	>13.5 or <4.5	<105
13 to <18 yrs	>110	N/A	>14	>11 or <4.5	<117

Table 3

Overlapping administration of ototoxic medications

Medication overlap was widespread in this cohort. Overlap was defined as at least one day of receiving either vancomycin or furosemide on the same day as gentamicin treatment. Fourteen (15%) of 91 subjects had overlap between gentamicin and vancomycin. Six (6.6%) of 91 subjects had overlapping gentamicin and furosemide treatment. There were three sepsis subjects who overlapped all three medications, and two subjects with SIRS who overlapped all three medications. Medication overlap was found to almost be a significant factor associated with referral on the DPOAE screen (p=0.05).

	91 TOTAL SUBJECTS IN COHORT	SUBJECTS WITH GENTAMICIN OVERLAP	SUBJECTS WITH GENTAMICIN OVERLAP AND ≥4 DAYS OF GENTAMICIN	7 SUBJECTS WITH SEPSIS	11 SUBJECTS WITH SIRS
Vancomycin exposure	16 (18%)	14 (15%)	11 (79%) 4 of whom were septic 4 of whom met SIRS criteria 3 without sepsis or SIRS	4 subjects with sepsis, who had overlapping vancomycin and gentamicin exposure	4 subjects with SIRS, who had overlapping vancomycin and gentamicin exposure
Furosemide exposure	13 (14%)	6 (6.6%)	5 (83%) 3 of whom were septic 2 of whom met SIRS criteria	3 subjects with sepsis, who had overlapping furosemide, vancomycin, and gentamicin exposure	2 subjects with SIRS, who had overlapping furosemide, vancomycin, and gentamicin exposure