Effect of gentamicin and levels of ambient sound on hearing screening outcomes in the neonatal intensive care unit: A pilot study

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ABSTRACT

Objective: Hearing loss rates in infants admitted to neonatal intensive care units (NICU) run at 2–15%, compared to 0.3% in full-term births. The etiology of this difference remains poorly understood. We examined whether the level of ambient sound and/or cumulative gentamicin (an aminoglycoside) exposure affect NICU hearing screening results, as either exposure can cause acquired, permanent hearing loss. We hypothesized that higher levels of ambient sound in the NICU, and/or gentamicin exposure affect NICU hearing screening results, as either exposure can cause acquired, permanent hearing loss. We hypothesized that higher levels of ambient sound in the NICU, and/or gentamicin dosing, increase the risk of referral on the distortion product otoacoustic emission (DPOAE) assessments and/or automated auditory brainstem response (AABR) screens.

Methods: This was a prospective pilot outcomes study of 82 infants (<37 weeks gestational age) admitted to the NICU at Oregon Health & Science University. An ER-200D sound pressure level dosimeter was used to collect daily sound exposure in the NICU for each neonate. Gentamicin dosing was also calculated for each infant, including the total daily dose based on body mass (mg/kg/day), as well as the total number of treatment days. DPOAE and AABR assessments were conducted prior to discharge to evaluate hearing status. Exclusion criteria included congenital infections associated with hearing loss, and congenital craniofacial or otologic abnormalities.

Results: The mean level of ambient sound was 62.9 dBA (range 51.8–70.6 dBA), greatly exceeding American Academy of Pediatrics (AAP) recommendation of <45.0 dBA. More than 80% of subjects received gentamicin treatment. The referral rate for (i) AABRs, (frequency range: ~1000–4000 Hz), was 5%; (ii) DPOAEs with a broad F2 frequency range (2063–10031 Hz) was 39%; (iii) DPOAEs with a low-frequency F2 range (<4172 Hz) was 29%, and (iv) DPOAEs with a high-frequency F2 range (>4172 Hz) was 44%. DPOAE referrals were significantly greater for infants receiving >2 doses of gentamicin dosing compared to fewer doses (p = 0.004). The effect of sound exposure and gentamicin treatment on hearing could not be determined due to the low number of NICU infants without gentamicin exposure (for control comparisons).

Conclusion: All infants were exposed to higher levels of ambient sound that substantially exceed AAP guidelines. More referrals were generated by DPOAE assessments than with AABR screens, with...
1. Introduction

Approximately 78 of 1000 live births are admitted into the neonatal intensive care unit (NICU) each year in the United States [1], placing them at greater risk for acquired sensorineural hearing loss [2]. The prevalence of hearing loss in NICU graduates (2–15%) is significantly higher than for full-term births (0.2–0.3%) [3]. Although management of NICU admissions is medically more challenging than regular births, the factors that contribute to this greater prevalence of hearing loss in NICU graduates remain poorly understood. Several risk factors have been identified, including low birth weight, prematurity, medications (including aminoglycosides), oxygen use, length of stay, and exposure to higher levels of ambient sounds [4–8]. This pilot study investigated two risk factors - cumulative sound exposure and aminoglycoside dosing - on the hearing of NICU neonates.

The Environmental Protection Agency (EPA) published data in 1974 to protect patients and staff in hospital environments from damaging levels of ambient sound [9]. The levels of ambient sound were measured over a 24 h period in decibels (dB) with an A-weighted filter, dBA, that is less sensitive to higher (typically >6 kHz) and lower frequencies (typically <1 kHz). This weighted filter is intended to be comparable to the loudness and frequency sensitivity of the human ear, and therefore has been used for developing national standards for sound exposures [10–12]. These levels are further reported as the steady sound level that has the same acoustic energy as the fluctuating level actually measured over a period of time, \( L_{eq} \), or the maximum level, \( L_{max} \). Based on these measurement standards, the EPA reported that levels of ambient sound be < 45 dBA in hospitals to provide a suitable environment for healing, development, staff communication and healthy family interactions. The EPA also reported that exposure to sounds >45 dBA put infants at risk for cochlear damage and abnormal development [9,13].

In 1997, the American Academy of Pediatrics (AAP) recommended that the mean level of ambient sound in the NICU should not exceed 45 dBA over 24 h based on EPA criteria [9,13]. However, recent studies in 2008 have reported that the average NICU has sustained levels of ambient sound (e.g., mostly generated by monitors, ventilators, and alarms) ranging between 53.9 dBA and 60.6 dBA [14,15]. Sustained higher levels of ambient sound cause significant changes in vital signs, physiology, and behaviors of infants in the NICU, including drops in oxygen saturation, altered heart rate, blood pressure, and disturbed sleep, with reduced healing and growth rates [16,17]. Graven [18] recommended that the \( L_{eq} \) be ≤ 50 dBA with an \( L_{max} \) of 70 dBA, as these criteria would “protect sleep, support stable vital signs, and improve speech intelligibility for many infants.”

These recommended levels for ambient sound in the NICU are much lower than the standards established for adults by the National Institute for Occupational Safety and Health (NIOSH) in 1998, which recommended a workplace exposure limit of 85 dBA as an 8-h time-weighted average (TWA) [19]. This limit differs slightly from the EPA and AAP guidelines due to differences in measurement. NIOSH recorded levels of ambient sound using special-purpose sound level meters called dosimeters, with a TWA output and/or “dose” expressed as a percent of the total permissible daily exposure and corresponds to an average level of 90 dB over 8 h. However, the World Health Organization (WHO) report that ambient sound exposures >70 dBA \( L_{eq} \) over a 24 h period (comparable to EPA measures) negatively impact stress and behavior, including increased risk of hearing loss, reduced performance of cognitive tasks, hypertension, neurosis, and sleep disturbance [20]. Taken together, these standards for adults (i.e., <70 dBA \( L_{eq} \)) allow for a much greater tolerance of sound exposure compared to those recommended for infants in the NICU (i.e., 45 dBA \( L_{eq} \)). Table 1 summarizes both adult and infant sound exposure recommendations for each organization.

Although previous studies have measured the levels of ambient sound in NICU settings, there are inconsistencies in study design, such as placing the dosimeter or sound level meter away from the occupied isonette [21,22], recording sound levels <24 h each day [14,15,17], or completing sound measurements in empty isolettes or empty rooms without ventilator noise [23]. Little to no evidence exists on the long-term effects of the higher levels of ambient sounds on the hearing of NICU infants. This is critical, as exposure to sustained levels of ambient sound can induce significant temporary and permanent hearing losses in adults and may have the same, or greater, effect on hearing in infants [24].

In addition to ambient sounds, as many as 57.5% of neonates receive gentamicin - an aminoglycoside antibiotic - for suspected or confirmed bacterial infections, because of its low-cost, broad spectrum and high bactericidal efficacy [25,26]. However, aminoglycosides can have deleterious effects on cochlear outer hair cells, initially resulting in, a higher frequency (>8 kHz) sensorineural hearing loss known as ototoxicity [27,28]. Aminoglycoside ototoxicity has been widely researched in adults, and despite some conflicting studies, substantial evidence for gentamicin-induced

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Definition</th>
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<tr>
<td>AABR</td>
<td>automated auditory brainstem response</td>
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<td>AAP</td>
<td>American Academy of Pediatrics</td>
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<td>ABR</td>
<td>auditory brainstem response</td>
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<td>ASHA</td>
<td>American-Speech Language-Hearing Association</td>
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<td>CPAP</td>
<td>continuous positive airway pressure ventilation</td>
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<tr>
<td>dBA</td>
<td>A-weighted decibels, accounting for relative loudness to the human ear</td>
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<tr>
<td>DP</td>
<td>distortion product</td>
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<tr>
<td>DPOAE</td>
<td>distortion product otoacoustic emission</td>
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<tr>
<td>EHDI</td>
<td>Early Hearing Detection and Intervention</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
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<tr>
<td>( L_{eq} )</td>
<td>equivalent continuous sound level</td>
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<tr>
<td>( L_{max} )</td>
<td>maximum sound level</td>
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<tr>
<td>NBHS</td>
<td>Newborn Hearing Screening</td>
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<tr>
<td>NICU</td>
<td>neonatal intensive care unit</td>
</tr>
<tr>
<td>NIOSH</td>
<td>National Institute for Occupational Safety and Health</td>
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<tr>
<td>SNR</td>
<td>signal-to-noise ratio</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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hearing loss also exists in neonates [8,29,30].

Both high sound exposures and aminoglycoside treatments can independently produce sensorineural hearing loss in adults, yet these effects are not as well-described in full-term or NICU infants. Adult studies show that chronic exposure to high level sounds can result in sensorineural hearing loss at 4000 Hz and 6000 Hz [31–33]. On the other hand, otoxic medications can initially induce sensorineural hearing losses at higher frequencies that often progress to lower (1–4 kHz) frequencies important for language development and speech discrimination [27,34–36]. Rees [37] reported that high levels of sound and aminoglycoside exposures synergistically increase the probability of high frequency hearing loss in pre-term infants [37], yet these data remain to be validated independently. Preclinical studies also suggest that co-therapeutics such as vancomycin synergistically potentiate the ototoxicity of aminoglycosides [38,39]. Data from preclinical and adult studies may not directly apply to infants, due to differences in auditory system maturation, particularly in pre-term NICU infants, and therefore should be investigated separately.

Since the approval of Early Hearing Detection and Intervention (EHDI) newborn hearing-screening legislation in 2000, the age for the initial diagnosis of hearing loss has decreased from a wide range between 11.5 and 32 months to a narrower, younger range between 2 and 10 months [40]. According to the American Speech-Language-Hearing Association (ASHA), all 50 states and the District of Columbia have set protocols for Newborn Hearing Screening (NBHS) prior to hospital discharge as part of a mandated law or voluntarily through a state program. The NBHS typically consists of two objective screening tests: (i) an automated click auditory brainstem response (AABR) screen that provides information about neural transmission of acoustic stimuli from the cochlea to upper brainstem and/or (ii) distortion product otoacoustic emissions (DPOAEs) that are byproducts of the activity of cochlear outer hair cells and are indicative of good cochlear function. Both screening tests are clinically useful for identifying auditory dysfunction when middle ear integrity is normal. However, test frequencies are typically limited to important speech frequencies (1–4 kHz), and cannot detect the initial onset of ototoxicity at higher frequencies. Current referral rates for NBHS tests are 0.8–6% for AABR and 3.1–5% for DPOAE screens for all newborns [41–44].

The AAP-Joint Commission on Infant Hearing position statement [4] recommends close monitoring of infants discharged from the NICU due to higher rates of hearing loss. Another important consideration is to monitor the progression of hearing loss after ototoxic drug treatment, such as gentamicin. To date, a newborn hearing screening protocol for ototoxicity has not been developed. We tested three hypotheses in the present study: (i) levels of ambient sound in the NICU are greater than AAP recommended guidelines; (ii) greater cumulative gentamicin dosing increases the prevalence of DPOAE and AABR referrals in NICU infants, and (iii) infants with exposure to higher ambient sound levels and greater gentamicin dosing will have increased rates of DPOAE and AABR referrals. We also assessed whether higher frequency-specific DPOAE assessments are more sensitive compared to the AABR screen in detecting auditory dysfunction caused by ambient noise and/or ototoxic medication. These pilot data will provide the framework for a larger study to investigate the synergistic effects of higher levels of ambient sounds and aminoglycosides on hearing in NICU graduates.

2. Methods

2.1. Enrollment and inclusion criteria

This pilot observational study was approved by the Institutional Review Board (IRB) at Oregon Health & Science University (OHSU). This study was conducted in the NICU at OHSU in accordance with The Code of Ethics of the World Medical Association. Informed consent was obtained from parents/guardians for all subjects recruited, and their privacy rights respected. Infants were eligible if < 37 weeks gestational age without a diagnosis of congenital hearing loss, intrauterine infection or congenital deformity known to cause hearing loss. Two hundred and twenty-five premature infants admitted into the OHSU NICU between August 2012 and October 2013 were screened, and 208 infants met inclusion criteria. Forty-four patients were excluded prior to enrollment. Exclusion criteria included diagnosis of congenital hearing loss or other known causes of hearing loss, including specific infections (herpes simplex, rubella, syphilis, cytomegalovirus, and meningitis), known craniofacial syndromes or otologic abnormalities like aural atresia. Of the remaining 164 eligible infants, 103 were enrolled into the study. Fifteen infants were lost to post-enrollment exclusions, leaving 88 infants with complete sound exposure data collection. Five subjects were discharged prior to completing the AABR screen and one patient was discharged prior to DPOAE assessment, leaving 82 who completed all study-related outcome measures.

2.2. NICU environment

This medical center’s NICU has a layout that includes “pods,” or open rooms, each containing eight beds at maximum capacity, including open and enclosed bed types. Upon entering the NICU, most infants are placed in pods, and are moved between pods based on their medical needs throughout their stay. In addition, occupied beds are moved based on available personnel and logistics of care. In all cases, the dosimeters (see below) followed the infant.

2.3. Measurement of ambient sound levels

Following study enrollment, a sound pressure level dosimeter (ER-200D, Etymotic Research Inc., Elk Grove Village, IL) was placed in the bed of each subject, with the dosimeter’s microphone mounted to point towards the infant’s head. A “dose” calculator [45] was created to determine the mean ambient level of sound exposure over each 24 h period. This dosimeter samples sound pressure levels every 220 ms, logging 16 data points each hour of use, each data point averaging ~1022 samples, for a TWA over 24 h. The threshold was set at 65 dBA, the lowest accurate measurement defined by manufacturer specifications, with an exchange rate of 3 dBA. SPL measurements below 65 dBA were recorded as 0 dBA by the dosimeter. Throughout the infant’s NICU stay, the dosimeter was replaced every 3–5 days prior to battery depletion. The
replacement dosimeter was placed in the isolette within five minutes of removing the previous device. NICU clinical staff were asked to record all clinical care events for each infant on a log attached to the side of the bed.

2.4. AABR screening protocol

Prior to discharge from the NICU, each infant received a clinical AABR using the Natus ALGO 5 as part of our medical center’s standard of care. Screening involves placement of three electrodes (forehead, nape of neck, and shoulder) and a set of earphones over the ears, to present soft click stimuli (35 dB nHL) to each ear with a broad frequency range of -1000–4000 Hz. Auditory electrical potentials were compared to normative data using the internal algorithm in the ALGO 5 for determining whether the screen was a “pass” or “refer.” If the infant was “referred” for either ear, the AABR is administered a second time for both ears prior to discharge. If the infant did not pass in one or both ears a second time, a follow-up diagnostic DPOAE and auditory brainstem response (ABR) evaluation was scheduled.

2.5. Diagnostic DPOAE research protocol

For each participant in this study, a diagnostic-grade DPOAE assessment for frequency-specific hearing abnormalities was completed using the Biologic Natus Scout Sport system. A small, soft probe was placed in the ear canal, and each ear was tested separately. The probe introduced a tone into the ear canal and measured the resulting DPOAEs. A DPOAE was evoked using two frequencies - a lower frequency tone (F1) and a higher frequency tone (F2). These two frequencies are introduced into the external ear canal, with F2 at a frequency ratio 1.22× higher than F1 and the emission, or response, measured at 2F1-F2. The F1 and F2 are introduced at two differing amplitudes, L1 is the higher amplitude (for F1) and L2 is the lower amplitude (for F2). The L1/L2 ratio of 65/55 dB SPL, respectively, is used in clinical protocols due to its greater sensitivity for ruling out sensorineural hearing loss. In the current study, the F2 frequencies used were 2063, 2531, 2953, 3563, 4172, 4969, 5953, 7031, 8391, 10031 Hz. We categorized the F2 frequencies into two groups, those <4000 Hz were categorized as “low frequency,” and those ≥4000 Hz as “high frequency.” A distortion product (DP) was defined as a normal value if ≥0 dB with a signal-to-noise ratio (SNR) of ≥6 dB above the noise floor. A present but reduced value was defined as a DP <0 dB with a SNR ≥6 dB above the noise floor. Lastly, absent values were noted when the SNR was <6 dB between the DPOAE and noise floor. Reduced and absent DPOAEs for any given frequency were defined as “abnormal.” A large review of outcomes from DPOAE screens found that passing criteria ranged from 60 to 100% of that for normal responses [46]. For comparison with the AABR, we analyzed our DPOAE data as a hearing screen at low frequencies, high frequencies, and all frequencies. Passing criteria required normal DPOAE responses for at least 2/3 (66%) of frequencies in each category: low frequency range (2063–3563 Hz), high frequency range (4172–10031 Hz) or all-frequency range (2063–10031 Hz).

2.6. Gentamicin and additional data collected

Information regarding gentamicin dosing was collected from each patient’s electronic medical record. Total gentamicin exposure was calculated for daily dosage based on body weight (mg/kg/day) and number of days received, where 4 mg/kg over a 24-h period was considered equivalent to 1 unit of exposure. Prior work from this group identified that a threshold of ≥4 days of gentamicin associated with an increased risk of referral using higher frequency DPOAE assessments. This indicated that detailed dosing information was necessary to accurately interpret results of the current study [47]. Other information collected included demographics, other drug exposures, length of stay, birth weight and length, one- and five-minute Apgar scores, additional procedures (e.g. ventilator placement, operations, bedside procedures), blood test results, and maternal prenatal information such as smoking status during pregnancy and blood titers/immunity status for known in utero infections that may cause permanent hearing loss.

2.7. Data analyses

Analyses were conducted using statistical and database software packages (SPSS v.22, IBM, Armonk, NY; Excel, Microsoft, Redmond, WA) to describe sample characteristics and assess for assumptions of normality and linearity where appropriate. Patient covariates included gender, gestational age at birth, length of NICU stay, race, binary birth weight (<1.5 kg vs. ≥1.5 kg), standardized doses of gentamicin, hyperbilirubinemia, seizures, administration of loop diuretics or vancomycin, machine ventilation, continuous positive airway pressure ventilation (CPAP), phototherapy or exchange transfusion, and procedures received (e.g. line placement, surgical procedures). The Apgar score, a method for reporting the health status of the newborn infant one- and five-minutes after birth, was also evaluated, with a higher score indicating better physical condition for each metric [48,49]. Study data was evaluated descriptively using means, standard deviations, ranges, and prevalence, where appropriate. Assumptions of distribution normality were verified for ordinal and continuous measures. Between group bivariate unadjusted comparisons were completed using either Mann Whitney U testing or Pearson’s chi-square (χ2) testing. Odds ratio (OR) values with 95% confidence intervals (CI) were calculated to determine a magnitude of effect for independent covariates associated with increased likelihood of referral. Statistically significant associations were reported using a 0.05 type-I error probability threshold (x-level).

3. Results

3.1. Prevalence of referral

All study participants (n = 82) had an AABR screen and a frequency-specific DPOAE assessment completed prior to discharge, with a ~5% AABR referral prevalence (n = 4). The enhanced DPOAE assessments had an all-frequency referral prevalence of 39% (n = 32), 44% referral prevalence (n = 36) when assessing only the higher frequency range, and a 29% referral prevalence (n = 24) for the low frequency range. Infants were significantly more likely to have abnormal high frequency DPOAE results compared to low frequency results (p <0.05). See Table 2 for all additional infant subject demographic factors and patient characteristics.

3.2. Levels of ambient sound in the NICU

Upon discharge from the NICU, 82 infants had their cumulative ambient sound exposure levels determined for their entire stay. The mean daily level of ambient sound exposure per infant was 62.9 dBA TWA over 24 h (range 51.8–70.6 dB; Table 3), more than 7.5 times greater than the daily exposure limit of 45 dBA Leq for infants in the NICU, per AAP recommendations [9,13]. Table 3 shows this exposure calculated as a ratio of the mean daily exposure according to WHO and I of Perinatology recommendations [18,20]. The mean level of ambient sound recorded in the NICU were not significantly different between infants with or without DPOAE.
referrals for the high frequency [62.6 (±3.6) dB vs. 63.3 (±3.6) dB; p = 0.393] or referrals for the all-frequency [62.6 (±3.7) vs. 63.2 (±3.6); p = 0.505] ranges. This effect was likely due to the lack of variability in ambient sound level recordings and dosimeter limitations (see Discussion for more details).

3.3. Gentamicin dosage

All infants in this sub-analysis received both an AABR screen and a DPOAE assessment. A total of 67/82 infants (82%) received some level of gentamicin dosing during the study duration. The average dose of gentamicin (4 mg/kg/day) received by all study participants was 2.3 (±3.1), with a range of 0.0–15.6 standardized doses. A total of 15 infants received no gentamicin (18%) while most infants received between 1.0 and 2.0 standardized doses (n = 36; 44%).

Table 2
Infant study participant demographics and health characteristics (n = 82).

<table>
<thead>
<tr>
<th>Patient characteristics:</th>
<th>Range [LL, UL]</th>
<th>Mean (±SD)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>[24.1, 36.9]</td>
<td>33.0 (±3.0)</td>
<td>52 (63%)</td>
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<tr>
<td>Gender: male/female</td>
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<tr>
<td>Length of stay in NICU (days)</td>
<td>[3, 132]</td>
<td>30.7 (±29.3)</td>
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<tr>
<td>Race:</td>
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<td></td>
<td>30 (37%)</td>
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<tr>
<td>White/Caucasian</td>
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<td>54 (66%)</td>
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<td>Asian</td>
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<td>American-Indian/Pacific Islander</td>
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<td>Multiracial</td>
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<tr>
<td>Birth weight (kg.)</td>
<td>[0.7, 3.3]</td>
<td>1.9 (±0.6)</td>
<td>22 (27%)</td>
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<tr>
<td>Birth weight (&lt;1.5 kg)</td>
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<td>One-Minute Apgar Score:</td>
<td>[0, 9]</td>
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LL, lower limit; UL, upper limit; SD, standard deviation; NICU, Neonatal Intensive Care Unit; Apgar, Appearance, Pulse, Grimace, Activity, Respiration; CPAP, continuous positive airway pressure; TSH, thyroid-stimulating hormone.

Table 3
Mean level of ambient sound exposure in this study, and as a ratio compared to mean daily exposures under different guidelines (dBA).

| Dosimeter data collection (n = 82): | Range [LL, UL] | Mean (±SD) | N (%).
<table>
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<tbody>
<tr>
<td>Average daily exposure, dBA (±SD)</td>
<td>[51.8, 70.6]</td>
<td>62.9 (±3.6)</td>
<td>25.0 (±18.2)</td>
</tr>
<tr>
<td>Time under threshold detection limit, % (±SD)</td>
<td>[0, 80.0]</td>
<td>25.0 (±18.2)</td>
<td>62.9 (±3.6)</td>
</tr>
</tbody>
</table>

LL, lower limit; UL, upper limit; SD, standard deviation; WHO, World Health Organization; AAP, American Academy of Pediatrics; dBA, decibels (A-weighted).

Categories of standardized dosing across DPOAE and AABR referral groupings are further described in Table 4. A total of 11 out of 82
The prevalence of DPOAE referrals for the low frequency range was significantly higher for infants who received 4.0 or more standardized doses of gentamicin compared to infants who received fewer doses (56% vs. 20%; \( \chi^2 = 13.6; p = 0.005 \)). The prevalence of DPOAE referrals for both high frequency and all-frequency ranges were found for infants receiving 4.0 or more standardized doses of gentamicin compared to fewer doses [(64% vs. 41%; \( \chi^2 = 2.01; p = 0.156 \)] and [64% vs. 35%; \( \chi^2 = 3.23; p = 0.072 \)], respectively, however this difference was not statistically significant at the predetermined 0.05 error rate.

A lower gentamicin dose cut-off was examined to determine if DPOAE referral rates were still significant. A total of 26/82 infants (32%) received 2.0 or more standardized doses of gentamicin. The prevalence of DPOAE referrals for the low frequency range was significantly higher for infants who received 2.0 or more standardized doses of gentamicin compared to infants who received fewer doses (50% vs. 20%; \( \chi^2 = 7.90; p = 0.005 \)). Likewise, the prevalence of DPOAE referrals for both high frequency and all-frequency ranges were also significantly higher for infants who received 2.0 or more standardized doses of gentamicin compared to infants who received fewer doses [(62% vs. 36%; \( \chi^2 = 4.81; p = 0.028 \)] and [(62% vs. 29%; \( \chi^2 = 8.11; p = 0.004 \)], respectively.

Due to the lack of variability in the level of ambient sound exposures (Table 3) among neonates, no significant associations between different levels of ambient sound and cumulative levels of gentamicin dosage were detected.

3.4. Additional patient co-factors

Additional variables (Table 2) were evaluated for any significant association with DPOAE and AABR referral prevalence. The prevalence of DPOAE referrals in the low frequency range was significantly higher for infants receiving vancomycin (in addition to gentamicin) during their NICU stay, compared to infants not receiving vancomycin (OR: 4.3; 95% CI: 1.3–14.4; 57% vs. 24%; \( p = 0.012 \)). Additionally, infants with one-minute Apgar scores <5 were significantly associated with higher prevalence of DPOAE referral in the lower frequency range, compared to infants with higher Apgar scores (OR: 3.1; 95% CI: 1.2–8.6; 46% vs. 21%; \( p = 0.022 \)). Similarly, infants with five-minute Apgar scores <7 were significantly associated with higher prevalence of DPOAE referral in the low frequency range, compared to those with higher Apgar scores (OR: 3.1; 95% CI: 1.1–8.7; 48% vs. 23%; \( p = 0.032 \)).

4. Discussion

Congenital and early onset of acquired hearing loss has lifelong consequences for children, families, and society. School-aged children with hearing loss are more likely to have difficulties creating and interacting in social relationships, as well as delayed academic progress [50,51]. Parents perceive a negative impact of hearing loss on the emotional well-being of children with hearing loss, with increased stress related to communication and behavioral problems [52,53]. Children with congenital or acquired hearing loss prior to speech and language development experience an estimated socioeconomic cost of >$1 million (in year 2000 dollars) over the course of their lifetime due to expenses associated with auditory rehabilitation, special education resources and reduced work productivity in adulthood [54]. This study is one of the first to prospectively measure the cumulative level of ambient sound within beds occupied by neonates throughout their NICU stay, and attempted to determine if cumulative levels of ambient sound exposure and/or gentamicin dosing correlates with frequency-specific DPOAE or AABR referrals.

The neonates in this study were exposed to a mean level of daily ambient sound exposures of 62.9 dBA TWA over 24 h during their NICU stay, which is more than 7.5 times greater than the daily exposure recommended by the AAP of 45 dBA Leq. Sustained higher levels of ambient sound can disrupt sleep and affects measures of respiration, blood pressure, heart rate, and brain development in premature infants [16,17]. Continued exposure to environmental noise affects school-aged children through increased psychologic stress, negative physiologic outcomes and elevated blood pressure [55]. As neonates have less developed neurological networks compared to school-aged children, it is possible that sustained higher levels of ambient and/or environmental sound may have a greater effect on their overall well-being that could continue to influence their overall health and neuro-cognitive development, even after discharge [56]. When ear muffs are provided to reduce exposure to NICU sound levels, neonates exhibit improved quality of sleep and respiratory function, suggesting that reduced exposure to ambient sound correlates with an improved physiologic state [57].

In NICUs with sustained levels of ambient sound >50 dBA Leq, lengths of stay that range from weeks to months are likely to have a greater risk for acquired sensorineural hearing loss, as there is no rest period (typically at night) to recover from continuous exposure to higher levels of ambient sounds [9]. However, identifying the etiology of acquired hearing losses in NICU graduates is confounded by other risk factors, including very low birth weight, continuous positive airway pressure support, hypoxia, hyperbilirubinemia, low APGAR scores and ototoxic medications [5,58–60]. Interestingly, in this study, infants with low one-minute and five-minute Apgar scores were significantly associated with a higher prevalence of DPOAE referral in the lower frequency range (2063–3563 Hz). This is similar to prior investigations in neonates with perinatal asphyxia and low Apgar scores that found significantly reduced...
low-frequency transient-evoked OAEs [61,62]. Thus, there may be a complex, synergistic relationship between any of these individual risk factors, as many NICU admissions have multiple medical needs.

One major limitation of this pilot study was the detection floor of the dosimeters (65 dBA), as these dosimeters were calibrated to NIOSH standards for adults. Measurements below 65 dBA were logged as 0 dBA. Thus, the level of ambient sound exposure in this study underestimate the actual sound exposures; nonetheless, these underestimates are still well above recommended guidelines. We calculated that about ~25% of logged data was under the threshold detection limit of 65 dBA (Table 3), emphasizing that the majority of logged data were >65 dBA. The affordability and portability of this particular dosimeter made this pilot study feasible, however, the data gathered was insufficient to demonstrate a synergistic relationship between higher levels of ambient sound and gentamicin exposure in inducing acquired hearing loss. This hypothesis will need to be more accurately tested using sound dosimeters with a detection floor for ambient sound levels at 45 dBA or lower. Another limitation is that although we attempted to log which factors might contribute to differences in levels of ambient sound exposures between infants, clinical staff participation in this activity was too inconsistent for rigorous analysis. In addition, direct comparison of recommended sound exposure limits is difficult due to the variability in measurement across organizations and studies, e.g., Leq vs TWA, or using a 3 vs 5 dB exchange rate in calculating exposure over time [63,64].

While the majority (82%) of infants in this study received gentamicin, those who received >4 standardized doses of gentamicin were significantly more likely to refer on the low-frequency DPOAE assessment compared to those receiving <4 standardized doses. Furthermore, 32% of infants received >2 standardized doses of gentamicin, and were significantly more likely to refer on the low-frequency, high-frequency and all-frequency DPOAE assessments compared to those receiving <2 standardized doses. Thus, gentamicin may be appropriate for NICU infants without obvious signs of infection or inflammation during the period of rule-out of sepsis (typically ~2–3 days). However, once an infection is suspected, or confirmed, continued antibiotic dosing should use alternative antibiotics with similar coverage, such as ceftriaxone, to decrease the risk of ototoxicity. These data also suggest that the frequency-specific DPOAE assessment may have greater sensitivity to identify higher-frequency hearing loss compared to the broadband click-evoked AABR screen. High frequency hearing in infants is critical for acquisition of speech (particularly in noisy settings), awareness of environmental sounds and neurological development [35,36].

Co-factors associated with significantly increased DPOAE referral rates in this study included vancomycin treatment and low Apgar scores, in the low frequency range tested. Evidence exists regarding the synergistic effects of concomitant aminoglycoside and vancomycin treatment in preclinical models and adults [38,39], however it is unclear about these effects in young infants. Conversely, there is a well-documented association between low Apgar scores and sensorineural hearing loss [65].

Furthermore, a synergistic interaction between aminoglycosides and higher levels of sustained ambient sounds may be present; however this could not directly evaluated in this pilot study, due to the similarities in ambient sound exposures between infants who passed, and those who were referred on the DPOAE assessment. A sub-cohort of infants without gentamicin treatment would also be needed for control comparisons. Thus, this remains an important clinical question to be addressed. Preclinical studies suggest that sustained levels of high ambient sound exposure potentiate cochlear and hair cell uptake of aminoglycosides [66,67], contributing one potential mechanism to the observed ototoxic synergy between aminoglycosides and higher ambient sound levels [68–71]. This kind of ototoxic synergism [37] has yet to be corroborated in humans, and assumes that the neonate auditory system reacts to ototoxic medications and sustained higher levels of ambient sounds in the same manner as a functional auditory system in preclinical models.

The NBHS is designed to identify infants at risk for prenatal hearing loss. However, due to the consequences associated with late- or non-identification of pre-lingual hearing loss, it is crucial to add a higher frequency DPOAE assessment along with the AABR screen, and these are relatively low-cost. The NBHS policy is to refer all NICU graduates for a follow-up diagnostic hearing evaluation regardless of whether they passed or referred on the AABR screen, since admission into the NICU places infants at a greater risk for late onset or progressive hearing loss [5]. We hypothesized that the DPOAE assessment would identify infants who pass the AABR screen, but who potentially may still have aminoglycoside-induced ototoxicity, or acoustic trauma, at higher frequencies. Our high frequency DPOAE assessment was significantly more likely to refer study participants for a diagnostic hearing evaluation compared to the AABR screen.

There are benefits and limitations to each screening test. The AABR uses a click-evoked (broadband) stimulus that encompasses a range of frequencies, and may result in a “pass” even when “mild” or high-frequency hearing loss is present [72]. Yet, if only an AABR is used for screening, 23% of infants with at least a unilateral sensorineural hearing loss will not be diagnosed by 9 months of age, but who otherwise would have been identified if screened with both DPOAE and AABR assessments [72]. However, DPOAE measurements are more unreliable than AABR, especially in the first 24 h after birth, due to temporary vernix in the ear canal or amniotic fluid within the middle ear [73]. DPOAEs are also affected by high physiologic (e.g. wheezing) or background noise that can lead to reduced response amplitudes or a “referral” on the screening [74]. These factors must be considered when interpreting newborn hearing screening results. Nonetheless, we had significantly more referrals on the high-frequency DPOAE assessment compared to the other DPOAE conditions, with several participants showing a response pattern consistent with possible high-frequency sensorineural hearing loss. However, since audiometric follow-up of subjects was not part of the pilot study design, we could not verify that subjects who referred only on the DPOAE assessment had diagnostic hearing loss using frequency-specific ABR testing. Future studies to address these limitations with a larger cohort of NICU infants are in consideration.

5. Conclusions

The levels of ambient sound within NICU beds remain substantially higher than recommended by current AAP guidelines. Gentamicin remains commonly used in the NICU prophylactically for its life-saving, broad-spectrum bactericidal efficacy, despite its potential for ototoxicity. Both sound and gentamicin, individually, and potentially synergistically, can affect the high frequency hearing sensitivity of NICU graduates, which may delay their acquisition of listening and spoken language skills. Our DPOAE assessment data suggests that performing only AABR testing has the potential to miss infants who should be referred for diagnostic audiology. Given the increased prevalence of hearing loss among NICU graduates, we recommend that both AABR screening and the addition of higher frequency-specific DPOAE (>4 kHz) assessments prior to discharge will better identify infants at risk for hearing loss who will benefit from a diagnostic hearing evaluation.
Contributors’ statements of authorship

Angela C. Garinis: Dr. Garinis reviewed the data analyses, edited, revised and reviewed the manuscript.
Selena Liao: Dr. Liao conceptualized and designed the study, consented and enrolled subjects, created the data collection instruments, coordinated data collection, drafted the initial manuscript, reviewed and revised the manuscript.
Campbell P. Cross: Dr. Cross coordinated data collection, calculated the cumulative gentamicin exposure of each subject, reviewed and completed the collected data, reviewed and revised the manuscript.
Johnathan Galati: Mr. Galati consented and enrolled subjects, coordinated and streamlined data collection and analysis, and reviewed the manuscript.
Jessica L. Middaugh: Dr. Middaugh reviewed the data analyses, edited and revised the manuscript.
Jess C. Mace: Mr. Mace carried out the statistical analyses, reviewed and revised the manuscript.
Anna-Marie Wood: Dr. Wood consented and enrolled subjects, coordinated data collection, and reviewed the manuscript.
Lindsey McEvoy: Dr. McEvoy consented and enrolled subjects, coordinated data collection, and reviewed the manuscript.
Lauren Moneta: Dr. Moneta consented and enrolled subjects, coordinated data collection, and reviewed the manuscript.
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Casey Nold: Mr. Nold consented and enrolled subjects, coordinated and supervised data collection, and reviewed the manuscript.
Heather Durham: Ms. Durham reviewed the data analyses, and reviewed the manuscript.
Carol MacArthur: Dr. MacArthur reviewed the data analyses, and reviewed the manuscript.

Cynthia McEvoy: Dr. McEvoy reviewed the data analyses, and reviewed the manuscript.
Peter S. Steyger: Dr. Steyger assisted in conceptualizing and designing the study, reviewed the data analyses, reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest

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References


