Progressive Hearing Loss among Patients with Cystic Fibrosis and Parenteral Aminoglycoside Treatment

Erika M. Zettner, PhD, CCC-A and Malcolm A. Gleser, MD, PhD

Abstract

Objective. Hearing loss is a significant and growing problem as patients with cystic fibrosis (CF) live longer and experience frequent courses of intravenous aminoglycoside antibiotics (hereafter, “IVs”). This study seeks to document that risk in a large adult population with CF, accounting for age and aminoglycoside exposure.

Study Design. Retrospective case review of patients with CF who had multiple audiograms over years.

Setting. Tertiary care cystic fibrosis setting.

Subject and Methods. The first and last audiograms recorded over a 10-year period were compared for 165 adult patients with CF. Patients were divided into 3 study groups: 34 patients with no intervening aminoglycoside IVs (0 IVs), 103 patients with 1 to 9 IVs, and 28 patients with ≥10 IVs. Threshold shift (TS) between the audiograms were examined for the 3 groups before and after age/sex adjustments. Two new hearing loss metrics were tested.

Results. At first examination, 48% of patients (average age, 30.0 years) already had hearing loss. At last examination (average, 4.4 years later), 64% of the patients had hearing loss even with age/sex adjustment. Use of the age/sex hearing threshold adjustment eliminated the TS in the 0 IVs group. Two new metrics calculated for each patient demonstrated that 48% of patients who had 1 to 9 IVs had ototoxic scores, while almost 80% of the ≥10 IV group had ototoxic scores.

Conclusion. The majority of adult patients with CF are (often repeatedly) exposed to parenteral aminoglycoside (AG) therapy and lose hearing at a rate that far exceeds that predicted from aging alone.

Keywords

ototoxicity, aminoglycoside, hearing loss, audiogram, cystic fibrosis

Patients with cystic fibrosis (CF) are living longer. Although inhaled tobramycin and oral antibiotics have diminished the use of parenteral aminoglycoside (AG) therapy among younger patients with CF, adult patients with CF receive an average of 1 parenteral AG treatment per year. Does the longer life span and cumulative AG therapy presage increased hearing loss?

Whereas the incidence of hearing loss in patients undergoing short courses of AG therapy (<3 weeks) is up to 20%,¹-⁴ hearing loss is even more common with longer-duration therapy. In South Africa and Iran, as many as 60% of patients with multiple drug-resistant tuberculosis develop hearing loss.⁵-⁷ Patients with nontuberculosis Mycobacterium, treated for up to 3 months with amikacin, have a 35% incidence of inner-ear issues, some requiring cessation of therapy.⁸

There is substantial variability in the reported prevalence of AG-related hearing loss among patients with CF, likely due to the population studied and the measurements employed. Almost all studies are retrospective. The majority report hearing loss as a comparison with a normal baseline, as opposed to a threshold shift (TS) of the patient’s own baseline. Table 1 summarizes the studies of the effects of parenteral AGs on hearing that are most commonly referenced in the literature. Several state that AGs have no effect or a minimal effect, while others show that up to 56% of patients have hearing loss, presumably at least partially as a result of cumulative parenteral AG treatments. Of the studies that compare the audiograms of patients with CF against normal baseline, the majority were done among young patients, typically defining hearing loss as a hearing threshold ≥25 dB HL at a single frequency or ≥15 dB HL at multiple adjacent frequencies. Those that tested only standard frequencies (0.25-8.0 kHz) found much less hearing loss than those that tested standard and extended frequencies (9.0-20.0 kHz).

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Otitotoxicity</th>
<th>Hearing Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Department of Surgery, University of California San Diego, La Jolla, California, USA</td>
<td>48%</td>
<td>64%</td>
</tr>
<tr>
<td>2CEO Oricula Therapeutics LLC, Seattle, Washington, USA</td>
<td>48%</td>
<td>80%</td>
</tr>
</tbody>
</table>

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Three studies tested the TS between the patient’s baseline and the test audiogram, usually with 1 intervening AG treatment administered intravenously (hereafter, “1 IV”). Of these, Pedersen et al9 and Scheenstra et al10 had small study populations (38 and 19 patients, respectively) and tested the patients on the final day of AG administration, rather than waiting longer for hearing loss to appear. Pedersen et al showed significant TSs only in the extended frequency range, whereas Scheenstra et al showed no significant TSs across all frequencies. In the largest prospective study, Mulheran et al11 reported on TSs observed at the end of therapy and 6 weeks later but found no significant changes in hearing at either time point; however, a selection criterion for this study was the absence of hearing loss in the baseline audiogram. Our findings suggest that patients who have experienced previous hearing loss with AG therapy are more likely to experience additional hearing loss with subsequent treatments.

The University of California San Diego (UCSD) has a database of sequential audiograms from 200 adult patients with CF captured over a 12-year period. Our goal was to determine the absolute amount of hearing loss as compared with normal baseline and the hearing TSs over the years and correlate these to the number of courses of parenteral AG therapy in between. To our knowledge, this is the largest study of hearing progression among adult patients with CF and the only such study that tracks hearing (loss) over years. Because of the age of our patients (18-73 years), we employed a new age/sex adjustment to not overstate hearing loss or TSs over extended times. To better compare large patient groups with varying baseline hearing, we suggest 2 new continuous metrics of hearing loss closely associated with the American Speech-Language-Hearing Association (ASHA) criteria for ototoxicity.

### Materials and Methods

#### Participant Selection

The UCSD Adult Cystic Fibrosis Clinic Team follows >200 adult patients with CF. The audiology staff has monitored the hearing of these patients over the last 12 years. This study was approved by the UCSD Institution Review Board (No. 170872).

In general, UCSD physicians use tobramycin as the parenteral AG of choice to treat adult patients with CF with...
Pseudomonas lung infections. The history of IV therapy was obtained from the Cystic Fibrosis Foundation Patient Registry and later confirmed by UCSD electronic medical records. Patients not registered in the registry or who did not have at least 2 extended frequency audiograms were eliminated from this study, leaving 165 patients (84 men and 81 women) as the study group. The mean ± SD age was 30.0 ± 10.8 years at first audiogram and 34.4 ± 11.1 years at final audiogram. The study group was divided into 3 groups: 34 patients with no IV AGs between audiograms (0 IVs), 103 patients with 1 to 9 IVs, and 28 patients who had ≥10 IVs. The group with ≥10 IVs was chosen because of the many literature references indicating that such patients have significantly more hearing loss.

Pure Tone Audiometry

Equipment. An Equinox 2.0 computer-based clinical audiometer was calibrated to ANSI S3.6-1996 standards with either Telephonics TDH-39 supra-aural headphones to deliver tones at 0.25 to 8.0 Hz or Sennheiser HDA 200 circumaural phones for 8.0 to 16.0 kHz. Beginning in 2011, circumaural phones were calibrated and used for all frequencies from 1.0 to 16.0 kHz. When the 8.0-kHz frequency was recorded with both the TDH and the HDA, the HDA measurement was used. To comply with UCSD infection control requirements of patients with CF not occupying the same room in a 36-hour period and to test up to 8 patients per clinic session, testing was completed in a quiet examination room. Because of ambient noise levels, 0.25 and 0.5 kHz were not tested or included in our analyses.

Procedures. Testing was done according to standard audiological procedures for threshold determination by a licensed clinical audiologist or supervised second-year doctoral students. Clear ear canals and intact tympanic membrane were established with otoscopy. To streamline testing for the team-clinic environment, the sensitive region of ototoxicity was used to define each patient’s test frequency range for monitoring, which consisted of only a portion of the standard frequencies and extended frequencies. The Hughson-Westlake ascending threshold search technique was used to determine pure tone air conduction thresholds for the sensitive region of ototoxicity.

Definitions

Standard frequency: the frequency range between 200 and 8000 Hz.

Extended frequency: the frequency range between 8000 and 20,000 Hz.

Threshold: the lowest sound level where responses occurred in at least one-half of a series of ascending trials, with a minimum of 2 of 3 presentations at a single level. These methods are standard of care meeting current ASHA guidelines (2005).

Hearing threshold measured in decibels: adjusted to a baseline such that 0 dB HL is the average sound level that is just distinguished—a common scale that adjusts sound pressure levels in decibels nominally generated by the audiometer, by subtracting a given dB number for each frequency to produce a median value of 0 HL dB for young adults with normal hearing.

Adjusted hearing thresholds: dB HL adjusted for age and sex.

Hearing loss: a hearing threshold ≥25 dB HL at any frequency in either ear.

TS: the dB difference obtained by subtracting the baseline threshold from the follow-up threshold for any specific pure tone frequency.

Ototoxicity: The ASHA standard (1994) for identifying ototoxicity with the criteria for serial audiograms dictates a ≥20-dB TS at (at least) 1 frequency or a ≥10-dB TS at 2 consecutive (adjacent) test frequencies. TS should be confirmed by a repeat audiogram to confirm that the TS is not temporary. A third criterion for an ototoxic shift—that is, a loss of response at 3 frequencies at which a response was previously recorded—was not examined in this study.

Study Data

The following data were collected for each audiogram comparison:

- Date of birth, sex, and age at the date of the follow-up study
- Days between audiograms
- The baseline and follow-up audiogram thresholds (dB HL) on both ears. (When no response was obtained at a particular frequency at the limits of the equipment, threshold was reported as the maximum output plus 5 dB.)
- The calculated TS for each ear for each frequency. (If either of the audiograms had a missing measurement at a given frequency, the TS was “undefined” and not used in any of the averages or standard errors.) Because this was a retrospective study, TS in the ototoxic range could not be confirmed by a repeat audiogram.
- For each ear, the largest TS for any frequency, termed the maximal single-frequency TS (MSFTS), and the largest average value of the TS of any adjacent 2 frequencies, termed the maximal adjacent-frequency TS (MAFTS), were identified. These continuous variables are derived from the ASHA (1994) standard for identifying ototoxicity. A MSFTS ≥20 dB would meet ASHA’s first definition of ototoxicity. A MAFTS ≥15 ensures that 1 TS is ≥20 or both are ≥10 dB. Therefore, a MAFTS score ≥15 dB is used here as a conservative definition of ototoxicity. MAFTS and MSFTS can be used as hearing loss metrics to compare...
groups of patients without regard to an arbitrary cutoff level of “ototoxicity.”

Age/Sex Adjustment

Hearing thresholds increase with age, and the increase is frequency dependent. To account for hearing change due to aging, the hearing thresholds used in this study were corrected with statistically derived median threshold deviations up to 12.5 kHz for otologically normal persons, with age- and sex-specific equations published in ISO-7029 (2017). In addition, Valiente et al.15 published comparable normative data for extended-frequency hearing thresholds across age groups, which were used to correct for age at 14.0 and 16.0 kHz. The ISO-7029 corrections account for the differences of hearing changes in males versus females with age, whereas the Valiente data did not apply sex-specific adjustments. Of course, lifestyle differences between the ontologically normal normative subjects and patients with CF could lead to some systematic differences in hearing loss, which would be hard to identify. The age/sex corrections range between 0 and 10 dB (at increasing frequencies) for a 30-year-old and between 13 and 76 dB for a 70-year-old.

Statistical Analyses

A repeated-measures analysis of variance tested differences between baseline thresholds and second-test thresholds. A multiple linear regression was used to test the contribution of age at first audiogram, age at last audiogram, time between audiograms, sex, and number of IVs between audiograms as predictors of the MAFTS metric. A P value <.05 was considered significant.

Results

Figure 1 provides 2 graphs summarizing the audiogram data from all study patients. In each graph, the thresholds from the first audiogram are averaged for all 165 patients. Also shown are the averaged last threshold for the 3 subgroups: 0, 1-9, and ≥10 IVs. On the left, the threshold data are presented as unadjusted threshold measurements (dB HL). On the right, the individual threshold data were adjusted for the patient’s age and sex as of the date of the audiogram. The effect of the age/sex adjustment was to move the mean thresholds toward 0, especially at higher frequencies, eliminating much of the TS. There remains a loss of almost 10 dB across the frequency range on the first audiogram for the entire group of study patients, perhaps because many have had AG therapy prior to their first audiogram (obtained in this study).

Table 2 presents the percentage of patients with hearing loss at the first audiogram (a threshold ≥25 dB HL) obtained by inspecting left and right ear thresholds across frequency as done by Garinis et al.16 Based on the unadjusted data across all frequencies, 59% of patients could be classified as having hearing loss, while 48% would qualify after the age/sex adjustment. Scanning only the standard frequencies, 30% of patients had hearing loss with unadjusted thresholds, while 22% of patients had adjusted hearing loss.

For the 0 IVs group, the time between the first audiogram and the last averaged 2.8 years. On the left in Figure 1, there is a small increase in hearing thresholds between the first audiograms of all 165 patients and the last for those with 0 IVs, which was not statistically significant per repeated-measures analysis of variance for any frequency (Table 3). On the right, the 0 IVs group thresholds were adjusted for age/sex, removing even the small difference
between audiograms and confirming that the age/sex hearing threshold adjustment works well. The patients in the 1-9 IVs group had statistically significant differences in thresholds at 12,500, 14,000, and 16,000 Hz, although only 16,000 Hz remained significantly different after the age/sex threshold adjustment. For the /C21 10 IVs group, thresholds were significantly different at 8000 to 16,000 Hz even after age/sex adjustments. There was a longer time between the first and last audiograms, with the 1-9 IVs group averaging 4.6 years and the /C21 10 IVs group averaging 6.1 years; however, a linear regression of the age/sex-adjusted TS did not detect “time between audiograms” as being significant in predicting the MAFTS score when number of IVs was also included as an independent variable.

Table 4 provides a classic method of looking at the same data. It shows the mean TS of the age/sex-adjusted threshold, the count of TS ≥20 dB, and the percentage of TS ≥20 dB for each frequency of the first and last audiograms broken down by patient group. The right ear was chosen arbitrarily for analyses. On the average, there was essentially no TS for the 0 IVs group. The TSs were not statistically significant at any frequency. In the 1-9 IVs group, 5% to 15% of patients had TS ≥20-dB at individual frequencies ≥8.0 kHz, but only at 16.0 kHz was the TS statistically significant (P < .04). In contrast, 25% to 39% of the ≥10 IVs group experienced a significant (P < .02) TS ≥20 dB at 8000 to 16,000 Hz.

By looking at TS at specific frequencies, one can easily miss the big picture. The new metrics (MSFTS and MAFTS) reveal a truer picture of ototoxicity. Table 5 shows how the new scores performed for identifying the effects of intervening IV AGs on the TS between the first and last audiograms. For the worse ear, even in the 0 IVs group, both scores demonstrated that between 24% and 29% of patients could be classified as having a TS consistent with ototoxicity. Also, both scores demonstrate that the 1-9 IVs group had high percentage of apparent ototoxicity, with between 48% and 51% of patients meeting the ASHA definition by the MSFTS or MAFTS scale. Based on the MAFTS or MSFTS, the ≥10 IVs group showed remarkable 75% to 79% scores consistent with ototoxicity. Not only did a higher proportion of patients in the IV groups have ototoxicity, but the amount of TS increased with increasing exposure. A multiple linear regression was applied to determine which variables were associated with the MAFTS score. Age at first audiogram, age at last audiogram, time between audiograms, and sex were not predictive (P > .25 for each). Number of IVs was significant at P < 6 × 10^{-10}.

Discussion

Forty-eight percent of adult patients with CF (age, 30 ± 10.8 years) already had hearing loss at the first audiogram (a threshold ≥25 dB HL), as obtained by inspection of the left and right ear thresholds across frequencies, even after
age/sex adjustment. But on average, those not exposed to additional AG IVs had no significant progression of hearing loss in the interval before their next audiogram (averaging 2.8 years). In contrast, over a period of 4.4 years, approximately 55% of those who did receive AG IVs suffered decrements in hearing thresholds meeting and exceeding the ASHA definition of ototoxicity, while 75% of patients who received ≥10 IVs had such TSs and lost hearing into the speech recognition frequency ranges.

At the time of the first audiogram, the average age of the patients with CF in this study was 30 years. Most patients had previous exposure to IV AGs. Perhaps that partly explains why there is a shift from normal baselines for these patients. The use of the age/sex adjustment eliminates part of that TS, but still 48% of patients met the definition of hearing loss. (If only the standard frequency range was examined, 22% of the patients would be classified as having hearing loss.) By an average of 4.4 years later, fully 64% of patients who received ≥10 IVs had such TSs and lost hearing into the speech recognition frequency ranges.

Comparing the first and last audiograms uses the patient as one’s own control and gives a clear view of hearing loss progression. Applying the sex/sex adjustment eliminates that part of the TS that we all experience with aging. As expected, patients with no intervening IVs mostly exhibited stable hearing over the 2.8 years between audiograms, whereas patients with 1 to 9 IVs exhibited a mean 5.2-dB shift in hearing between 8.0 and 16.0 kHz. Patients exposed to ≥10 IVs exhibited a mean 16.5-dB TS between 8.0 and 16.0 kHz. Individually, many patients exhibited more TS than what might be revealed by averaging changes at specific frequencies. Because the frequencies where hearing loss occurred were inconsistent across patients, much of the evidence of hearing loss averaged out. Two new scores, MSFTS and MAFTS, revealed that far more patients experienced significant TSs between audiograms. These scores identify TSs wherever they occur in the recorded frequency range. Based on the MAFTS, 48% of patients treated with 1 to 9 IVs over a 4-year period demonstrated clinically testing 9000 to 16,000 Hz, not all clinics are so equipped. Clinics caring for individuals at risk for ototoxicity should consider investing in audiometers with high-frequency test capability; additional headphones (eg, Sennheiser HDA 200) are needed to assess these higher frequencies, which typically require fewer than 3 to 5 minutes of additional test time.

One limitation of this study was the lack of results from a word recognition test, which provides a basic measure of the functional impact of hearing loss. Because ototoxic monitoring programs typically focus on change in thresholds as a metric of significant ototoxicity, word recognition is not monitored on a regular basis. Future studies should focus on the functional impact of ototoxicity by including some measure of speech perception in quiet as well as in noise.

### Table 4. Mean TS between the First and Last Audiogram and Patients with ≥20-dB TS (Age and Sex Adjusted) in the Right Ear by Study Group.

<table>
<thead>
<tr>
<th>Group: Measure</th>
<th>Sound Frequency, kHz</th>
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<tbody>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>0 IVs</td>
<td>Mean TS, dB</td>
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<tr>
<td></td>
<td>≥20 dB, n</td>
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<td></td>
<td>≥20 dB, %</td>
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<tr>
<td>1-9 IVs</td>
<td>Mean TS, dB</td>
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<td>≥20 dB, n</td>
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<tr>
<td>≥10 IVs</td>
<td>Mean TS, dB</td>
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<td></td>
<td>≥20 dB, n</td>
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<tr>
<td></td>
<td>≥20 dB, %</td>
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</tbody>
</table>

**Abbreviations:** IV, intravenous treatment; TS, threshold shift.
significant ototoxicity, while >75% of patients treated with ≥10 IVs exhibited ototoxicity. Clearly, patients with CF receiving parenteral AG therapy continue to lose hearing at a rate that far exceeds that predicted from aging alone.

Acknowledgment
We acknowledge the suggestion of Edwin Rubel of the Virginia Bloedel Hearing Research Center, University of Washington, to apply an age adjustment to the audiogram results. We also acknowledge the UCSD Adult Cystic Fibrosis Clinic Team for its commitment to the hearing health care of its patients.

Author Contributions
Malcolm A. Gleser, design, drafting, approval, and accountable; Erika M. Zettner, design, drafting, approval, and accountable.

Disclosures
Competing interests: Malcolm A. Gleser, employment at Oricula.
Sponsorships: None.
Funding source: None.

References


