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Hearing loss perception in adults with cystic fibrosis

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HEARING LOSS PERCEPTION IN ADULTS WITH CYSTIC FIBROSIS

by

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Abstract: Assess the validation in perception of hearing loss in adults with cystic fibrosis using the Hearing Handicap Inventory for Adults questionnaire, a full audiological examination and affects of aminoglycosides.

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LIST OF ABBREVIATIONS

AGs	Aminoglycosides
ART	Acoustic Reflex Threshold
CF	Cystic Fibrosis
dB HL	Hearing Level in Decibels
dB SL	Sensation Level in Decibels
HF	High Frequency
HHIA	Hearing Handicap Inventory for Adults Questionnaire
HHIA-S	Hearing Handicap Inventory for Adults – Screening Questionnaire
HHIE	Hearing Handicap Inventory for Elderly Questionnaire
HRPO	Human Research Protection Office
IRB	Institutional Review Board
Hz	Hertz
IV	Intravenous (therapy)
kHz	Kilohertz
MLV	Monitored Live Voice
NBN	Narrow Band Noise
NU-6	Northwestern University Test Number 6
PI	Personal Investigator
PTA	Pure-tone Air Conduction Average
SNHL	Sensorineural Hearing Loss
SRT	Speech Recognition Threshold
WRS	Word Recognition Score

INTRODUCTION AND LITERATURE REVIEW

History

Cystic Fibrosis (CF) is an inherited disease and affects mostly the respiratory and digestive system, causing increased viscosity of the secretions in the lungs and the pancreas, thus reducing life expectancy (Davis, 2006). Symptoms of CF have been documented as early as 3,000 BC (Busch, 1990); however, the entire spectrum of CF was not recognized and well documented until the 1930s. In 1936, a Swiss pediatrician named the illness "celiac syndrome", and defined it as changes in the pancreas and bronchiectasis as observed in children (Fanconi, Uehlinger & Knauer, 1936). The disease was characterized by malabsorption of fat and protein, steatorrhea, growth failure, and pulmonary infection. Then in 1938 an American pathologist, Dr. Dorothy Andersen, described the illness in the medical literature as "cystic fibrosis of the pancreas", after performing numerous autopsies on patients with this issue (Anderson, 1938). It was due to her efforts that it was identified as a distinct clinical entity and identified as familial in nature. Prior to this many cases of CF in general pediatrics were misdiagnosed as whooping cough, chronic bronchitis, or pneumonia. When this was identified as a pathologic diagnosis, life expectancy was approximately six months. It was theorized that CF was an autosomal recessive disease believed to arise from abnormal mucus plugging of the exocrine ducts and death often occurred from lung infection (Davis, 2006). Studies mainly focused on abnormalities in mucus however, later in 1948 it was noted that many of the infants with CF presented with heat prostration (excessive sodium and chloride concentration in sweat), which offered a convenient diagnostic sweat test that is still used today (Davis, 2006). In the mid-1950's, patients with CF began to assemble into centers for care for physicians to become familiar with clinical manifestations of the disease and gained experience with treatment.

Matthews and colleagues (1964) established three pillars of treatment: nutritional repletion (pancreatic enzyme supplements); relief of airway obstruction (postural drainage and clapping); and antibiotic therapy of the lung infection (e.g., oral, intravenous). In the late 1980s, another breakthrough occurred which was the identifying of the CF gene (Knowles et al, 1983; Boucher, Stuffts, Knowles, Cantley, & Gatzy, 1986; Kerem et al, 1989). The diagnosis could then be made by direct identification of two mutant CF alleles (*CFTR*, CF transmembrane conductance regulator protein) in a cAMP-regulated chloride channel, which lead to more possibilities of gene replacement therapies as part of the treatment for CF (Gibson, Burns & Ramsey, 2003).

Current

Substantial advances in basic and clinical research catalyzed therapeutic improvements due to earlier diagnosis through screening. Better treatment and access to health care have improved care and treatments of patients with CF. In America, approximately 30,000 people are living with CF as of 2013, with half the population being 18 years or older (Cystic Fibrosis Foundation Patient Registry, 2013). By obtaining a better understanding of the disease and through improving treatment options, life expectancy has been increasing continuously over the past 20 years. The prognosis for CF has improved dramatically from about six months to the median survival age to now exceeding more than 35 years today (FitzSimmons, 1993; Davis, 2006; Cystic Fibrosis Foundation Patient Registry, 2013; MacKenzie et al, 2014). As of this time there is still no known cure for CF, but aggressive management and treatment can ease these symptoms and reduce complications. CF requires an intensive, time-consuming treatment of various therapies, such as gene therapy, protein modulation, rehydration of airway surface and/or mucolytics, anti-inflammatories, and anti-infective agents (Davies, Ebdon & Orchard, 2014), which provides an individual with CF to live a fuller life less encumbered by their

condition.

One of the known therapies to assist with cystic fibrosis is the use of aminoglycoside (AGs) antibiotics. Since their introduction in 1944, multiple AG preparations have become available, including gentamycin and tobramycin, and are often used when serious *Pseudomonas aeruginosa* infections are treated (Flume et al, 2009; Ruhl, Cable & Martell, 2014). As CF patients are prone to developing infections of the pulmonary and sinonasal systems, AG antibiotics have a role in the management of exacerbations, maintenance therapy after acquisition of *Pseudomonas aeruginosa* and its eradication (Prayle & Smyth, 2010; Davies et al, 2014). AG antibiotics, mainly tobramycin, are used as regular treatments for some patients with CF. This class of antibiotic has concentration-dependent effects on bacteria (i.e., increased killing as concentrations are increased), suggesting there is greater efficacy at higher concentrations (McKinnon & Davis, 2004), although the optimum concentration for treatment of lung infections in CF has not been established. AGs may be administered intravenously or by inhalation of a nebulized solution. Both approaches aim to maximize AG delivery to the airways, the site of chronic infection, usually dosed according to body weight or surface area, and serum levels guide subsequent doses in a course. Inhaled therapy delivers AGs directly to the site of infection whereas intravenous doses achieve lower airway concentrations, but deliver the medication to poorly ventilated lung regions (Prayle & Smyth, 2010). It is reported that the use of AG ototoxicity may range between 60 to 85% of the population (Cystic Fibrosis Foundation, 2013; Prescott, 2014). Typically patients with CF will be on a regimen of using inhaled tobramycin daily for a cycle of 28 days then it will be discontinued for a cycle of another 28 days. When tobramycin is used in this fashion many patients with CF will be utilizing this medication for many years. In addition to this many patients with CF will also receive the

medication intravenously when admitted to the hospital.

Tobramycin is a bactericidal antibiotic that may adversely affect renal and cochleovestibular systems however; no clear correlation exists between degree of nephrotoxicity and ototoxicity (Henley & Schacht, 1988; Sone, Schachern & Paparella, 1998; Mulheran, Degg, Burr, Morgan & Stableforth, 2001). Cochlear toxicity that results in hearing loss usually begins in the high-frequencies and is secondary to irreversible destruction of outer hair cells in the organ of Corti, predominantly at the basal turn of the cochlea. The exact mechanism of tobramycin ototoxicity remains unknown however, many cellular processes have been implicated, and this continues to be an active area of research (Gonzalez-Garrido, Vega, Mercado, Lopez & Soto, 2015).

There is a need to consider the benefit of the tobramycin treatment and its potential for serious toxicity (Phillips & Bell, 2001; Al-Aloul et al, 2005; Glass, Plant & Spencer, 2005). Patients with CF are particularly susceptible to side effects from exposure to usage of tobramycin and their ototoxicity, but whether or not the potential risk of hearing loss is associated is imperative. In the CF population, tobramycin has been shown to cause renal, nephrotoxicity and ototoxicity (McCracken, 1986; Munckhof, Grayson & Turnidge, 1996; Forge & Schacht, 2000; Nakashima, Teranishi, Hibi, & Kobayashi, 2000; Schacht, Talaska & Ryback, 2012; Huth et al, 2015), particularly when used for long and repeated courses (Sone et al, 1998; Phillips & Bell, 2001). It has also been shown that tobramycin ototoxicity is associated with the likelihood to occur with larger doses, higher blood levels, or longer duration of therapy (Mulheran et al, 2001; Prayle & Smyth, 2010; Ruhl et al, 2014). Specifically, a recent article estimated that approximately 7% of all patients with cystic fibrosis exposed to tobramycin experience some form of cochleotoxicity, although there is significant uncertainty associated with the risk, with a

range of reported values from 0% to 16% (Mulheran et al, 2001).

More research have focused on prevalence of sensorineural hearing loss (SNHL) in CF pediatric patients and its relationship to antibiotic use, however, research still varies in adults with CF. Clinical assessment of these patients through pure-tone audiometry and brainstem evoked response audiometry shows a prevalence of SNHL ranging from 0% to 17% of the CF pediatric population (Haddad, Gonzalez, Kurland, Orenstein & Casselbrant, 1994; Ozcelik et al, 1996; Jorrisen, Boeck & Feenstra, 1998; Mulheran & Degg, 1997; Mulheran et al, 2001; Cheng et al, 2009; Piltcher, Teixeira, Oliveira, Scattolin & Piltcher, 2003) and the adult population (Kimberley, Brown & Eggermont, 1993; Mulheran et al, 2001; Suryanarayanan, Taylor & Tan, 2005). In opposition, studies have found no significant hearing loss in patients with CF, even after an average of four repeated courses of tobramycin (Pedersen, Jensen, Osterhammel & Osterhammel, 1987; Mulheran et al, 2001; Scheenstra, Heijerman, Zuur, Touw, & Rijntjes, 2010) or after single courses (Mulheran et al, 2006; Martins, Camargos, Becker, Becker & Guimarães, 2010). It is typically seen and recommended across various publications of the use of once-daily dosing to achieve optimal levels for efficacy while reducing the risk of toxicity (Soulsby, Bell, Greville & Doecke, 2009; Smyth, 2010).

Due to the ototoxic effects of tobramycin it is recommended that ototoxic monitoring be performed on patients with CF. Although assessing hearing acuity in the frequency range from .25 to 8 kHz has become routine clinical practice, evaluating hearing sensitivity beyond 8 kHz is necessary when monitoring hearing patients with CF that are receiving ototoxic medication(s). High-frequency pure-tone audiometry is the most common method for assessing ototoxicity as it begins to cause hearing loss at higher frequencies (i.e., 10, 12, 14, 16, 18, and 20 kHz). It is known that these ultra high-frequencies are affected earlier than conventional frequencies due to

exposure to ototoxicity (Fausti et al, 1999; Fausti et al, 1992). Therefore, high-frequency pure-tone audiometry is a useful tool to detect hearing damage at the earliest possible time. The early detection of hearing damage not only warns clinicians to the status of the auditory insult but also provides an opportunity for them to balance the therapeutic effects of drugs with the risks of permanent hearing loss. It is recommended that patients receiving ototoxic medication have hearing evaluations weekly to monitor the potential ototoxic effects of medication (ASHA, 1994; AAA, 2009). However, as patients with CF receive treatments daily, every other month for years it may not be feasible to monitor hearing weekly to determine hearing threshold shift. Currently there is no other standard to potentially monitor hearing. The question then arises as to whether or not there is a less time consuming option for the assessment of hearing on individuals that may be relatively accurate in predicting and/or detecting early hearing loss.

Self-assessment tools have been developed to quantify patient's subjective perceptions of their hearing handicap regarding communication difficulties and their subsequent social and emotional consequences. Some of the most common subjective questionnaires used today include the original and screening versions of the Hearing Handicap Inventory for Adults (HHIA) (Newman, Weinstein, Jacobson & Hug, 1990), and the Hearing Handicap Inventory for the Elderly (HHIE) (Newman & Weinstein, 1988), which both provide individual's subjective impressions of their hearing status. The HHIE (used for adults over 64 years of age) and the HHIA (later modified to be used for adults less than 65 years of age) have demonstrated to be useful tools to quantify consequences of hearing loss for those with a hearing impairment (Newman & Weinstein, 1988; Newman, Weinstein, Jacobson & Hug, 1991). The HHIA original (25 items) and screening (10 items) versions have high internal consistency of its questions, test-retest reliability and low standard error (Newman et al, 1991; Newman et al, 1990; Aiello, de

Lima & Ferrari, 2011; Wolters, Johnson & Isaac, 2011). Such items cover various situations where a hearing problem might cause difficulties or embarrassment, as shown in Appendix A, with three possible answers to each item (i.e., 'yes', 'sometimes' and 'no'). This tool can be worthwhile additions to the audiologists and other professionals' (e.g., physicians, primary care) test battery as information obtained from the responses can help substantiate patient's hearing complaints not readily apparent. By results of conventional audiometric testing for example, this may facilitate decisions regarding candidacy for amplification, assist in a counseling process, serve as a guide designing a client-centered rehabilitation program and serve as a criterion measure in documenting the effects of rehabilitation efforts, including hearing aid benefit. It can also be used to better identify those that may be in need of a full audiometric evaluation, especially where a hearing test cannot be administered in person in other health clinics.

There's limited research in using subjective tools by other medical professionals other than audiologists for other health conditions that can be at risk of hearing loss, such as adults with cystic fibrosis. Other common medical areas regarding ear related issues include tumors, traumatic injuries, autoimmune inner ear disease etc., however whether subjective tools express patients' concerns of any hearing disabilities is rare as these medical areas are addressing more severe concerns of first priority. Such tools can be used in studies and other medical clinics where a hearing test cannot be administered in person to detect patients who might display possible hearing difficulties.

The present study aimed to verify the prevalence of SNHL in patients with CF using the HHIA and HHIA-S questionnaires, and a comprehensive audiological evaluation to assess its association with the use of AGs. Specifically, three questions were examined:

1. If there is a difference between the original version (HHIA) and screening version (HHIA-S) self-report questionnaires when administered to patients with CF.
2. Whether the HHIA and/or HHIA-S could be used to detect any hearing perception difficulties in adult patients with CF.
3. If any factors related to aminoglycoside usage affects how patients with CF subjectively perceive having any hearing loss or objectively show affected audiological results.

METHODOLOGY

Participants

47 participants were recruited from Washington University in St. Louis School of Medicine's (WUSM) Center for Advanced Medicine at the Adult Cystic Fibrosis Clinic in the Division of Pulmonary and Critical Care Medicine via either a telephone script or flyer approved by the Human Research Protection Office (HRPO). Using *a priori* power analysis and sample size calculation utilizing G-Power 3.1.9.2 (http://mac. softpedia.com/get/Math-Scientific/G-Power.shtml) calculated that 94 participants were needed to investigate differences in subjective responses to hearing perception and results from the audiological evaluation testing (comparing normal to mild hearing loss). The calculation was completed using a two-tailed test, alpha level of 0.05, and power of 0.80. Due to limited time constraint of this study and lack of awareness in patients with CF and varying hearing loss, the number of participants needed couldn't be achieved to have high statistical power.

Each participant signed an informed consent form approved by HRPO's Institutional Review Board (IRB) at the initial visit. For every participant, each testing session took

approximately one hour or less. No compensation was provided and testing was only performed on a voluntary basis.

The database used for the current study was de-identified, as to eliminate the possibility of participant identification from data included within the database. In order to qualify for entrance of the study, each participant was required to (a) be between the ages of 18 and 55 years; (b) be medically diagnosed with CF; (c) have not had any surgical procedures to their ears; (d) be cleared via ear otoscopic examination bilaterally as to not have any potential causes of sound blockage. Two participants were dropped from the study; one because he/she did not fit the inclusion criteria (i.e., history of ear surgery), and the other did not complete the second half of the study (i.e., audiological examination). Therefore, 45 participants were included for data analysis.

This study required one visitation at the Vision and Hearing Center located at the Center for Advanced Medicine where the Primary Investigator (PI) and the PI's advisor evaluated participants. Participants were seated in a double-walled sound-treated booth. The audiology equipment is calibrated annually following American National Standards Institute (ANSI, 2004b) and quarterly by the audiology faculty. A case history was taken to collect demographic information. Example responses included any usage of tobramycin AG antibiotics via intravenous (IV) therapy and/or inhaler, duration of use of the medication and other factors related to ear problems (i.e., tinnitus, pressure, otalgia, dizziness, family history of hearing loss, and noise exposure). Otoscopy was completed to ensure the ear canals were clear bilaterally.

HHIA & HHIA-S

The HHIA is a 25-item, self-assessment scale composed of 13-item emotional and 12-item social/situational subscales (Appendix A) that was administered to each participant. The

HHIA-S contains 10 items, five emotional and five social/situational, selected from the 25-item version of the HHIA. The items comprising the HHIA-S are denoted with an asterisk (*), as seen in Appendix A. Example items exhibiting as emotional scenarios include, *Does a hearing problem cause you to feel embarrassed when meeting new people?* and *Do you feel handicapped by a hearing problem?* Example items exhibiting as social/situational scenarios include, *Does a hearing problem cause you difficulty in the movies or theater?* and *Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?* For both scales, a "yes" response to an item was given four points, "sometimes" of two points, and "no" response of zero points. Scores for the total HHIA range from 0 to 100, with categorical ranges of 0 to 20 having *no handicap*, 22 to 60 having *mild to moderate handicap*, and 62 to 100 having *severe handicap*. Scores for the total HHIA-S range from 0 to 40, with categorical ranges of 0 to 8 having *no handicap*, 10 to 24 having *mild to moderate handicap*, and 26 to 40 having *severe handicap*. Higher score values indicate greater perceived handicap in hearing. HHIA-S scores were determined by extracting responses of the appropriate 10 items from the longer version. Both questionnaires evaluated the total scores, and subtotal scores representing only emotional items and only social/situational items. If the total scores fall in the handicap range (i.e., *Mild to Moderate Handicap*, or *Severe Handicap*) of severities of subjectively perceiving hearing loss, this could be a possible indication that the patient should be referred for an audiological evaluation, however no studies used specific cut-offs for patient medical referral.

All participants received in-person administration of the HHIA before the audiologic evaluation, allowing privacy to complete each item. Each participant responded to each item, and once finished, the HHIA was collected and not scored until after the entire test session.

Audiologic Evaluation

Prior to testing, each participant underwent otoscopic examination with a standard otoscope utilized to view each ear canal and tympanic membrane (eardrum). Any abnormalities that could potentially affect test results or prevent sound passing through the ear(s), such as cerumen and/or debris impaction, absent or abnormal visual of the eardrum, or other obstructions were not further tested and excluded from the study.

A comprehensive audiologic evaluation was performed on each participant in a sound-treated booth using the protocols from the Adult Division of Audiology clinic using the Grason Stadler GSI-61 audiometer (ANSI, 2004a). Conventional pure-tone air-conduction (pulsed tones) was measured per ear using TDH-50P Telephonic supra-aural headphones at octave and mid-octave interval frequencies (i.e., .25, .5, 1, 2, 3, 4, 5, and 8 kHz) to determine the participant's thresholds (softest hearing level). Pure-tone bone-conduction (pulsed tones) was measured per ear using a bone oscillator at each standard and octave frequency (i.e., .25, .5, 1, 2, 3, and 4 kHz) to determine the participant's thresholds. If there was a significant difference between right and left ear thresholds (≥40 dB HL) at the same frequency, a masking procedure took place to separate the two ears, acoustically, using narrow band noise (NBN) to determine accurate thresholds. Thresholds for pure-tone air-conduction and bone-conduction of 15 dB HL or less indicated normal hearing, 16 to 25 dB HL indicated sight hearing loss, 26 to 40 dB HL indicated mild hearing loss, 41 to 55 dB HL indicated moderate hearing loss, 56 to 70 dB HL indicated moderately-severe hearing loss, 71 to 90 dB HL indicated severe hearing loss, and 91 dB HL and above indicated profound hearing loss. To determine type of hearing loss, an air-bone gap (ABG) difference of more than 10 dB HL indicated a conductive hearing loss, an ABG difference of less than or equal to 10 dB HL indicated a sensorineural hearing loss, and a combination of conductive and sensorineural indicated a mixed hearing loss.

Speech recognition thresholds (SRTs) were determined at the softest level of intensity (dB HL) using monitored live voice (MLV) (with voice peaking at 0 dB on the VU meter) at which familiar two-syllable spondee words (e.g., “baseball”, “toothbrush”, “railroad”) may be heard and repeated by the participant per ear. SRTs that are within ±6 dB HL of pure-tone average (PTA) air-conduction thresholds are considered to be in an agreement of each other, with an addition indicator that speech thresholds of 15 dB HL or less to be considered normal speech understanding. Word recognition (WRS) percentage scores were determined by the correct number of one-syllable words from the NU-6 word lists (e.g., “boat”, “home”, “knock”) using a recording of a female speaker. This was presented at comfortable listening levels of 40+ dB Sensation Level (SL) (louder) in reference to their SRT score per ear. Participants repeated 25 word-lists if two or less words were incorrectly produced, otherwise repeated the full 50 word-list. WRS scores ranging from 90% to 100% indicated normal word recognition, 76% to 88% indicated slight difficulty, 60% to 74% indicated moderate difficulty, 50% to 58% indicated poor recognition, and scores less than 50% indicated very poor recognition.

Ultra high-frequency evaluation was administered per ear using the high-frequency Madsen Itera II audiometer inside the booth with Senheiser HAD 200 supra-aural headphones. This was tested using high-frequency octaves (i.e., 9, 10, 11.2, 12.5, 14, and 16 kHz) to find the participant’s softest hearing level. Thresholds ≤15 dB HL for each high-frequency measurement was considered normal hearing.

Immittance audiometry was administered outside of the audiometric test booth using the GSI Tympstar (immittance machine). Tympanometry procedure recorded compliance and middle ear pressure per ear for each participant using a 226 Hz tone via probe. Normal tympanometry measurements and results per ear include a canal volume to be from 0.6 to 2.0 ml,

peak pressure to range ±100 daPA, and static admittance to be from 0.3 to 1.5 mmhos. Acoustic reflex thresholds were recorded for middle ear reflex muscle retractions at high-intensity stimuli per ear, measuring ipsilateral and contralateral responses at different frequencies (i.e., .5, 1, 2, and 4 kHz). Normal (present) results indicated acoustic reflex thresholds to range between 70 to 100 dB HL with repeatable compliance change of 0.02 ml or greater. If acoustic reflex thresholds are present and at adequate intensity levels (i.e., ≤100 dB HL), acoustic reflex decay was performed to measure the decline of muscle contraction at 10+ dB SL in reference to their previous acoustic reflex threshold (tested only at .5 and 1 kHz, if applicable). Normal acoustic reflex decay needed to remain steady for 10 seconds, revealing present amplitude.

Statistical Analysis

Correlational studies were completed to allow for analysis of relationships between each of the variables of interest. Using the software program R (R Core Team, 2015; Revelle, 2015), bivariate correlational analyses were completed for demographic characteristics, self-report questionnaire items, and audiometric evaluation results. Pearson correlational coefficients were calculated for each set of variables and significance was determined at the $p < 0.05$ levels, as specified by asterisks in the Tables used for this study. Tables were compiled using the stargazer package (Hlavac, 2015) and graphs were compiled using tidry (Wickham, 2016) and ggplot2 packages (Wickham & Chang, 2015).

RESULTS

General Characteristics

Participants

Data from all 45 qualified participants was analyzed to determine the validity of the HHIA and HHIA-S in correlation to their audiometric evaluation and demographic variables.

The CF participants ranged from 18 to 51 years, with the average age at 31.2 (SD = 8.2) years. Forty percent were female, with a mean age of 30.4 (SD = 8.87) years and sixty percent were male, with a mean age of 31.7 (SD = 8.04) years. There is no significant difference ($p > .05$) between men ($N = 27$) and women ($N = 18$) in pure-tone audiometry results, as well as no significant difference ($p > .05$) between right and left ears across conventional and high-frequency pure-tone testing. Those who have reported tinnitus ($N = 21$) compared to those who did not report having tinnitus ($N = 24$) were compared and they are not significant ($p > .05$).

HHIA and HHIA-S

The HHIA and HHIA-S were examined to find a relationship between the two self-report scales and were very highly correlated ($r > .85$), giving identical results. The relationship of total scores and subscales (i.e., Emotional vs. Social/Situational) from the questionnaires were examined and the average correlation was 0.92 and the smallest correlation was 0.82. Therefore, the two scales are nearly identical and will focus on using the longer questionnaire (i.e., HHIA) for better estimates of self-report perception of hearing loss for the remaining of this study.

Audiological Evaluation

In Figure 1, hearing thresholds (dB HL) for all participants are represented on an audiogram-like representation across conventional frequencies (i.e., .25 to 8 kHz) for right and left ear. Average hearing thresholds, the red line as demonstrated from Figure 1, are displayed for each ear. Average hearing thresholds for the right ear are as followed: 15 dB HL at .25 kHz; 13 dB HL at .5 kHz; 9 dB HL at 1 kHz; 9 dB HL at 2 kHz; 11 dB HL at 3 kHz; 10 dB HL at 4 kHz; 12 dB HL at 6 kHz; 14 dB HL at 8 kHz. Average hearing threshold for the left ear are as

followed: 11 dB HL at .25 kHz; 10 dB HL at .5 kHz; 8 dB HL at 1 kHz; 6 dB HL at 2 kHz; 12 dB HL at 3 kHz; 13 dB HL at 4 kHz; 16 dB HL at 6 kHz; 19 dB HL at 8 kHz.

In Figure 2, hearing thresholds for all participants are represented on an audiogram-like representation across ultra high-frequencies (i.e., 9 to 16 kHz) for right and left ear. Average hearing thresholds, the red line as demonstrated from Figure 2, are displayed for each ear. Average hearing thresholds for the right ear are as followed: 19 dB HL at 9 kHz; 19 dB HL at 10 kHz; 21 dB HL at 11.2 kHz; 18 dB HL at 12.5 kHz; 23 dB HL at 14 kHz; 23 dB HL at 6 kHz. Average hearing threshold for the left ear are as followed: 22 dB HL at 9 kHz; 22 dB HL at 10 kHz; 25 dB HL at 11.2 kHz; 26 dB HL at 12.5 kHz; 25 dB HL at 14 kHz; 20 dB HL at 16 kHz.

The comparison of all participants was examined against baseline levels of normal hearing threshold (≤15 dB HL) and is shown in Table 1. This sample showed significantly poorer hearing on several of the high-frequency variables in the left ear (i.e., 9, 10, 11.2, 12.5, and 14 kHz) and right ear (i.e., 11, 14, and 16 kHz).

HHIA Scores and Audiological Evaluation

Correlations were examined between the HHIA total and subtotal scores (i.e., Emotional and Social/Situational) and results of the air-conduction and bone-conduction conventional audiometry. Values that are statistically significant ($p < .05$, greater than $r = .4$) are shown in Table 2. Air-conduction frequencies are significant ($p < .05$, greater than $r = .4$) for total and subtotal HHIA scores for both ears at .25 and .5 kHz and for pure-tone average. In the right ear, there's significance ($r = .4$) across all HHIA scores at 1, 4, 6, and 8 kHz, and in the left ear, there's significance across all HHIA scores at 2 kHz. Only bone-conduction at .25, .5 and 4 kHz right ear only show significance across all HHIA scores. The rest of the conventional audiometry results show substantially large non-significant correlations with the HHIA. Figures

3 and 4 show graphical correlations between the relationships of the HHIA scores and conventional audiometry results (i.e., pure-tone air-conduction and bone-conduction), showing a stronger correlation.

Correlations were examined between the HHIA total and subtotal scores (i.e., Emotional and Social/Situational) and results of ultra high-frequency audiometry as shown in Table 3. As all correlations were approximately .2 or .3, it is not statistically significant (greater than $r = .4$) across all frequencies. Figure 5 shows small correlations, again, not statistically significant.

There were no significant correlations between the HHIA questionnaire and speech audiometry (i.e., SRT and WRS), as well as immittance audiometry (i.e., tympanometry, ART and reflex decay), therefore will not be discussed regarding statistical analyses for the remainder of the study.

Of the 45 participants, a comparison was made between the self-report response scores (i.e., *Normal Handicap*, *Mild to Moderate Handicap*, and *Severe Handicap*) to the objective audiological results of the hearing test (i.e., normal hearing vs. abnormal hearing). For example in Table 4, you'll see pure-tone averages of the right (Table 4A) and left (Table 4B) ears were compared to self-report responses. Very few participants (i.e., Table 4A Right Ear: $N = 3$ report *Mild to Moderate Handicap*; $N = 1$ report *Severe Handicap*; Table 4B Left Ear: $N = 1$ report *Mild to Moderate Handicap*; $N = 1$ report *Severe Handicap*) experience abnormal hearing, as measured both objectively and subjectively. This sample size is too small to compare differences between objectively hearing impaired participants and normal hearing participants. However, there seems to be a number of participants with normal hearing (Table 4A Right Ear: $N = 35$; Table 4B Left Ear: $N = 37$) who report perceiving of having a mild hearing impairment (i.e., *Mild Handicap* response range).

Of all participants, only 39 reported *Mild to Moderate Handicap* or *Severe Handicap* on the HHIA (defined as 22+ points). Only 1 participant reported *Severe Handicap* (defined as 62+ points) so they cannot be assessed separately. Therefore, those reported *Mild to Moderate Handicap* or *Severe Handicap* is compared to the baseline of *Normal* hearing (≤15 dB HL), as shown in Table 5. Despite reporting hearing loss, participants only demonstrated significance ($p < 0.5$) objectively at two of the ultra high-frequencies (i.e., left ear at 11 and 12 kHz) and no significance ($p > 0.5$) at conventional frequencies.

Aminoglycoside - Tobramycin, HHIA Scores, and Audiological Evaluation

The relationship between the age of CF diagnosis and the age onset of receiving tobramycin treatment is compared to self-report questionnaire responses, and conventional and ultra high-frequency pure-tone audiometry tests, as shown in Table 6. There are significant correlations (greater than $r = .4$; $p < .05$) between the age of CF diagnosis and the age receiving tobramycin treatment with results of ultra high-frequency audiometry testing. Participants who were diagnosed at a later age showed affected ultra high-frequency audiometry ($r = .52$, $p < .05$). Increase in age at diagnosis is also correlated with increase in age of tobramycin treatment received ($r = .56$, $p < .05$); however there is some variability in how much later after CF diagnosis that treatment of tobramycin began.

At the time of the study, all participants were asked if he or her were currently taking any tobramycin medication or not, whether it was via inhale or IV therapy. As there was only one affected frequency (i.e., air-conduction at 2 kHz in right ear) correlated between the status of intake at time of test with the self-report responses and audiometric pure-tone testing, this data was not enough to show any significance in this relationship.

Type of Tobramycin Intake

Between type of intake of tobramycin, 16 participants have only used inhaled, 1 participant only used IV therapy and 26 participants have used both. Because only one participant used IV therapy only, this cannot be comparable to inhaled participants only or those that use both. Shown in Table 7, participants who inhale tobramycin ($N = 0$) were compared to participants who do not ($N = 45$), and shown in Table 8, those who use IV therapy ($N = 27$) to all participants who do not ($N = 18$). None of the tests are significant ($p > .05$) in regards to the comparisons of participants inhaling to those not, and participants who use IV therapy to those do not.

An independent sample t-test was used to compare ages of participants using inhalation to those not using inhalation. There is no difference in age between patients who inhaled ($M = 31.19$, $SD = 8.44$) and those who did not ($M = 30.67$, $SD = 7.51$; $t(43) = -0.1$, $p = 0.92$). An independent sample t-test was used to compare ages of patients using IV therapy to those not using an IV. There is no difference in age between participants who use IV therapy ($M = 31.11$, $SD = 7.81$) and those who did not ($M = 31.22$, $SD = 9.23$; $t(43) = 0.04$, $p = 0.97$). An independent sample t-test was used to compare the ages of participants using tobramycin at the time of testing and those not using tobramycin. There is no difference in age between participants who were using tobramycin at the time of testing ($M = 31.17$, $SD = 77.63$) and those who did not ($M = 31.14$, $SD = 9.14$; $t(43) = -0.01$, $p = 0.99$).

Duration of Tobramycin

Two groups were separated in the duration of using tobramycin, Group 1 consisting of 25 participants (56%) using tobramycin 10 years or less, and Group 2 consisting of 20 participants (44%) using tobramycin more than 10 years. Table 9 shows the means and SD of each group on each of the conventional air-conduction pure-tone frequencies and the statistical test of the

difference ($p = .05$). Only one of the tests is significant ($p < .05$), which was 250 Hz in the right ear. However, in general, there is no correlation between duration of tobramycin and conventional audiometry testing. Yet, it is observed that participants with CF who had been taking tobramycin for 10 years or fewer scored lower ($M = 4.2$, $SD = 6.56$) on the self-report questionnaire than participants with CF who had been taking tobramycin for more than 10 years ($M = 14.5$, $SD = 23.78$; $t(43) = -2.07$, $p < .\ 05$).

The comparison of participants using tobramycin for 10 years or fewer were examined against baseline levels of normal hearing threshold (≤ 15 dB HL) and is shown in Table 10. This sample showed significantly worse hearing on a few high-frequency variables in the right ear (i.e., 14 and 16 kHz) and left ear (i.e., 14 Hz). In Table 11, it's showing the comparison of participants using tobramycin for more than 10 years compared to baseline normal hearing threshold (≤ 15 dB HL). This sample showed significant worse hearing on several of the high-frequency variables in the right ear (i.e., 9 and 11 kHz) and in the left ear (i.e., 8, 9, 10, 11, and 12 kHz). Figure 6 graphically represents the average hearing thresholds (dB HL) across conventional and ultra high-frequencies, differentiating the duration of tobramycin medication intake in participants with CF (10 years or fewer compared to more than 10 years). Again, there is no correlation however those using tobramycin more than 10 years shows poorer hearing thresholds on the graph than those using tobramycin for 10 years or fewer.

DISCUSSION

Recent studies have shown patients with CF to be at high risk for SNHL (Cheng et al, 2009; Mulheran et al, 2001; Tarshish et al, 2016), however others have not (Mulheran et al, 2006; Scheenstra et al, 2010). In this study of patients with CF, there is no validity in hearing perception from the subjective questionnaire responses with the audiometric testing to detect

hearing loss. Even though the original (HHIA) and screening (HHIA-S) questionnaires can either be administered as they reveal similar outcomes and high correlations, this self-report may not be an efficient tool to detect hearing perception difficulties in adults with CF.

HHIA Scores and Audiological Evaluation

Positive values at frequencies listed in Table 2 indicate that as a patient self-reports greater hearing loss (i.e., *Mild to Moderate*, and *Severe Handicap*), the results of the objective hearing test indicated greater hearing loss. However, many non-significant correlations are still substantially large. With the limited number of participants, there is not enough correlation in the relationship between the self-reports of hearing loss and the objective tests across frequencies and there are discrepancies in the interpretation. For example, of the participants who self-report normal hearing (HHIA score ranging from 0 – 20), most do have normal hearing. However, of the participants who report *Mild to Moderate Hearing Handicap* (HHIA score ranging from 22 – 60), objectively normal hearing in conventional audiometry is found. Clinically, this can lead to difficulty with decision-making regarding referrals from a medical professional, due to lack of consistency. Overall, this suggests that even though there is a strong relationship between self-reported hearing loss and objective measures of hearing loss, not all patients show consistency. Therefore, some patients who are suffering from hearing loss are subjectively experiencing hearing loss; however some patients report hearing loss when they actually have normal hearing.

Even though there weren't enough participants with CF showing various objective hearing loss results, it was anticipated that ultra high-frequency thresholds would be affected more, as there is potential side effects of tobramycin and its ototoxicity at pitches above 8000 Hz (Fausti et al, 1999; Fausti et al, 1992). There was no statistical significance between the HHIA scores and ultra high-frequency audiometric results, therefore this shows that the HHIA self-

report questionnaire would not be a good tool to detect a patient's hearing loss in this population at those measured frequencies (i.e., >8 kHz). However it should be noted that common speech sounds, used in daily communication, are produced more at conventional frequencies (i.e., between .25 and 8 kHz), which is why those frequencies are commonly tested for a conventional audiological evaluation (Jongman, Wayland & Wong, 2000; Pittman, Stelmachowicz, Lewis, & Hoover, 2003). Decrease in hearing thresholds at conventional frequencies may cause patients to realize difficulty with missing speech or have trouble hearing in a variety of listening environments. Even if patients demonstrated hearing loss at higher frequencies but normal hearing at conventional frequencies, hearing difficulty might not be noticeable to the patient regardless. Therefore, the HHIA would not be useful in medical clinics that assist patients with risks of ototoxicity, as it may not detect changes in hearing at ultra high-frequencies. It may be useful in detecting hearing loss at more conventional speech frequencies, however if ototoxicity is the cause of the hearing loss, irreparable damage may already have occurred to the ultra high-frequency region of the cochlea resulting in permanent hearing loss and tinnitus.

As seen in Table 5, again, there is no correlation with self-reported hearing loss and pure-tone testing when comparing *Mild to Moderate Handicap* and *Severe Handicap* to *Normal* hearing on the self-report questionnaire. Using the cutoffs (i.e., ≤15 dB HL for conventional and ultra high-frequencies), the HHIA does not adequately assess hearing loss. Different audiological clinics may use various cutoffs of what is considered normal hearing in the adult population or during ototoxic monitoring, ranging from 15 – 25 dB HL whether in conventional and/or higher frequency testing. It should also be noted that during ototoxic monitoring, there is more importance in monitoring ultra high-frequency thresholds to stay within ±10 dB HL

(Konrad-Martin et al, 2005), which is why there may be a lack in standard norms of cutoffs in those higher regions of audiometry testing.

As there was a lack of CF participants that demonstrated abnormal hearing, sufficient data was not available to demonstrate any correlations with speech audiometry testing (i.e., SRT and WRS) or immittance testing (i.e., tympanometry, ART). These two tests are typically performed at baseline testing, however subsequent testing may not be performed for ototoxic monitoring unless a significant change occurs in hearing threshold (AAA, 2009; Campbell & Durrant, 1993; Campbell, 2004). Even though some patients might report little to no hearing difficulties, it does not appear that any of these individuals meet threshold for objective hearing loss, therefore speech audiometry and immittance tests do not capture true hearing loss in the CF population.

Aminoglycoside - Tobramycin, HHIA Scores, and Audiological Evaluation

From Table 6, correlations with the age that participants with CF have been diagnosed and when they received treatment, in relationship with pure-tone testing are demonstrated. As patients with CF were diagnosed later in age as well as when they received treatment, it seems as though regions at higher frequencies (>8 kHz) are more affected (poorer hearing) than conventional frequencies (≤ 8 kHz) (better hearing). This supports various research studies as to the importance in monitoring ultra high-frequency thresholds in populations who undergo treatment with tobramycin (Mulheran et al, 2001; Schacht et al, 2012; Huth et al, 2015; Fausti et al, 1999; Fausti et al, 1992). There should be some consideration in frequent ototoxic monitoring if a patient with CF is later diagnosed and treated than earlier, but whether or not there's an age cut-off of onset of diagnosis or treatment is needed to be further investigated.

No difference was noted whether or not participants with CF were currently being medicated with tobramycin or not at the time of testing. Therefore, this area may be more useful in a longitudinal study that examines repeatable audiological testing (e.g., monthly following 28 day cycles) and whether or not actively using tobramycin is correlated with hearing thresholds in pure-tone testing.

Type of Tobramycin Intake

There are no significant correlations with the type of tobramycin usage (i.e., inhale, IV therapy) or age of the CF participants in comparison to their audiological evaluation. This is most likely due to the small sample size and limited number of participants that demonstrated hearing loss. In relation, other literature has found no differences in type of tobramycin therapy that was associated with detectable renal toxicity or ototoxicity in this population (Wagener et al, 2013; Hennig et al, 2014). Therefore, further research should investigate this area in a larger sample population and include groups who objectively have hearing impairment.

Duration of Tobramycin

Inhalation of tobramycin for 10 years and fewer or greater than 10 years, did not affect the audiological tests at conventional frequencies. Even though there is statistical significance at one frequency, it is not enough data to support a relationship. However, it is interesting to note that patients with CF who had been taking tobramycin for greater than 10 years have higher threshold averages in conventional air-conduction pure-tones (poorer hearing) than patients who had been taking tobramycin for 10 years or less (as shown in Figure 6). This relationship demonstrates that there might be some association in whether or not patients with CF need to be referred for audiological test(s) depending on duration of ototoxic medications, however there is no set guideline that discusses this.

The comparison of participants using tobramycin for 10 years or less were examined against baseline levels of normal hearing threshold (≤ 15 dB HL) and is shown in Table 10. This sample demonstrated significantly worse hearing on a few high-frequency variables in the right ear (i.e., 14 and 16 kHz) and left ear (i.e., 14 Hz). A comparison of participants using tobramycin for greater than 10 years compared to baseline normal hearing threshold (≤ 15 dB HL) is shown in Table 11. This sample demonstrated significant worse hearing on several of the ultra high-frequency variables in the right ear (i.e., 9 and 11 kHz) and in the left ear (i.e., 8, 9, 10, 11, and 12 kHz). It should be noted that patients with CF who use tobramycin for greater than 10 years have shown to have more frequencies affected, specifically at ultra high-frequencies, than those who use tobramycin for 10 years or fewer. However, this data is not similar across ears, with the exception at 14 kHz, for those using tobramycin 10 years or less, and at 9 and 11 kHz for those using tobramycin greater than 10 years. Insufficient affected frequencies were obtained to prove that the duration of tobramycin intake could potentially be associated to harming ultra high-frequency regions. However, with more data a clearer picture could be obtained. McRorie, Bosso, and Randolph's study (1989) examined patients with CF who were treated with AGs for more than 20 years compared to those treated less than 20 years and found elevated thresholds in all frequencies tested in (elevations only in frequencies higher than 16 kHz). This may support the consideration that duration of treatment may have an impact on potential risks of hearing loss.

AAA and ASHA (AAA, 2009; ASHA, 1994) recommend weekly audiological evaluations for patients receiving ototoxic medications regardless of duration of use, however, for the CF population receiving ototoxic medication this recommendation would not be feasible. As stated previously many of the patients with CF are receiving ototoxic medication may be

using this medication for years at a time. Having an audiological evaluation every week would become overly time consuming and increase the already high medical costs for the population. More data is needed to determine the best course of treatment for this population. When more information is gathered a testing schedule could be implemented to assure that hearing loss is monitored without causing difficulty for the patient financially as well as follow up appointments.

The duration of use of and dosage of tobramycin could be of some importance of whether or not a patient with CF should have an audiological referral, however, there is no sufficient data to determine these questions. Various studies have shown a prevalence of SNHL in the CF population (Mulheran et al, 2001; Cheng et al, 2009; Piltcher et al, 2003) however even with repeated courses of tobramycin, others have found no significant hearing loss (Mulheran et al, 2001; Scheenstra et al, 2010). Until this could be established more fully it would be recommended that patients receiving tobramycin whether inhaled or IV should have an annual audiological evaluation. An audiological evaluation should be performed more often if the patient notes any change in hearing, tinnitus, fullness in the ear, otalgia or dizziness.

Through this it may be determined at what duration of use in years, is potentially considered a significant difference that would be significant and may guide the physicians or audiologists to recommend audiological evaluations more often. Determining when testing may become more appropriate may be beneficial as the life expectancy of patients with CF increases. As life expectancy increases the use of tobramycin will increase and the likelihood of ototoxicity would increase. Therefore an appropriate protocol for patient receiving ototoxic medications should be established to monitor these possible changes.

Limitations

There are several limitations to this study that need to be addressed. A lack of documentation in the medical database system and in patient knowledge regarding certain demographic related questions was noted. For example, patients with CF estimated the age they were diagnosed, when they began tobramycin treatment, and/or the amount of antibiotic medication they received. Many patients with CF had difficulty remembering their treatment cycle(s) or duration of treatment. In addition to inaccurate subjective in-person responses, patient chart information in the database was not clear, as the reports would not specify the dosage of tobramycin. This was especially the case regarding the use of IV tobramycin as typically this is provided in the hospital and many patients could not accurately determine the number of times he or she was admitted to the hospital. Hospital records were also inaccessible, as documentation was maintained by other medical clinics. These variables were considered to be important and should be concise and accurate across patient history.

Although self-report questionnaires can be a popular methodology in behavioral studies because of their utility (less time consuming and efficient), there can be many problems with assessing them. The HHIA item scores (i.e., Total, Emotional, Social/Situational) may have been affected by the individual's responses from lack of introspective ability (honesty and accuracy), interpretation differences of items, limited rating of scale, response bias, and state of health at time of assessment (e.g., personality, concentration, attitude etc.). These difficulties should be noted and in need to be countered through a careful design and application of self-report measures.

More importantly, there was a lack of participants with CF in this study due to the time constraint of the recruitment period and testing timeframes, lack of motivational factors of individual's participation, and availability during restricted participating test sessions. As there

was already a low statistical power, this negatively affected the likelihood that a nominally statistically significant finding may truly reflect the effect. Specifically, there was a lack of patients with CF who demonstrated having objective hearing impairment (i.e., poorer than mild hearing loss, ranging from moderate to profound). Most of the participants had normal hearing results, regardless of the various demographic variables or self-report responses analyzed and discussed. Insufficient participants with various types of hearing impairment were obtained that would show any potential correlations discussed in this study.

During patient recruitment, it is possible that some patients with CF volunteered due to his or her perceived hearing loss. While others may have not volunteered due to a lack of perceived hearing loss. Therefore, some patients with hearing loss may not have been evaluated and could have provided additional value to the research.

Further Research

Future research should examine the duration of tobramycin usage in the CF population to further investigate the potential risk correlations to hearing loss. In addition to this, type of tobramycin intake (i.e., inhalation, IV therapy) should be taken into consideration with a larger sample size to determine, if any, differences in treatment. It would be interesting to see a different direction in research in regards to type and/or duration of treatment methods and ototoxicity monitoring outside of weekly standard guidelines taken from ASHA and AAA. For example, weekly monitoring compared to monthly or annually ototoxic monitoring and its possible association to hearing loss. This could notify and aware other medical professionals about additional factors that could assist in better medical referrals.

Improved recruitment procedures could be implemented to recruit participants with CF that have various degrees in hearing loss to determine if these participants would be more likely

to notice differences between tobramycin characteristics, such as intake type and duration in use, and testing at conventional and at ultra high-frequency pure-tone thresholds. Recruiting a larger sample size will also benefit results as mentioned and to have a higher statistical power.

A longitudinal study could be useful in the methodology used in this present study to show any changes in tobramycin intake and audiological evaluation thresholds, specifically at ultra high-frequency thresholds over time. This could also assist with the referral base of other medical professionals in regard the duration of use of ototoxicity and when a patient with CF may be at risk of hearing loss.

CONCLUSION

Adult patients with CF may be at high risk for developing SNHL due to frequent exposure to AGs. From this present study, self-report questionnaire(s) may not be a valuable tool to detect potential hearing loss, especially at unnoticed ultra high-frequency regions of hearing. Therefore further investigation is warranted to determine a protocol that is efficient and that is cost effective. This should be appropriately available to other medical professionals to administer to patients with CF in a timely manner (as well as to other health conditions at risk of hearing loss). As life expectancy in the CF population continues to increase, there may be more exposure to tobramycin intake; hence patients are at higher risk of developing bilateral SNHL, potentially impacting his or her quality of life. Since SNHL has been shown to have a significant impact on social and emotional development, it is recommended that an increased awareness of the possibility of hearing loss in patients with CF among clinicians, patients and families with anticipatory planning regarding habilitation of HL should it occur. The CF population should have routine and longitudinal audiometric evaluations as part of their overall management, however other factors need to be justified (e.g., duration of ototoxicity by age, onset of treatment,

type of tobramycin intake etc.) to delineate the optimal treatment without causing potential risk of hearing loss. The addition of SNHL to the already extensive set of health challenges that patients with CF face creates a need for intensified identification, prevention, and education, potentially through changes to the CF care guidelines, which currently varies in recommend routine audiometric screening. The incidence of hearing loss in the CF population requires further investigation of etiology and the determination of preventive and treatment measures.

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TABLE 1

Auditory Test	Sample Mean	Sample SD	t statistic	df	p
APT.25R	14.78	16.17	-0.09	44	0.54
APT.25L	11.44	7.43	-3.21	44	1.00
APT.5R	13.44	16.27	-0.64	44	0.74
APT.5L	10.22	8.19	-3.92	44	1.00
APT1R	8.78	15.19	-2.75	44	1.00
APT1L	8	7.93	-5.92	44	1.00
APT2R	8.78	17.16	-2.43	44	0.99
APT2L	5.89	8.21	-7.45	44	1
APT3R	10.89	18.96	-1.45	44	0.92
APT3L	11.56	10.27	-2.25	44	0.99
APT4R	12.33	18.97	-0.94	44	0.82
APT4L	13.07	12.77	-1.00	43	0.84
APT6R	14.33	17.63	-0.25	44	0.60
APT6L	16.11	13.05	0.57	44	0.29
APT8R	15.56	20.46	0.18	44	0.43
APT8L	19	16.15	1.66	44	0.05
HF9R	19.32	18.45	1.55	43	0.06
HF9L	21.67	20.89	2.14	44	0.02*
HF10R	18.64	21.47	1.12	43	0.13
HF10L	22.33	23.22	2.12	44	0.02*
HF11R	21.36	22.42	1.88	43	0.03*
HF11L	24.78	23.86	2.75	44	0.004**
HF12R	18.05	21.73	0.90	40	0.19
HF12L	26.36	26.90	2.80	43	0.004**
HF14R	23.33	22.49	2.31	38	0.01*
HF14L	24.46	21.07	2.73	36	0.005**
HF16R	23.33	18.53	2.58	32	0.01*
HF16L	20	18.97	1.47	30	0.08

*. Correlation is significant at the 0.05 level (2-tailed)

Table 1: Correlation of all participants to baseline hearing threshold of ≤15 dB HL as shown above. Labeled with an asterisk above, there is significant ($p < .05$) ultra high-frequency variables: HF9L, HF10L, HF11R, HF11L, HF12L, HF14R, HF14L, and HF16R.

TABLE 2

	HHIA.E	HHIA.S	HHIA
APT.25R	0.585*	0.605*	0.616*
APT.25L	0.65*	0.61*	0.656*
APT.5R	0.604*	0.618*	0.633*
APT.5L	0.558*	0.603*	0.6*
APT1R	0.478*	0.526*	0.518*
APT1L	0.458	0.499*	0.494*
APT2R	0.347	0.406	0.387
APT2L	0.484*	0.498*	0.509*
APT3R	0.444	0.462	0.469*
APT3L	0.371	0.348	0.374
APT4R	0.541*	0.582*	0.58*
APT4L	0.402	0.323	0.381
APT6R	0.648*	0.618*	0.659*
APT6L	0.49*	0.399	0.466
APT8R	0.555*	0.53*	0.564*
APT8L	0.483*	0.337	0.434
PTAR	0.501*	0.543*	0.539*
PTAL	0.551*	0.593*	0.591*
BPT.25R	0.694*	0.724*	0.73*
BPT.25L	-0.033	0.053	0.006
BPT.5R	0.676*	0.695*	0.705*
BPT.5L	0.637	0.699*	0.673*
BPT1R	0.413	0.491	0.467
BPT1L	0.446	0.527	0.487
BPT2R	0.358	0.352	0.366
BPT2L	-0.069	0.086	-0.002
BPT3R	0.505	0.496	0.516
BPT3L	0.287	0.374	0.329
BPT4R	0.585*	0.594*	0.606*
BPT4L	0.283	0.332	0.308

*. Correlation is significant at the 0.05 level and greater than r = .4 (2-tailed)

Table 2: Correlations between HHIA questionnaires subtotal and total scores and results of conventional audiometry tests (air- and bone-conduction). Columns ending in “E” indicate E subtotals (emotional), in “S” indicates S subtotals (social/situational), and the HHIA indicates total score. Values with an asterisk indicate that these correlations are statistically significant ($\alpha < .05$). A correlation greater than $r = .4$ is considered a substantial relationship.

TABLE 3

	HHIA.E	HHIA.S	HHIA
HF9R	0.32	0.221	0.289
HF9L	0.417	0.255	0.357
HF10R	0.325	0.181	0.273
HF10L	0.395	0.241	0.339
HF11R	0.338	0.233	0.305
HF11L	0.382	0.302	0.36
HF12R	0.137	0.128	0.144
HF12L	0.404	0.359	0.398
HF14R	0.299	0.221	0.286
HF14L	0.303	0.262	0.309
HF16R	0.297	0.198	0.274
HF16L	0.469	0.338	0.437

*. Correlation is significant at the 0.05 level (2-tailed)

Table 3: Correlations between HHIA questionnaire subtotal and total score and results of ultra high-frequency audiometry. Columns ending in "E" indicate E subtotals (emotional), in "S" indicates S subtotals (social/situational), and the HHIA indicates total score. No correlations are statistically significant ($\alpha < .05$).

TABLE 4

4A: Right Ear

	SR None	SR Mild	SR Severe
Hearing Test Normal	4	35	0
Hearing Test Abnormal	2	3	1

SR = Self-Report. Normal hearing can hear at less than 20 dB HL

4B: Left Ear

	SR None	SR Mild	SR Severe
Hearing Test Normal	5	37	0
Hearing Test Abnormal	1	1	1

SR = Self-Report. Normal hearing can hear at less than 20 dB HL

Table 4: Comparison of HHIA self-report perception of hearing with pure-tone average hearing test results from the right ear (Table 4A) and left ear (Table 4B). Normal hearing is ≤15 dB HL.

TABLE 5

Auditory Test	Mean	SD	t statistic	df	p
HHIA.E	1.74	5.99	-13.83	38	1
HHIA.S	1.69	4.41	-18.83	38	1
HHIA	3.44	10.23	-7.06	38	1
APT.25R	12.18	8.64	-2.04	38	0.98
APT.25L	10.77	7.66	-3.45	38	1.00
APT.5R	11.15	9.70	-2.48	38	0.99
APT.5L	9.49	7.76	-4.44	38	1.00
APT1R	6.28	7.67	-7.10	38	1
APT1L	7.69	7.42	-6.15	38	1.00
APT2R	7.05	11.63	-4.27	38	1.00
APT2L	5.38	8.38	-7.16	38	1
APT3R	8.21	9.70	-4.38	38	1.00
APT3L	11.15	10.42	-2.31	38	0.99
APT4R	9.62	9.96	-3.38	38	1.00
APT4L	12.76	13.24	-1.04	37	0.85
APT6R	11.67	10.28	-2.02	38	0.98
APT6L	15.51	13.56	0.24	38	0.41
APT8R	13.21	16.24	-0.69	38	0.75
APT8L	17.95	16.41	1.12	38	0.13
HF9R	19.62	19.28	1.50	38	0.07
HF9L	20.26	20.49	1.60	38	0.06
HF10R	18.85	22.20	1.08	38	0.14
HF10L	20.90	22.33	1.65	38	0.05
HF11R	20.90	23.62	1.56	38	0.06
HF11L	22.69	22.76	2.11	38	0.02*
HF12R	15.97	21.64	0.27	35	0.39
HF12L	23.29	26.31	1.94	37	0.03*
HF14R	19.85	21.72	1.30	33	0.10
HF14L	21.41	20.88	1.74	31	0.05
HF16R	20.18	18.23	1.50	27	0.07
HF16L	16.67	17.92	0.48	26	0.32

*. Correlation is significant at the 0.05 level (2-tailed)

Table 5: Comparison of self-reported impairment (i.e., *Mild to Moderate Handicap*, *Severe Handicap*) to baseline normal hearing (≤15 dB HL).

TABLE 6

	Age.Diagnosed	TreatmentAge
HHIA.E	0.02	0.2
HHIA.S	-0.04	0.08
HHIA	-0.01	0.16
APT.25R	-0.04	-0.01
APT.25L	0.05	0.27
APT.5R	-0.08	0.01
APT.5L	0.04	0.21
APT1R	-0.06	-0.03
APT1L	0.04	0.23
APT2R	-0.07	-0.15
APT2L	-0.05	0.02
APT3R	0.01	-0.09
APT3L	-0.04	0.12
APT4R	-0.02	-0.05
APT4L	-0.02	0.13
APT6R	0.1	0.05
APT6L	0.06	0.17
APT8R	0.3*	0.14
APT8L	0.28	0.15
HF9R	0.34*	0.17
HF9L	0.26	0.23
HF10R	0.36*	0.29
HF10L	0.21	0.28
HF11R	0.39*	0.35*
HF11L	0.23	0.31*
HF12R	0.42*	0.45*
HF12L	0.3	0.44*
HF14R	0.19	0.41*
HF14L	0.35*	0.46*
HF16R	0.36*	0.51*
HF16L	0.51*	0.53*

*. Correlation is significant at the 0.05 level and greater than r = .4 (2-tailed)

Table 6: Correlation between age of participant diagnosed with CF and age of participant that received treatment, in comparison to the self-report questionnaire, conventional and ultra high-frequency pure-tone testing.

TABLE 7

Auditory Test	Non-Inhale Mean	Non-Inhale SD	Inhale Mean	Inhale SD	t statistic	df	p
HHIA.E	0	0	3.76	7.69	-0.84	43	0.41
HHIA.S	0	0	3.43	6.17	-0.95	43	0.35
HHIA	0	0	7.19	13.35	-0.92	43	0.36
APT.25R	11.67	2.89	15	16.71	-0.34	43	0.73
APT.25L	10	5	11.55	7.61	-0.34	43	0.73
APT.5R	6.67	2.89	13.93	16.73	-0.74	43	0.46
APT.5L	10	5	10.24	8.41	-0.05	43	0.96
APT1R	8.33	2.89	8.81	15.73	-0.05	43	0.96
APT1L	11.67	2.89	7.74	8.13	0.83	43	0.41
APT2R	10	0	8.69	17.77	0.13	43	0.90
APT2L	11.67	12.58	5.48	7.87	1.27	43	0.21
APT3R	13.33	5.77	10.71	19.59	0.23	43	0.82
APT3L	15	5	11.31	10.54	0.60	43	0.55
APT4R	11.67	7.64	12.38	19.58	-0.06	43	0.95
APT4L	18.33	7.64	12.68	13.04	0.74	42	0.47
APT6R	13.33	7.64	14.40	18.19	-0.10	43	0.92
APT6L	21.67	17.56	15.71	12.86	0.76	43	0.45
APT8R	26.67	20.21	14.76	20.48	0.97	43	0.34
APT8L	31.67	20.21	18.10	15.73	1.42	43	0.16
HF9R	25	20	18.90	18.52	0.55	42	0.59
HF9L	31.67	23.63	20.95	20.81	0.86	43	0.40
HF10R	20	21.79	18.54	21.72	0.11	42	0.91
HF10L	26.67	22.55	22.02	23.51	0.33	43	0.74
HF11R	25	22.91	21.10	22.65	0.29	42	0.77
HF11L	26.67	27.54	24.64	23.95	0.14	43	0.89
HF12R	25	21.79	17.50	21.93	0.57	39	0.57
HF12L	31.67	28.43	25.98	27.12	0.35	42	0.73
HF14R	41.67	17.56	21.81	22.37	1.49	37	0.14
HF14L	32.50	31.82	24	20.89	0.55	35	0.59
HF16R	40	7.07	22.26	18.57	1.33	31	0.19
HF16L	15		20.17	19.27	-0.26	29	0.79

*. Correlation is significant at the 0.05 level (2-tailed)

Table 7: Comparison of inhalation and non-inhalation participants across HHIA scores, conventional and ultra high-frequency testing. None of the tests are significant; therefore there is no difference between participants who inhale than those who do not.

TABLE 8

Auditory Test	Non-IV Mean	Non-IV SD	IV Mean	IV SD	t statistic	df	p
HHIA.E	1.33	3.50	4.96	9.02	-1.62	43	0.11
HHIA.S	1.33	2.38	4.44	7.32	-1.74	43	0.09
HHIA	2.67	5.49	9.41	15.76	-1.74	43	0.09
APT.25R	10	4.20	17.96	20.11	-1.65	43	0.11
APT.25L	9.17	5.49	12.96	8.23	-1.72	43	0.09
APT.5R	8.61	4.13	16.67	20.24	-1.66	43	0.10
APT.5L	8.06	4.89	11.67	9.61	-1.47	43	0.15
APT1R	3.89	4.04	12.04	18.77	-1.81	43	0.08
APT1L	5.83	4.93	9.44	9.23	-1.52	43	0.14
APT2R	3.06	4.58	12.59	21.14	-1.88	43	0.07
APT2L	4.17	6.91	7.04	8.91	-1.15	43	0.26
APT3R	5.56	5.66	14.44	23.55	-1.57	43	0.12
APT3L	11.39	8.37	11.67	11.52	-0.09	43	0.93
APT4R	8.33	8.04	15	23.41	-1.16	43	0.25
APT4L	16.47	11.96	10.93	13.01	1.42	42	0.16
APT6R	11.94	8.43	15.93	21.75	-0.74	43	0.46
APT6L	17.22	13.64	15.37	12.85	0.46	43	0.65
APT8R	15.56	16.44	15.56	23.05	0	43	1
APT8L	20.83	18.49	17.78	14.63	0.62	43	0.54
HF9R	20.28	21.59	18.65	16.34	0.28	42	0.78
HF9L	22.78	23.59	20.93	19.32	0.29	43	0.77
HF10R	18.89	24.10	18.46	19.94	0.06	42	0.95
HF10L	24.72	24.64	20.74	22.56	0.56	43	0.58
HF11R	23.61	25.71	19.81	20.22	0.55	42	0.59
HF11L	27.22	24.51	23.15	23.74	0.56	43	0.58
HF12R	17.35	25.38	18.54	19.31	-0.17	39	0.87
HF12L	25.88	24.76	26.67	28.62	-0.09	42	0.93
HF14R	20	22.52	25.42	22.69	-0.73	37	0.47
HF14L	29.33	22.82	21.14	19.64	1.17	35	0.25
HF16R	22.86	19.39	23.68	18.40	-0.12	31	0.90
HF16L	23.08	18.09	17.78	19.79	0.76	29	0.45

*. Correlation is significant at the 0.05 level (2-tailed)

Table 8: Comparison of IV and non-IV participants across HHIA scores, conventional and ultra high-frequency testing. None of the tests are significant, therefore there is no difference between participants who use IV that those who do not.

TABLE 9

Auditory Test	Group1 Mean	Group1 SD	Group2 Mean	Group2 SD	t statistic	df	p
APT.25R	11.60	8.38	18.75	22.06	-1.49	43	0.14
APT.25L	10	5.59	13.25	9.07	-1.48	43	0.15
APT.5R	10.40	9.46	17.25	21.73	-1.42	43	0.16
APT.5L	9.20	7.46	11.50	9.05	-0.94	43	0.35
APT1R	6	9.13	12.25	20.16	-1.39	43	0.17
APT1L	8	7.77	8	8.34	0	43	1
APT2R	4.20	6.56	14.50	23.78	-2.07	43	0.04
APT2L	4.60	7.49	7.50	8.96	-1.18	43	0.24
APT3R	6.60	8.50	16.25	26.20	-1.74	43	0.09
APT3L	10	8.04	13.50	12.47	-1.14	43	0.26
APT4R	7.80	8.43	18	26.13	-1.84	43	0.07
APT4L	12	11.27	14.47	14.71	-0.63	42	0.53
APT6R	10.80	7.02	18.75	24.91	-1.53	43	0.13
APT6L	14.80	11.68	17.75	14.73	-0.75	43	0.46
APT8R	10.80	11.52	21.50	27.10	-1.79	43	0.08
APT8L	15.80	13.44	23	18.60	-1.51	43	0.14

*. Correlation is significant at the 0.05 level (2-tailed)

Table 9: Comparison of duration of tobramycin intake. Group 1 represents 10 years or less usage of tobramycin and Group 2 represents more than 10 years usage of tobramycin.

TABLE 10

Auditory Test	Sample Mean	Sample SD	t statistic	df	p
APT.25R	11.60	8.38	-2.03	24	0.97
APT.25L	10	5.59	-4.47	24	1.00
APT.5R	10.40	9.46	-2.43	24	0.99
APT.5L	9.20	7.46	-3.89	24	1.00
APT1R	6	9.13	-4.93	24	1.00
APT1L	8	7.77	-4.50	24	1.00
APT2R	4.20	6.56	-8.23	24	1
APT2L	4.60	7.49	-6.94	24	1.00
APT3R	6.60	8.50	-4.94	24	1.00
APT3L	10	8.04	-3.11	24	1.00
APT4R	7.80	8.43	-4.27	24	1.00
APT4L	12	11.27	-1.33	24	0.90
APT6R	10.80	7.02	-2.99	24	1.00
APT6L	14.80	11.68	-0.09	24	0.53
APT8R	10.80	11.52	-1.82	24	0.96
APT8L	15.80	13.44	0.30	24	0.38
HF9R	14	11.73	-0.43	24	0.66
HF9L	15.20	15.64	0.06	24	0.47
HF10R	14.60	16.20	-0.12	24	0.55
HF10L	16.20	15.70	0.38	24	0.35
HF11R	17.40	19.37	0.62	24	0.27
HF11L	19	17.56	1.14	24	0.13
HF12R	16.20	21.76	0.28	24	0.39
HF12L	21	22.87	1.31	24	0.10
HF14R	23.12	22.21	1.79	23	0.04*
HF14L	25	20.23	2.37	22	0.01*
HF16R	22	17.50	1.79	19	0.04*
HF16L	21	17.21	1.56	19	0.07

*. Correlation is significant at the 0.05 level (2-tailed)

Table 10: Comparison of participants who use tobramycin for 10 years or fewer compared to baseline threshold ≤ 15 dB HL. There is significant ($p < .05$) worse hearing in high-frequency variables: HF14R, HF14L, and HF16R.

TABLE 11

Auditory Test	Sample Mean	Sample SD	t statistic	df	p
APT.25R	18.95	22.64	0.76	18	0.23
APT.25L	13.16	9.31	-0.86	18	0.80
APT.5R	17.63	22.26	0.52	18	0.31
APT.5L	11.58	9.29	-1.61	18	0.94
APT1R	12.37	20.71	-0.55	18	0.71
APT1L	7.89	8.55	-3.62	18	1.00
APT2R	14.47	24.43	-0.09	18	0.54
APT2L	7.63	9.18	-3.50	18	1.00
APT3R	16.58	26.88	0.26	18	0.40
APT3L	13.42	12.81	-0.54	18	0.70
APT4R	18.68	26.66	0.60	18	0.28
APT4L	14.44	15.14	-0.16	17	0.56
APT6R	19.21	25.51	0.72	18	0.24
APT6L	17.37	15.03	0.69	18	0.25
APT8R	22.37	27.56	1.17	18	0.13
APT8L	22.89	19.10	1.80	18	0.04*
HF9R	27.50	23.28	2.28	17	0.02*
HF9L	28.16	23.58	2.43	18	0.01*
HF10R	25	26.79	1.58	17	0.07
HF10L	28.16	28.29	2.03	18	0.03*
HF11R	27.78	25.68	2.11	17	0.02*
HF11L	30.26	28.50	2.33	18	0.02*
HF12R	20.33	22.71	0.91	14	0.19
HF12L	31.11	29.78	2.30	17	0.02*
HF14R	21.79	23.42	1.08	13	0.15
HF14L	23.57	23.16	1.38	13	0.09
HF16R	23.33	20.04	1.44	11	0.09
HF16L	18.18	22.61	0.47	10	0.33

*. Correlation is significant at the 0.05 level (2-tailed)

Table 11: Comparison of participants who use tobramycin for more than 10 years compared to baseline hearing threshold ≤ 15 dB HL. There is significant ($p < .05$) worse hearing at ultra high-frequency variables: APT8L, HF9R, HF9L, HF10L, HF11R, HF11L, and HF12L.

FIGURE 1

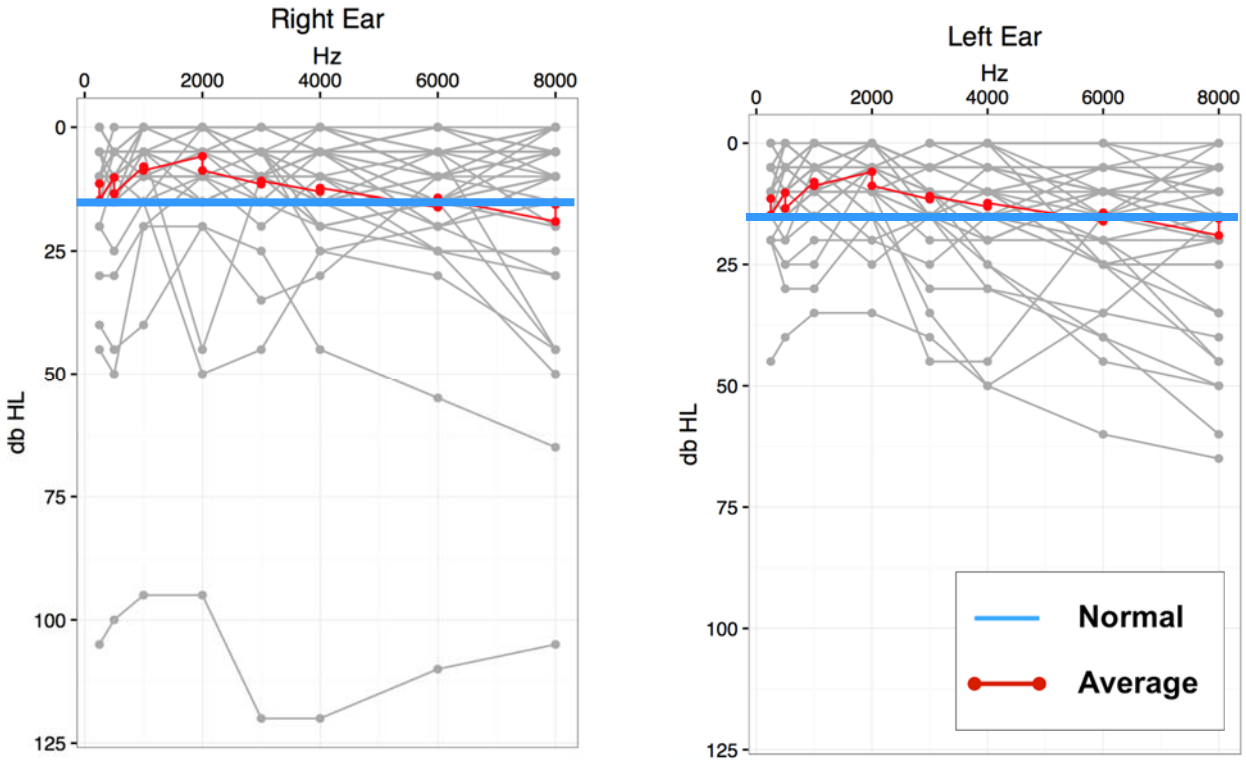

Figure 1: Graphical representation of an audiogram of hearing thresholds (dB HL) across conventional frequencies (Hz), one displaying the right ear and one for the left ear, as shown above. Average hearing thresholds from all participants with CF per ear are defined from the red line and normal hearing thresholds are indicated from the blue line, as shown in key.

FIGURE 2

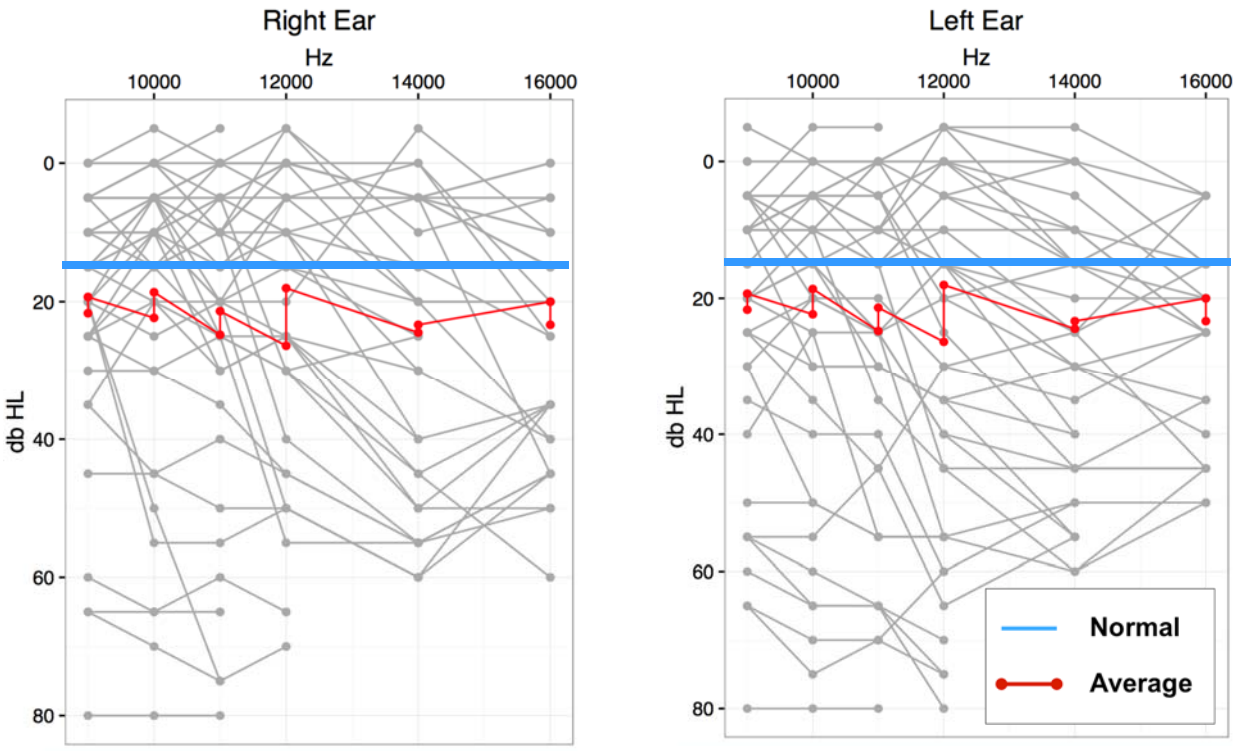

Figure 2: Graphical representation of an audiogram of hearing thresholds (dB HL) across ultra high-frequencies (Hz), one displaying the right ear and one for the left ear, as shown above. Average hearing thresholds from all participants with CF per ear are defined from the red line and normal hearing thresholds are indicated from the blue line, as shown in key.

FIGURE 3

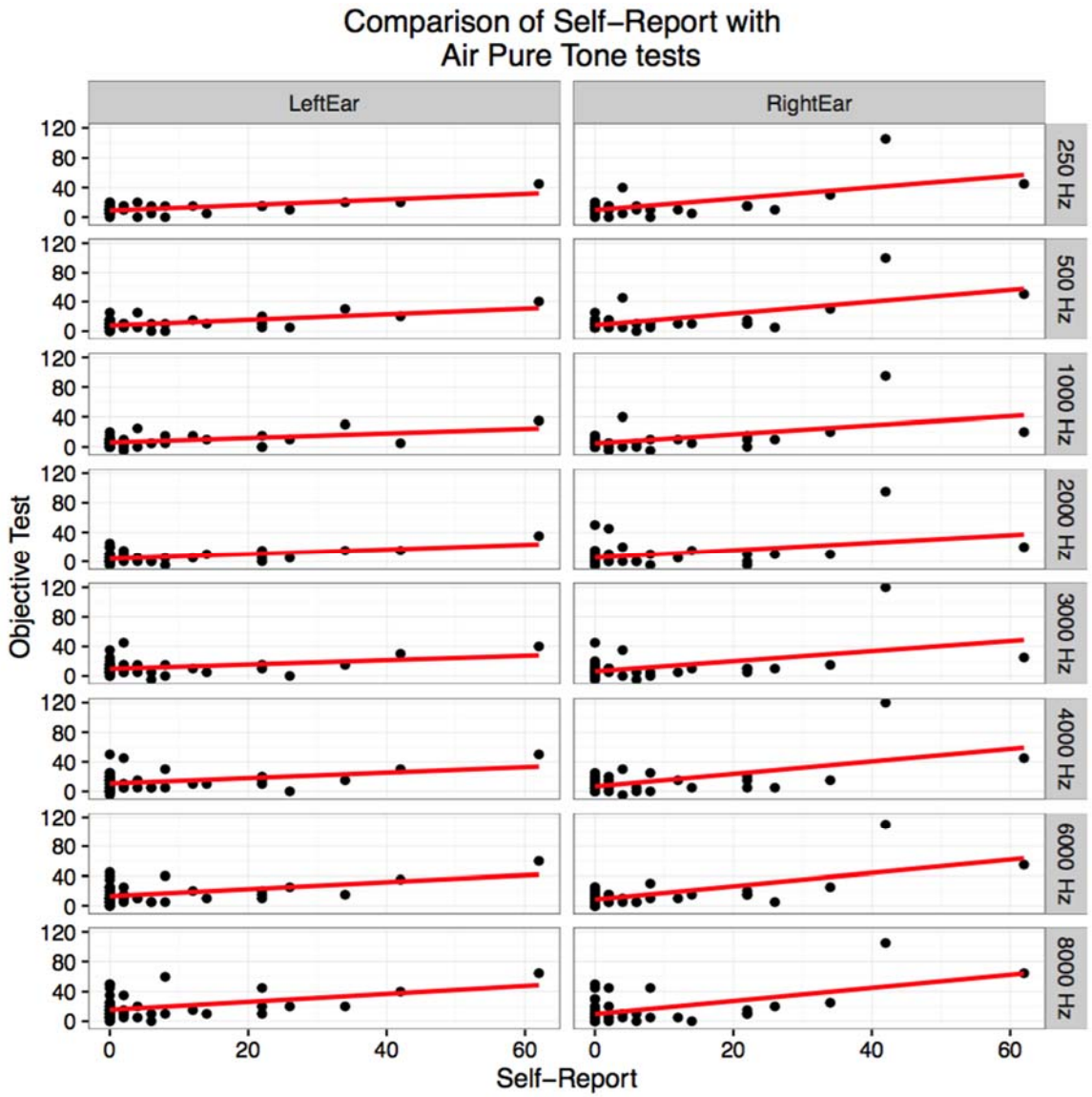

Figure 3: The graphical relationship between the self-report HHIA scores and objective test of air-conduction pure-tone audiometry for each ear.

FIGURE 4

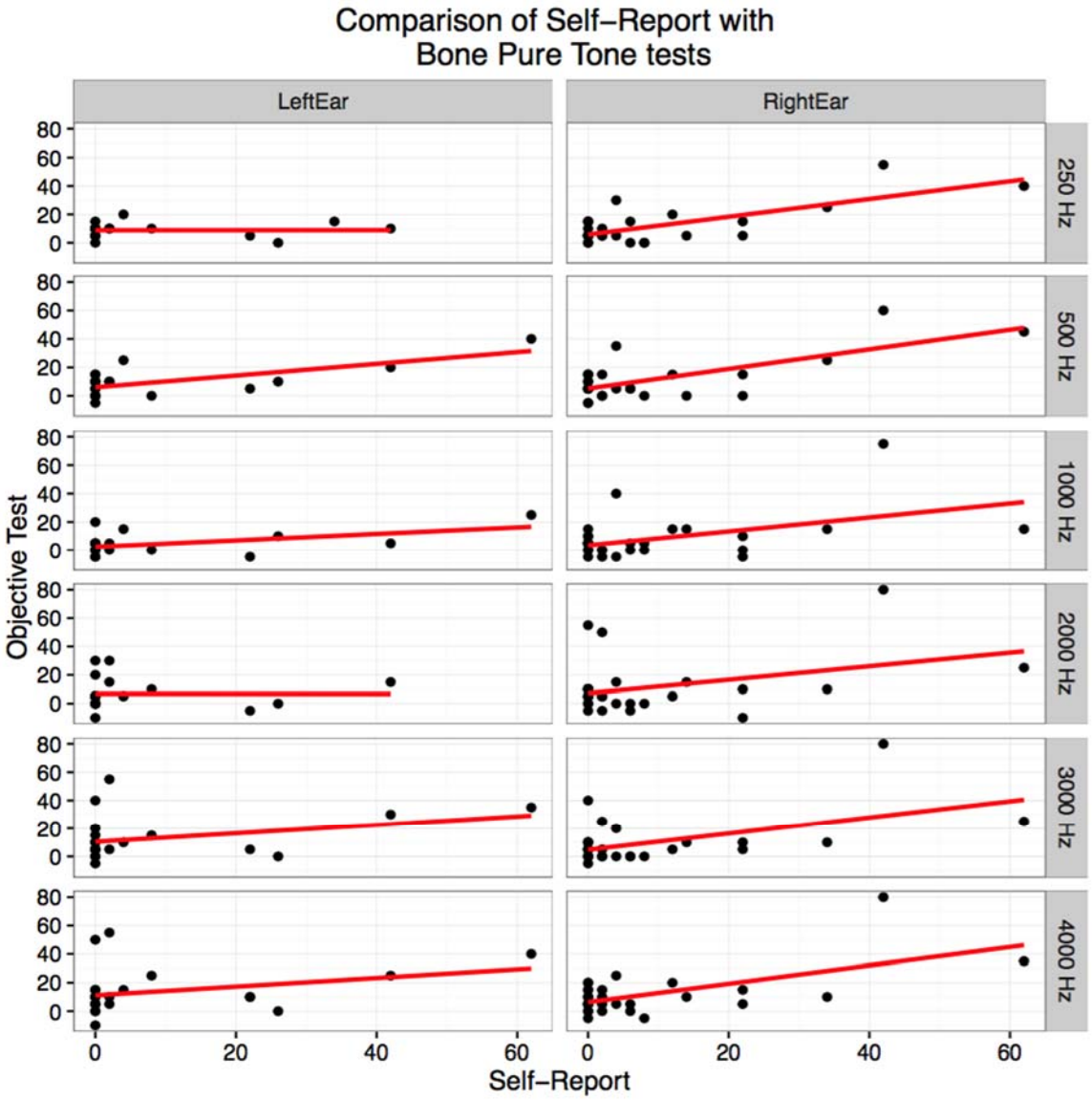

Figure: 4: The relationship between the self-report HHIA scores and objective test of bone-conduction pure-tone audiometry for each ear.

FIGURE 5

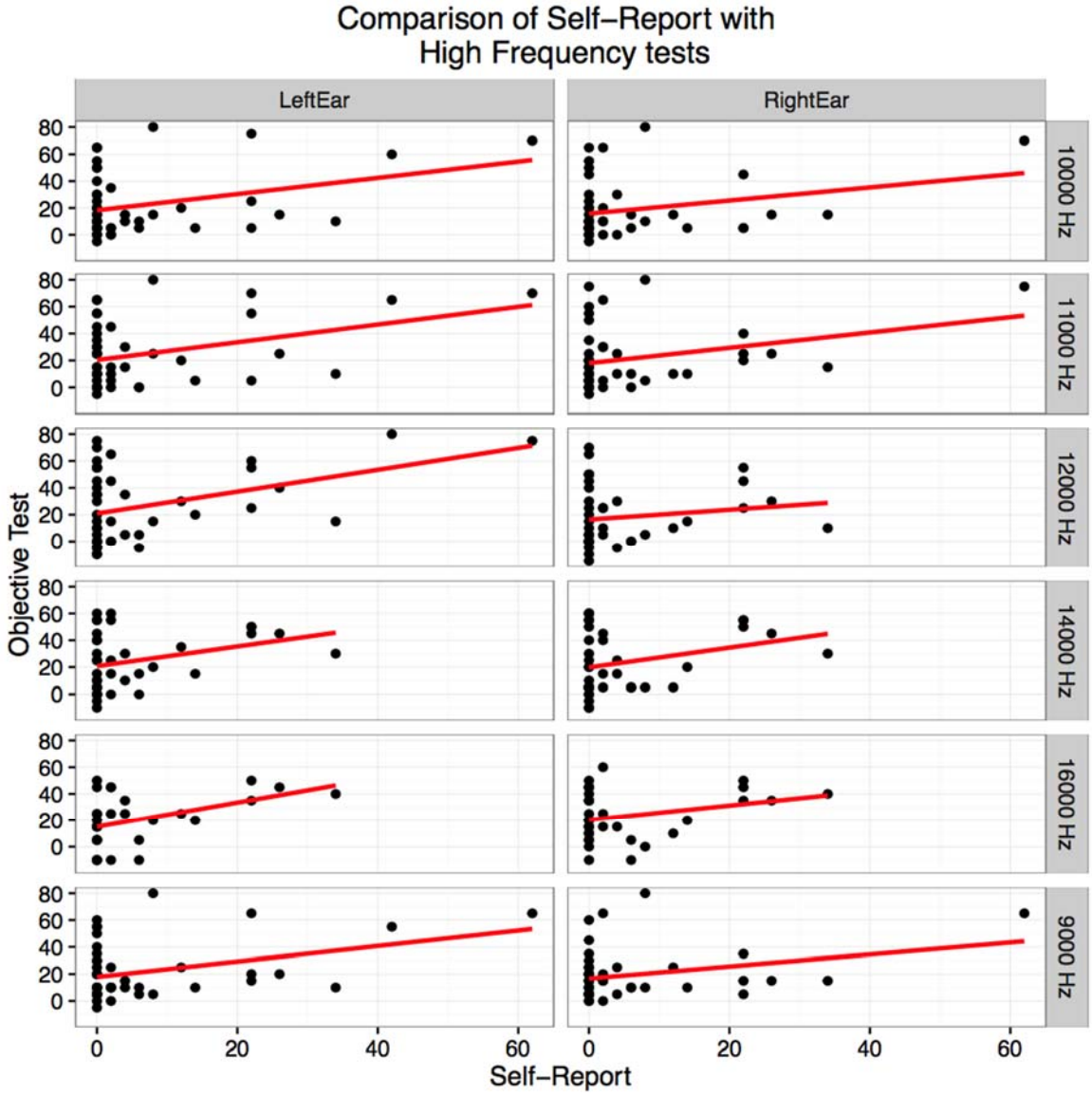

Figure: 5: The relationship between the self-report HHIA scores and objective test of ultra high-frequency pure-tone audiometry for each ear.

FIGURE 6

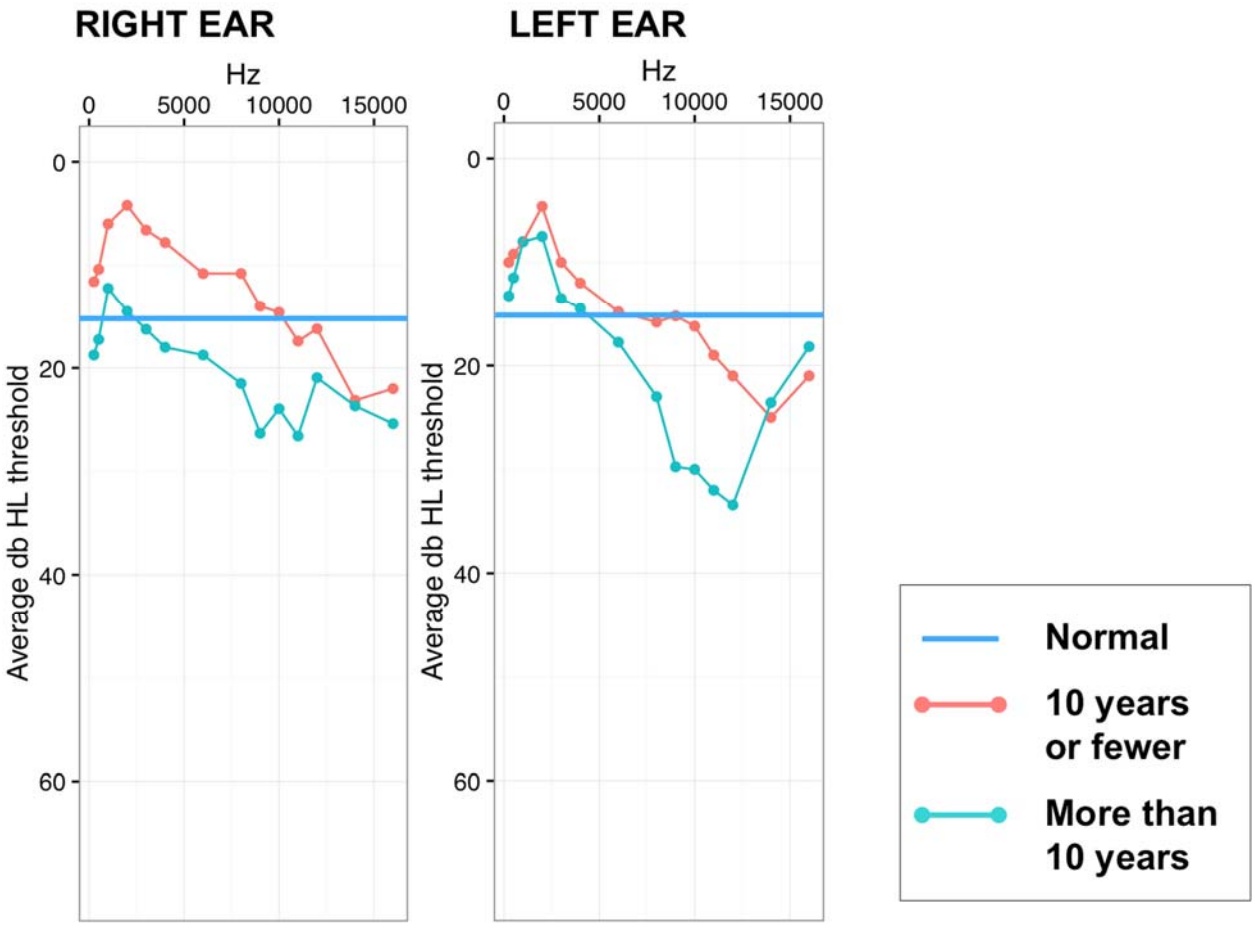

Figure 6: Graphical representation of an audiogram of average hearing thresholds (dB HL) across conventional and ultra high-frequencies (Hz), one displaying the right ear and one for the left ear, as shown above. A key is shown above representing the difference between those participants with CF taking tobramycin for 10 years or fewer and those taking tobramycin for more than 10 years, and the blue line indicating normal hearing thresholds.

APPENDICES

Appendix A: Hearing Handicap Inventory for Adults (HHIA) – Original Version
Granted permission from Dr. Craig Newman, Ph.D.
Revised to use at WUSM Center for Advanced Medicine, Adult Audiology
* = Designated items comprising of the HHIA-S – Screening Version

	ITEM	YES (4)	SOMETIMES (2)	NO (0)
S-1	Does a hearing problem cause you to use the phone less often than you would like?			
E-2*	Does a hearing problem cause you to feel embarrassed when meeting new people?			
S-3	Does a hearing problem cause you to avoid groups of people?			
E-4	Does a hearing problem make you irritable?			
E-5*	Does a hearing problem cause you to feel frustrated when talking to members of your family?			
S-6	Does a hearing problem cause you difficulty when attending a party?			
E-7*	Does a hearing problem cause you to feel frustrated when talking to coworkers, clients, or customer?			
E-8*	Do you feel handicapped by a hearing problem?			
S-9	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?			
E-10	Does a hearing problem cause you to feel frustrated when talking to coworkers, client or customers?			
S-11*	Does a hearing problem cause you difficulty in the movies or theater?			
E-12	Does a hearing problem cause you to be nervous?			
S-13	Does a hearing problem cause you to visit friends, relatives, or neighbors less often than you would like?			
E-14*	Does a hearing problem cause you to have arguments with family members?			

S-15*	**Does a hearing problem cause you difficulty when listening to TV or radio?**			
S-16	**Does a hearing problem cause you to go shopping less often than you would like?**			
E-17	**Does any problem or difficulty with your hearing upset you at all?**			
E-18	**Does a hearing problem cause you to want to be by yourself?**			
S-19	**Does a hearing problem cause you to talk to family members less often than you would like?**			
E-20*	**Do you feel that any difficulty with your hearing limits or hampers your personal or social life?**			
S-21*	**Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?**			
E-22	**Does a hearing problem cause you to feel depressed?**			
S-23	**Does a hearing problem cause you to listen to TV or radio less often than you would like?**			
E-24	**Does a hearing problem cause you to feel uncomfortable when talking to friends?**			
E-25	**Does a hearing problem cause you to feel left out when you are with a group of people?**			