

# OTOTOXICITY MONITORING OF ADULT PATIENTS WITH CYSTIC FIBROSIS

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A Doctoral Project Presented to the Faculty  
of  
San Diego State University  
and  
University of California, San Diego

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In Partial Fulfillment  
of the Requirements for the Degree  
Doctor of Audiology (Au.D.)

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By

AARON C. JONES  
JUNE 2008

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## ABSTRACT

Cystic fibrosis (CF) results in thickened mucus in the respiratory tract leading to chronic airway infections and eventually respiratory failure. These respiratory infections are treated using aminoglycoside antibiotics like tobramycin that can be ototoxic. Optimizing the care of CF patients requires treating the classical effects of CF while maintaining cochleovestibular function. Ototoxicity monitoring can ensure medication regimens are balanced with audiologic care when possible, but currently there is no monitoring standard. Nationwide there are 115 care centers accredited by the Cystic Fibrosis Foundation (CFF) including 95 adult programs and over 50 affiliate sites. Despite considerable data showing aminoglycoside ototoxicity, it is not clear if the CFF care facilities routinely identify patients with ototoxicity-related hearing loss and dizziness, or more importantly to what extent they are monitoring. Accordingly the aim of this doctoral project was to develop a practical ototoxicity monitoring protocol for adult patients with CF based on the following: recommendations from published scholarly and/or clinical research, analysis of data from the University of California, San Diego Medical Center-Thornton Adult CF Center's patient database, and survey of the CFF-accredited care facilities. Pure-tone thresholds and DPOAEs from adult CF patients revealed a high incidence of ototoxicity-related hearing loss and dizziness. Furthermore, many care center survey respondents reported suspected cochleotoxicity and vestibulotoxicity, but less than half monitor and few follow a protocol. These data illustrate the significance of ototoxicity in this population and the need for a monitoring standard.

## INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease that results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Riordan, Rommens, & Kerem et al., 1989). The normally translated CFTR protein functions as an ion channel regulator in cell membranes lining the respiratory, digestive and reproductive tracts as well as the pancreas, liver and skin (Online Mendelian Inheritance in Man, 2006). CFTR is involved in the appropriate function of mucus, sweat and digestive enzymes. The nonfunctional protein causes thickening of mucus secreted by tissues such as those lining the respiratory tract and pancreatic duct. Normal mucus forms a barrier that protects the cells of these tissues, but thickened mucus can block passages thereby fostering environments suitable for bacterial infection. Over 1,500 different CFTR disease-causing mutations have been identified in the Cystic Fibrosis Mutation Database (2006), but inheritance of a mutated CFTR gene from both parents is required for CF to develop.

Together with thickened respiratory mucus, defining characteristics of CF include pancreatic fibrosis and cysts. Diagnosis of the disease, however, is typically done using a sweat chloride test. Expressed CFTR mutation causes impaired salt absorption in sweat ducts resulting in excessively salty sweat that is both measurable and symptomatic of CF (Gibson & Cooke, 1959). Genetic tests using blood samples or buccal cells from the inside of the cheek are now used to supplement ambiguous sweat chloride test results and to provide the only fetal evidence of CF. According to the Cystic Fibrosis Foundation (CFF, 2006), diagnosis of CF occurs from birth to three years of age in more than 80% of cases, but diagnosis may occur in adulthood.

Difficulty breathing resulting from respiratory system blockage and infection is the most common symptom with which CF patients present although there are numerous other

symptoms ranging from sinusitis to diarrhea (National Heart, Lung and Blood Institute, 1995). Frequent coughing and daily physical therapy are required to facilitate drainage of mucus from the lungs. In addition, antibiotics and other medications are used to alleviate these symptoms. Regardless of physical therapy and medication, CF patients typically exhibit a pattern of persistent, low-grade respiratory infection often due to *Pseudomonas aeruginosa* bacteria which is the leading cause of lung infection and death among persons with CF (National Institute of Diabetes and Digestive and Kidney Diseases, 1997). Periodic intravenous and inhalation therapies as well as hospitalization are required to manage these respiratory infections, but the infections gradually damage the lungs and ultimately cause respiratory failure and premature death. Susceptibility to infections introduces a clinical challenge when treating CF patients because those infected with, for example, *Pseudomonas aeruginosa* pose a significant infection risk to other CF patients.

#### *Incidence and Prevalence of CF*

According to the CFF (2006), CF is most prevalent among Caucasians of northern European descent. Approximately 30,000 people in the United States (US) have the disease, corresponding to approximately 0.01% of the national population. In addition roughly 20,000 Europeans and 3,000 Canadians are affected. Approximately 1 in 3,000 Caucasian babies are born with CF in the US each year, totaling approximately 2,500 births per year (National Heart, Lung and Blood Institute, 1995). There is no cure for CF but increased understanding of the mechanisms underlying CF pathophysiology is leading to the development of new therapies. In 2005 the median age of survival among the CF population was 37 years (CFF, 2006).

### *Treatment of CF*

CF is medically treated using aminoglycosides, mucolytics, anti-inflammatories and bronchodilators. Generally aminoglycosides include neomycin, kanamycin, gentamicin, tobramycin, amikacin, streptomycin and netilmicin (Govaerts et al., 1990). Today tobramycin is the most widely used aminoglycoside to treat the *Pseudomonas aeruginosa* and other respiratory infections in CF patients thanks to its balance of effectiveness and side effects (Thomsen, Friis, Jensen, Bak-Pedersen, & Kildegård-Larsen, 1979). However, other aminoglycosides like gentamicin and amikacin are also used when tobramycin proves ineffective. In 2004 over 15,300 persons with CF were prescribed tobramycin at least once (CFF, 2004). Tobramycin can be administered intravenously or inhaled, but intravenous treatment is required for the best penetration of these airway infections. Typically intravenous tobramycin has greater effectiveness and is used with patients having chronic or acute *Pseudomonas aeruginosa* infection. Inhaled tobramycin is used as a regular maintenance therapy to reduce the risk of infection relapse (Littlewood, 1986). The nebulized tobramycin, which is more expensive to administer than intravenous tobramycin, directly reaches infected lung tissue thereby reducing the required dosage and the systemic toxicity relative to intravenous tobramycin.

### *Pathophysiology of Ototoxicity*

Aminoglycosides such as tobramycin are known to be ototoxic (Matz, 1993). ‘Ototoxic’ means having a damaging effect on the organs or nerves of the auditory or vestibular systems (Govaerts et al., 1990). Specifically ‘cochleotoxicity’ and ‘vestibulotoxicity’ are terms used to describe toxicity to the auditory and vestibular systems, respectively. Numerous studies have been performed to better understand the mechanisms of ototoxicity with aminoglycosides. Govaerts et al. (1990) estimated the incidence of aminoglycoside-

induced ototoxicity based on review of publications from 1975 to 1984 and reported incidences of cochleotoxicity (5 publications) and/or vestibulotoxicity (2 publications) among various populations and using various criteria for ototoxicity. Populations included children and older adults. Ototoxicity criteria ranged from a unilateral, 15-dB hearing loss at any one frequency to a unilateral, 20-dB hearing loss at two frequencies. Table I shows the calculated incidences of cochleotoxicity and vestibulotoxicity for tobramycin, as well as for other aminoglycosides, reproduced from Govaerts et al. (1990).

Table I. Incidence of aminoglycoside-induced ototoxicity as recalculated from literature data by Govaerts et al. (1990).

	Cochleotoxicity		Vestibulotoxicity	
	Incidence (%)	Sample size (n)	Incidence (%)	Sample size (n)
Gentamicin	8	437	14	171
Tobramycin	14	307	3	117
Amikacin	5	556	13	104
Netilmicin	3	1824	1	1382

Govaerts et al. (1990) further described the progression of degenerative cochlear changes from the basal end to the apical end. Outer hair cells (OHCs) are affected first followed by inner hair cells (IHCs), then supporting cells, spiral ganglia, Reissner's membrane and the stria vascularis. Degeneration propagates from the innermost row of OHCs to the outermost row, then further to the IHCs (Bamonte, Melone, Monopoli, Ongini, & Forlani, 1986). Govaerts et al. (1990) also noted that differences in cochleotoxicity and vestibulotoxicity might occur due to variable uptake of the various aminoglycosides by the endolymph and perilymph. Vestibulotoxic damage with aminoglycoside administration has been observed in the ampullary hair cells as well as the otoconial membranes (Lindeman, 1969).

The mechanisms of aminoglycoside ototoxicity are not completely understood, but evidence exists that suggests aminoglycosides cause the formation of free radicals (Priuska & Schacht, 1995), the disruption of normal mitochondrial function (Dehne, Rauen, de Groot, & Lautermann, 2002), and the overactivation of N-methyl-D-aspartate (NMDA) receptors (Segal & Skolnick, 1998). Aminoglycosides can interact with free transition metals like iron to form free radicals that are reactive and can damage hair cells and neurons (Priuska & Schacht, 1995). Specifically, these free radicals play a role in mitochondrial membrane permeability and mitochondrial protein synthesis, and can therefore lead to apoptosis of outer hair cells (Dehne et al., 2002). In addition, aminoglycosides can increase the influx of calcium ions to hair cells by way of NMDA receptor channels thereby causing hair cell and neuronal degeneration (Segal & Skolnick, 1998).

#### *Risk Factors for Ototoxicity*

Regardless of the ototoxicity mechanisms, results from numerous studies indicate the existence of specific patient risk factors for aminoglycoside ototoxicity. Dulon, Aran, Zajic, and Schacht (1986) as well as others concluded that the severity of cochleotoxicity and vestibulotoxicity varies between the different aminoglycosides. Gatell et al. (1987) further pointed out that advanced age, aminoglycoside type, “aminoglycoside serum levels, total aminoglycoside dose, duration of therapy, sex, peak temperature, presence of bacteremia, shock, liver cirrhosis, dehydration, previous otic pathology or renal failure, and development of renal toxicity” are possible risk factors predisposing patients to ototoxic damage with aminoglycoside administration. However, using results from univariate and multivariate analyses they also concluded that aminoglycoside type, patient age, and abnormally high trough aminoglycoside levels in serum are the primary risk factors for development of cochleotoxicity. Black and Pesznecker (1993) also emphasized the significance of renal

impairment on the rate of aminoglycoside ototoxicity. Furthermore, Lim (1986) noted that the progression of cochleotoxic damage with aminoglycoside administration appears similar to acoustic damage and hypothesized that both might be the result of impaired protein synthesis. In fact results from several research studies illustrate synergistically damaging effects of noise and aminoglycosides (Bhattacharyya & Dayal, 1984). Cochleotoxic and vestibulotoxic damage can occur quickly or slowly depending on the aforementioned risk factors and genetic predisposition (Fischel-Ghodsian et al., 1997). Genetic predisposition may result from a familial mitochondrial DNA mutation such as an A-to-G substitution at nucleotide 1555 (Prezant et al., 1993).

CF patients with tobramycin-induced ototoxicity may present with cochleotoxic and/or vestibulotoxic symptoms. As noted in Table I, the incidences of cochleotoxicity and vestibulotoxicity in patients specifically receiving tobramycin are reportedly 14 and 3%, respectively (Govaerts et al., 1990). Oftentimes the initial reported symptom of ototoxicity is high-frequency continuous tinnitus, which results from basal hair cell damage (Black & Pesznecker, 1993). Hearing loss begins in the high frequencies and progresses to lower frequencies commensurate with the etiopathological mechanism of ototoxicity. This hearing loss, which can range from mild to profound, can occur during or after aminoglycoside treatment and is sometimes reversible but usually permanent (Gatell et al., 1987). According to Black and Pesznecker (1993), the most common symptoms of vestibulotoxicity are imbalance, disequilibrium and ataxia.

In light of the known ototoxic effects of aminoglycosides, it is imperative to audiotically monitor patients receiving tobramycin or other aminoglycosides. In addition to tobramycin, other ototoxic medications are administered to help alleviate the symptoms of CF. Bronchodilators like albuterol are used to help maintain open respiratory passages

and can reportedly cause dizziness (U.S. National Library of Medicine & National Institutes of Health, 2007). In addition, salicylate analgesics (aspirin and aspirin-containing drugs) and non-steroidal anti-inflammatory drugs like ibuprofen are known to cause tinnitus and furthermore may be ototoxic in large doses. Although there appears to be no conclusive literature reporting hearing loss specifically as a result of ibuprofen use, McCabe and Dey (1965) reported temporary hearing loss (up to 28 dB) and tinnitus following aspirin treatment (925 mg four times a day) in five people with otherwise normal hearing sensitivity. Ibuprofen is currently administered to reduce inflammation in the respiratory system secondary to CF. Mucus-thinning drugs like pulmozyme, which are not known to be ototoxic, are used to help decrease mucus viscosity.

Persons suffering from CF inhale, take orally, or intravenously receive aminoglycosides and other ototoxic medications to fight infection and alleviate respiratory symptoms, but maximizing the quality of life among CF patients requires simultaneously ensuring the maintenance of hearing and balance. Serial audiologic monitoring is necessary to provide real-time feedback to the team of caregivers and thereby ensure that the administration of medications is balanced with audiologic care when possible. While there are general suggested guidelines, there is no standard for ototoxicity monitoring that addresses either specific diagnostic techniques or monitoring schedules. Together the audiologist and physician must determine an appropriate ototoxicity monitoring protocol based on expedience to patient care and resource availability.

#### *Current Guidelines for Ototoxicity Monitoring*

In 1994 the American Speech-Language-Hearing Association (ASHA) published guidelines for the “Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy”, indicating that the benefits of drugs such as aminoglycosides must be considered

in light of their potential to damage the auditory and/or vestibular systems. ASHA emphasized the importance of using a serial monitoring program to detect ototoxicity early during treatment and wrote that the goal of any ototoxicity monitoring program should be to detect changes in the auditory and vestibular systems before they are noticeable to the patient and thereby prompt intervention and modification of the medicinal regimen. The audiologist's scope of practice (ASHA, 2004) indirectly includes both defining and administering such a cochleotoxicity and vestibulotoxicity monitoring program through coordination with the physician, pharmacist and other caregivers.

No accepted clinical techniques for vestibulotoxicity monitoring exist despite reported cases of possible vestibulotoxicity (ASHA, 1994; Baarsma & Rijntjes, 1979; Black & Pesznecker, 1993; Black, Pesznecker, Homer, & Stallings, 2004). Baarsma and Rijntjes (1979), for example, detailed two case studies of patients who reported dizziness and unsteady gait associated with tobramycin administration, culminating in total and permanent loss of peripheral vestibular function. According to Black and Pesznecker (1993), vestibulotoxic drugs can affect both the vestibulo-ocular reflex (VOR) and the vestibulospinal system but patients often complain of vestibular abnormalities before they are notable in vestibular testing. To corroborate a patient's vestibular complaints, VOR testing can be performed by actively turning a patient's head and either visually observing nystagmus or analyzing associated recorded data (O'Leary & Davis, 1990). The dynamic visual acuity test may also be performed. Other bedside verifications of vestibular pathology include tests of gaze nystagmus as well as the Romberg standing test, Fukuda stepping test (Fukuda, 1959) and Unterberger stepping test. A description of these tests is beyond the scope of this paper, but they may prove useful in vestibulotoxicity monitoring of adult CF

patients because the tests can be performed quickly and do not require additional diagnostic instrumentation.

In the absence of an accepted vestibulotoxicity monitoring protocol, ASHA (1994) described an effective cochleotoxicity monitoring program to include the following elements:

“(a) specific criteria for identification of toxicity, (b) timely identification of at-risk patients, (c) pretreatment counseling regarding potential cochleotoxic effects, (d) valid baseline measures (pretreatment or early in treatment), (e) monitoring evaluations at sufficient intervals to document progression of hearing loss or fluctuation in sensitivity, and (f) follow-up evaluations to determine post-treatment effects.”

ASHA (1994) defined the criteria to indicate ototoxicity-induced hearing loss as follows: “(a) 20 dB decrease [sensitivity] at any one test frequency, (b) 10 dB decrease at any two adjacent test frequencies, or (c) loss of response at three consecutive test frequencies where responses were previously obtained.” These criteria are largely based on the research of Dobie (1983) who reported that the reliability and validity of a hearing loss determination are increased when the loss in hearing sensitivity occurs at adjacent test frequencies. ASHA further emphasized that repeat testing within 24 hours is required to verify changes in hearing sensitivity.

CF inpatients and outpatients receiving nebulized or intravenous tobramycin are at-risk for cochleotoxicity and vestibulotoxicity effects. ASHA (1994) specified that patients receiving cochleotoxic drugs should be counseled prior to drug delivery about the ototoxic risks, cochleotoxicity symptoms, as well as the synergistic effects of noise exposure and ototoxic medications. Prior to or within 72 hours of initiating treatment with a known

ototoxic drug like tobramycin, a baseline comprehensive audiologic evaluation should be performed (Fausti et al., 1992b). These data serve as a basis for making future clinical judgments regarding hearing loss due to the medication. The optimal ototoxicity monitoring and follow-up monitoring schedules are unique for each patient and are affected by their specific risk factors such as age, trough aminoglycoside levels, renal impairment, and noise exposure as well as responses on the patient questionnaire. Generally, however, weekly monitoring is recommended for patients receiving aminoglycosides (ASHA, 1994) unless specific patient symptoms warrant more frequent testing. Fausti et al. (1992b) recommended testing patients every 2-3 days during aminoglycoside administration in order to more quickly identify cochleotoxicity. Lerner and Matz (1979) even recommended daily questioning of patients receiving aminoglycosides regarding symptoms of ototoxicity. ASHA (1994) recommended follow-up evaluations immediately following, after 3 months, and after 6 months following cessation of medication with an ototoxic drug.

The patient questionnaire for adult CF patients receiving tobramycin should be focused on symptoms of ototoxicity as well as known risk factors. The patient should be queried regarding tinnitus, both unilateral and bilateral, since it is often the first reported symptom associated with ototoxicity (Black & Pesznecker, 1993). Likewise the patient should be asked if they have perceived any changes in hearing sensitivity or have had any dizziness or imbalance. Since loud noise and ototoxic medications have a synergistic effect (Bhattacharyya & Dayal, 1984), the patient should be questioned regarding noise exposure. Rabinowitz (2000) recommended asking the patient the following three questions regarding noise exposure since the definitions of both noise and exposure are subjective:

1. “Are you exposed to excessive noise in your workplace or through music or hobbies?”

2. Do you often have to shout to talk to someone at arm's length because it's so noisy around you?
3. How often do you use earplugs, earmuffs, etc.?"

The patient questionnaire should be completed during each patient evaluation, although questions regarding noise exposure may be abbreviated depending on the period since the most recent audiologic evaluation. In the absence of a validated ototoxicity questionnaire, these subjective data are readily obtained while recording patient histories; the need for a validated ototoxicity questionnaire, however, is apparent.

ASHA (1994) recommended serial cochleotoxicity monitoring by using air-conduction pure-tone thresholds in both ears for responsive patients. Octave frequencies from 500 to 8,000 Hz plus the half-octaves 3,000 and 6,000 Hz were recommended for bedside monitoring. Pure-tone threshold testing at frequencies >8,000 Hz should be done if possible since attempts to detect ototoxicity via monitoring of only pure-tone thresholds below 8,000 Hz have had mixed results. Meyerhoff, Maale, Yellin, and Roland (1989), for example, found no indisputable cases of ototoxicity in 44 patients receiving tobramycin or vancomycin for osteomyelitis.

Published data have illustrated the benefits of monitoring with high-frequency pure-tone audiometry (Fausti et al., 1983; Fausti et al., 1994; Fausti et al., 1999; Fausti et al., 2003; McRorie, Bosso, & Randolph, 1989). Fausti et al. (1983) reported that in an evaluation of 77 patients receiving aminoglycosides, hearing loss began at frequencies above 8,000 Hz; both asymmetric bilateral and unilateral hearing losses were identified, further justifying the simultaneous monitoring of both ears. Other early studies (Jacobson, Downs, & Fletcher, 1969; Tange, Dreschler, & van der Hulst, 1985; Dreschler, van der Hulst, Tange, & Urbanus, 1989) also illustrated earlier detection of ototoxicity by monitoring frequencies from 8,000 to

20,000 Hz since the basal end of cochlea is affected first. Dreschler, van der Hulst, Tange, and Urbanus (1989) concluded from a study of 119 subjects that high-frequency damage presents earlier than low-frequency damage and is 15 to 20 dB greater on average. Recent studies by Fausti et al. (1994, 1999, 2003) provided further evidence that high-frequency hearing is affected early by ototoxic medications and that identification of ototoxicity before frequencies below 8,000 Hz are affected can help prevent an impact to hearing at frequencies important for communication.

Even though some studies have shown it may be possible to establish an efficient, patient-specific set of frequencies for ototoxicity monitoring (Fausti et al., 1999; Fausti et al., 2003; Vaughan et al., 2002), ultra-high frequency audiometry still requires specific equipment not necessarily consistent with monitoring ototoxicity in CF clinics. In addition, it may be difficult to obtain reliable responses throughout a prolonged threshold test that includes both conventional and ultra-high frequencies, especially with patients whose responsiveness is sometimes limited by illness. Lastly there are no published ultra-high frequency threshold norms stratified by age and/or gender, which thereby necessitates the establishment of clinic norms prior to making cochleotoxicity judgments based on ultra-high frequency monitoring data.

Considerable research has demonstrated the benefits of cochleotoxicity monitoring using DPOAEs (Hotz, Harris, & Probst, 1994; Stavroulaki et al., 2006; Katbamna, Homnick, & Marks, 1998; Katbamna, Homnick, & Marks, 1999). Katbamna, Homnick, and Marks (1998) suggested that enhanced contralateral suppression of DPOAEs in pediatric CF patients receiving tobramycin might be an early indicator of ototoxicity. Katbamna, Homnick, and Marks (1999) further showed that longer DPOAE latencies and higher thresholds with steeper growth function may be earlier indicators of ototoxicity than are

DPOAE amplitude measures. In CF patients receiving tobramycin, the authors reported DPOAE latency increments with low-to-moderate doses of tobramycin, latency decrements with higher doses, and elevated high-frequency thresholds of response growth detection.

Results from recent research indicate a possible connection between ultra-high frequency (defined as 11,200 to 20,000 Hz) hearing, and DPOAEs at lower frequencies (4,000 to 8,000 Hz). Arnold, Lonsbury-Martin, and Martin (1999) proposed that DPOAEs at 4,000 to 8,000 Hz are sensitive to subtle changes in OHCs that are not detectable using pure-tone audiometry in that same 4,000 to 8,000 Hz range because these DPOAEs originate more apically in the cochlea and pass through the high-frequency area before exciting the cochlea. In another study, patient interviews, pure-tone thresholds and DPOAEs at <8,000 Hz from approximately 160 adult CF patients treated at the University of California San Diego's Thornton Hospital were analyzed (Zettner, Smith, & Lindeman, 2006). Patients with ototoxicity hearing loss had unexpectedly low DPOAEs on average relative to patients with comparable hearing loss due to noise. This finding is evidence that ototoxicity monitoring using DPOAEs at only conventional frequencies might be both expedient to patient care and a clinically efficient alternative to recording pure-tone thresholds at >8,000 Hz. Measurement of DPOAEs still requires, however, special equipment that may not be accessible to all CF clinics.

Other methods of cochleotoxicity monitoring have been proposed including auditory brainstem response (ABR) (Fausti, Frey, Henry, Olson, & Schaffer, 1992a; Mitchell, Ellingson, Henry, & Fausti, 2004) and electrocochleography (Keene & Graham, 1984). While these sensitive monitoring techniques may be appropriate for unresponsive patients (ASHA, 1994), they are not ideal for use with CF patients due in part to time constraints. Attempts to monitor ototoxicity using transient evoked otoacoustic emissions (TEOAEs)

have been made as well (Stavroulaki et al., 1999; Stavroulaki et al., 2002; Hotz, Harris, & Probst, 1994). However, Stavroulaki et al. (2002) reported compelling evidence that DPOAEs are preferred over TEOAEs for ototoxicity monitoring. In addition to showing greater frequency specificity with DPOAEs than with TEOAEs, the authors noted that DPOAEs seem preferable because they can be measured in the presence of greater patient hearing loss and over a broader range of frequencies.

#### *Proposed Protocols for Ototoxicity Monitoring*

Since the publication of ASHA's guidelines (1994), attempts have been made to develop effective ototoxicity monitoring protocols. Vasquez and Mattucci (2003) proposed a protocol for both cochleotoxicity and vestibulotoxicity monitoring of patients taking ototoxic drugs. The authors proposed routine testing of patients at every visit using the following: pure-tone audiometry at conventional frequencies and ultra-high frequencies up to 18,000 Hz, word recognition testing, tympanometry, OAEs, ABR if the patient is unable to provide behavioral responses, electronystagmography if applicable, and patient interview. Unfortunately implementation of this ideal ototoxicity monitoring protocol in a busy clinic is not realistic. Konrad-Martin et al. (2005) outlined the following specific questions that must be answered when developing an ototoxicity monitoring program: "What is the purpose of identifying ototoxic changes? What is the target population to be monitored? What are the methods to be used for identifying patients? What are the timelines to be used for baseline and monitoring tests? What are the tests to be used, and how can they be adapted for the target population in order to meet the program goals?" The importance of communicating between the pharmacy and the audiologist regarding specific medication regimens was emphasized. In addition, the sensitivity and specificity, speed, required equipment and cost of the tests must be considered (Konrad-Martin et al., 2005).

The ototoxicity monitoring protocol proposed by ASHA (1994) may not be appropriate for adult CF patients. Its proposal has generated debate and led to considerable research aimed at earlier detection of ototoxic effects. This research has provided evidence suggesting monitoring methods like DPOAEs may be more sensitive than pure-tone thresholds at  $\leq 8,000$  Hz. In addition these recent data have further highlighted the importance of monitoring pure-tone thresholds at  $>8,000$  Hz as well as monitoring for vestibulotoxicity. The adult CF population, however, presents numerous challenges for any ototoxicity monitoring effort.

#### *Challenges of Ototoxicity Monitoring*

Numerous obstacles exist to effective monitoring of ototoxicity in CF patients receiving tobramycin. Coordinating and communicating with the team of caregivers and patients, scheduling the ototoxicity monitoring of both inpatients and outpatients, and analyzing audiologic data are all challenges facing the ototoxicity monitoring team. The ototoxicity monitoring team is led by the audiologist and consists of a physician, pharmacist, and supporting staff ranging from a registered nurse to an audiology intern. Identification of current and upcoming CF inpatients and outpatients as well as their tobramycin regimen helps the audiologist schedule resources. In addition the patients themselves have specific schedules (often extensive) while in the clinic or hospital that can make arrangement of audiologic testing difficult. It is critical for the ototoxicity monitoring team to emphasize the importance of ototoxicity monitoring so patients understand its significance and priority in relation to their overall health and quality of life.

Interpretation of audiologic data is perhaps the greatest obstacle to effective ototoxicity monitoring of adult CF patients. Differentiating hearing loss due to ototoxicity

from other causes such as noise exposure, age, otologic disorders, genetics, and other medications makes identifying ototoxicity in this population particularly difficult since high-frequency hearing loss and compromised OHC function are common audiologic findings across these etiologies. The patient interview, therefore, is paramount to deciphering the audiologic data. Furthermore, ototoxicity monitoring of CF patients is sometimes not initiated until many years after their first exposure to aminoglycosides. The coupled effect of intravenous and inhaled tobramycin administered at home and in the hospital further confounds the audiologic baseline test results; for these patients the audiologic baseline may itself include effects of ototoxic medications. As previously described, CF patients may be administered multiple drugs simultaneously thereby making it difficult to correlate specific patient claims and audiologic data with tobramycin ototoxicity.

Variability of background acoustic noise in a typical physicians office/clinic setting makes effective audiologic testing difficult especially at frequencies below 1,000 Hz, although some research suggests repeated pure-tone thresholds obtained at frequencies up to 14,000 Hz are repeatable within  $\pm 10$  dB in a hospital room (Valente, Gullledge-Potts, Valente, French-St. George, & Goebel, 1992). A standard exists for permissible background noise levels (defined as causing  $< 2$  dB masking) when measuring pure-tone thresholds at 125 to 8,000 Hz (American National Standards Institute, 1999) but not for ultra-high frequency pure-tone thresholds ( $> 8,000$  Hz) and not for DPOAEs. In a study of DPOAE repeatability in normal-hearing adults, Dreisbach, Long and Lees (2006) found that DPOAE absolute levels varied no more than 10 dB (measured in a sound booth) for 98.4 and 87.5% of subjects with the stimulus level condition  $L_1/L_2=70/55$  dB SPL at frequencies at or below 8,000 Hz and between 8,000 and 16,000 Hz, respectively. In fact DPOAEs are used in practice for newborn hearing screening and other applications outside the sound booth. Due

to background noise and the numerous other sources of audiologic variability, it is imperative to have normative data unique to the specific CF clinical environment and test equipment.

Normative data are necessary for all tests in an ototoxicity monitoring protocol. For an adult CF clinic, these norms should be for people ages 16 through 60 years and should be obtained in environments and with equipment equivalent to those used for testing the CF patients. For example, normative data should be obtained for both pure-tone thresholds and DPOAEs if those tests are to be used in the protocol. These norms provide a basis for making ototoxicity judgments and if necessary affecting the tobramycin regimen. When discriminating between ototoxicity and presbycusis, age-specific normative thresholds published by the International Organization for Standardization (ISO) can be used (ISO, 2000). Figure 1 shows an example pure-tone audiogram for a 60 year old man with a cochleotoxicity diagnosis as well as the age- and gender-matched ISO norm.

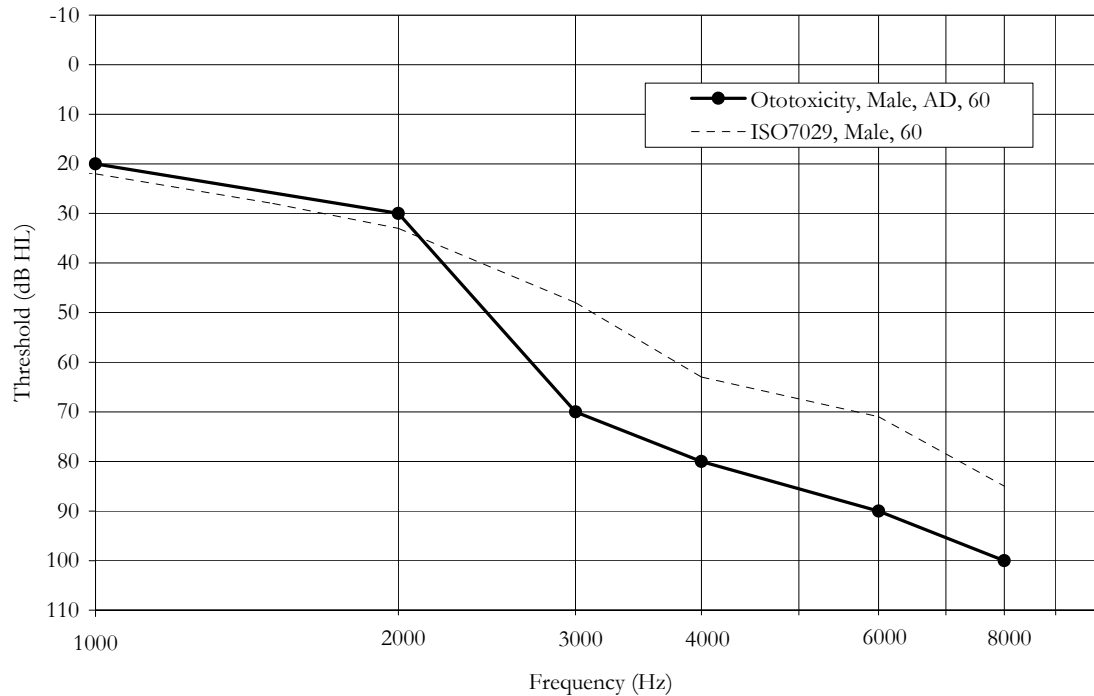


Figure 1. Example pure-tone audiogram for 60 year old male with cochleotoxicity (right ear) compared with age- and gender-matched ISO 95<sup>th</sup> percentile norm.

There 115 CF care centers, including 95 adult CF care programs, and over 50 affiliate sites nationwide that are accredited by the CFF. These centers are staffed by teams of medical professionals who provide CF-specific nutritional, psychosocial, pulmonary and gastroenterological care. Included among these adult care programs is the Adult CF Center at the University of California, San Diego Medical Center-Thornton (UCSD). Anecdotal evidence obtained from conversation with CF care center personnel suggests few of the CFF-accredited care centers are systematically or routinely monitoring for ototoxicity perhaps because they are uninformed or have financial and/or logistical constraints. However, the UCSD Adult CF Center began audiologic monitoring of its patients in 2005 using interviews, pure-tone audiometry and DPOAEs at standard frequencies. Initial analysis of these audiologic data revealed 49% incidence of ototoxicity related hearing loss ranging from very slight to profound among 104 patients (mean age 31.9 years). Over 45% of these

patients were tested two to seven times. Additionally, approximately 44 and 10% reported tinnitus and dizziness or imbalance, respectively, at the time of at least one test.

Regardless of the challenges associated with ototoxicity monitoring of patients with CF, this evidence suggests it is necessary to monitor the hearing and balance of people with CF as part of patient care programs. Accordingly the aim of this doctoral project was to develop a practical ototoxicity monitoring protocol for adult patients with CF based on the following: recommendations from published scholarly and/or clinical research, analysis of data from the UCSD Adult CF Center's patient database, and survey of the CFF-accredited care facilities.

## METHODS

### *Patients and Subjects*

This research was approved by the Institutional Review Board (IRB) at San Diego State University (#3700) as well as the IRB at UCSD (#071362X).

Medical records spanning nearly three years between 10/26/2004 and 7/25/2007 were retrospectively reviewed. Specifically, bilateral audiologic records for adult CF inpatients and outpatients treated at UCSD were reviewed for this study. Inpatients were tested whenever possible during their hospital stay, and outpatients were tested on Wednesday nights between 5:00 PM and 9:00 PM. There were 114 patients (58 males, 56 females), ages 17 to 62 years (mean 32) tested audiologically as of 7/25/07. The number of tests for each patient over that time frame ranged from one to nine. Medical records included subjective patient responses regarding symptoms of dizziness or imbalance, tinnitus, and loud noise exposure. Additionally objective audiologic data included in the medical records are pure-tone air conduction thresholds and DPOAE levels. Pure-tone air

conduction thresholds were obtained at octave frequencies from 500 to 8,000 Hz plus the inter-octave frequencies 3,000 and 6,000 Hz, and DPOAEs were obtained below 8,000 Hz.

Survey subjects were CF care facility administrators or their delegates. One hundred one (101) care facility administrators were sent a request for their participation in the survey as well as the Statement of Informed Consent (Appendix Figure A-1). Survey responses were collected from 10/22/07 to 12/20/07.

### *Instruments*

Outpatients and most inpatients were tested in a quiet clinic room using a Teledyne Avionics TA-7B portable audiometer with Telephonics TDH-50P supra-aural earphones. DPOAEs were recorded at 14 frequencies (4 points per octave) from 842 to 7,996 Hz using an Otodynamics ILO OAE system with a stimulus frequency ratio ( $f_2/f_1$ ) of 1.20 and stimulus levels of 65 ( $L_1$ ) and 55 ( $L_2$ ) dB SPL. Some inpatients were tested in a sound booth using a VIASYS Healthcare GSI 61 clinical audiometer with TDH-50P or E-A-RTONE 3A insert earphones. For the purpose of infection control, the test equipment was disinfected between use with each CF patient, and sound booth usage was limited to one CF patient every 24 hours.

Contact information for survey subjects was obtained using the online CFF care center database ([www.cff.org](http://www.cff.org)) and Internet searches. Survey respondents were solicited via email and anonymous responses were collected using the online service SurveyMonkey.com. The 10-question survey is shown in Appendix Figures A-2a through A-2c.

### *Analysis*

All audiologic interpretations, which were based on the worst ear, were provided by the same clinical audiologist using the established ISO 7029 (2000) pure-tone threshold

norms, UCSD DPOAE amplitude and noise floor norms (Zettner et al., 2006), and patient histories. Possible audiologic interpretations were as follows: normal pure-tone thresholds and DPOAEs, abnormal pure-tone thresholds and DPOAEs (ototoxicity), normal pure-tone thresholds and abnormal DPOAEs (early ototoxicity), noise exposure, noise exposure and ototoxicity, presbycusis, presbycusis and ototoxicity, noise exposure and presbycusis, and other (such as middle ear disorder). Pure-tone thresholds were judged on a frequency-by-frequency basis and were considered abnormal if they were poorer than the ISO 7029 (2000) 95<sup>th</sup> percentile norms. DPOAEs, which were also assessed on a frequency-by-frequency basis, were considered abnormal if they were more than one standard deviation poorer than the mean UCSD DPOAE amplitude norms. Diagnosis was made for the cause of hearing loss based on pure-tone thresholds, DPOAE absolute level data, patient age at the time of the test, and subjective patient responses regarding tinnitus, dizziness or imbalance, and loud noise exposure. DPOAE data obtained with a noise floor above the 90<sup>th</sup> percentile norm were considered invalid.

All data reduction and statistical analyses of both patient data and survey data were performed using Microsoft Excel.

## RESULTS

### *Patient Data*

As illustrated in Figure 2, 78 (68.4%) of the 114 patients had an abnormal audiologic interpretation based on pure-tone thresholds and/or DPOAEs; these 78 patients are comprised of those with ototoxicity (31), early ototoxicity (19), noise (9), noise and ototoxicity (5), presbycusis and ototoxicity (5), noise and presbycusis (4), other (4), and presbycusis (1) interpretations. Abnormal audiologic results were most often a result of ototoxicity (including early ototoxicity) and/or loud noise exposure and it comes as no

surprise that presbycusis is rare in this relatively young population. Furthermore, 60 (52.6%) of the 114 adult CF patients in this study had cochleotoxicity identifiable based on pure-tone thresholds and/or DPOAEs; this was comprised of 31 with ototoxicity, 19 with early ototoxicity, 5 with a combination of noise exposure and ototoxicity, and 5 with both presbycusis and ototoxicity.

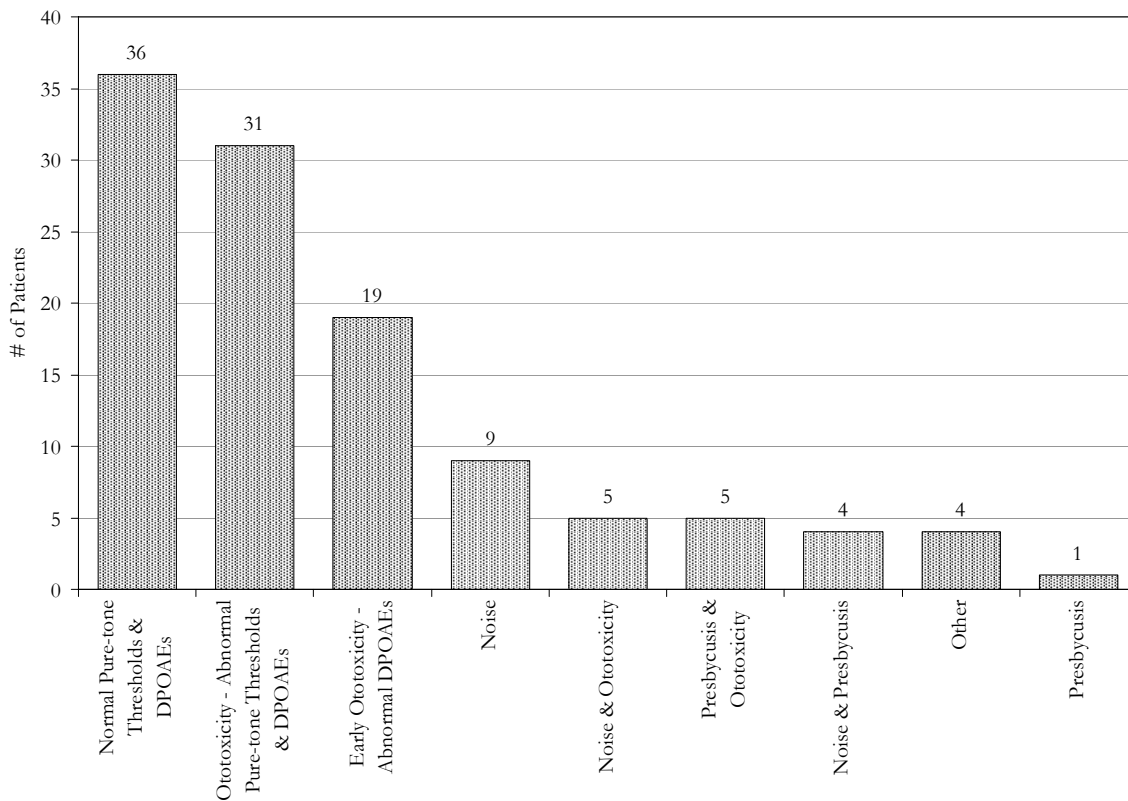


Figure 2. Audiologic interpretations for 114 patients at the UCSD Adult CF Center.

Figures 3a and 3b show example pure-tone thresholds from 1,000 to 8,000 Hz and DPOAEs from 841 to 7,996 Hz, respectively, for each of the audiologic interpretations illustrated in Figure 2. The ISO 7029 (2000) normative thresholds (95<sup>th</sup> percentile) are provided for reference in Figure 3a. Similarly the UCSD DPOAE level and noise floor norms are provided for reference in Figure 3b. Although data are not shown for all 114

patients, the examples provided are representative of the various audiologic interpretations indicated. Note that data obtained below 1,000 Hz are not shown because the pure-tone threshold data there are missing for some patients and are questionable for others due to background noise; it was only with patients tested in the sound booth that thresholds below 1,000 Hz were reliably obtained.

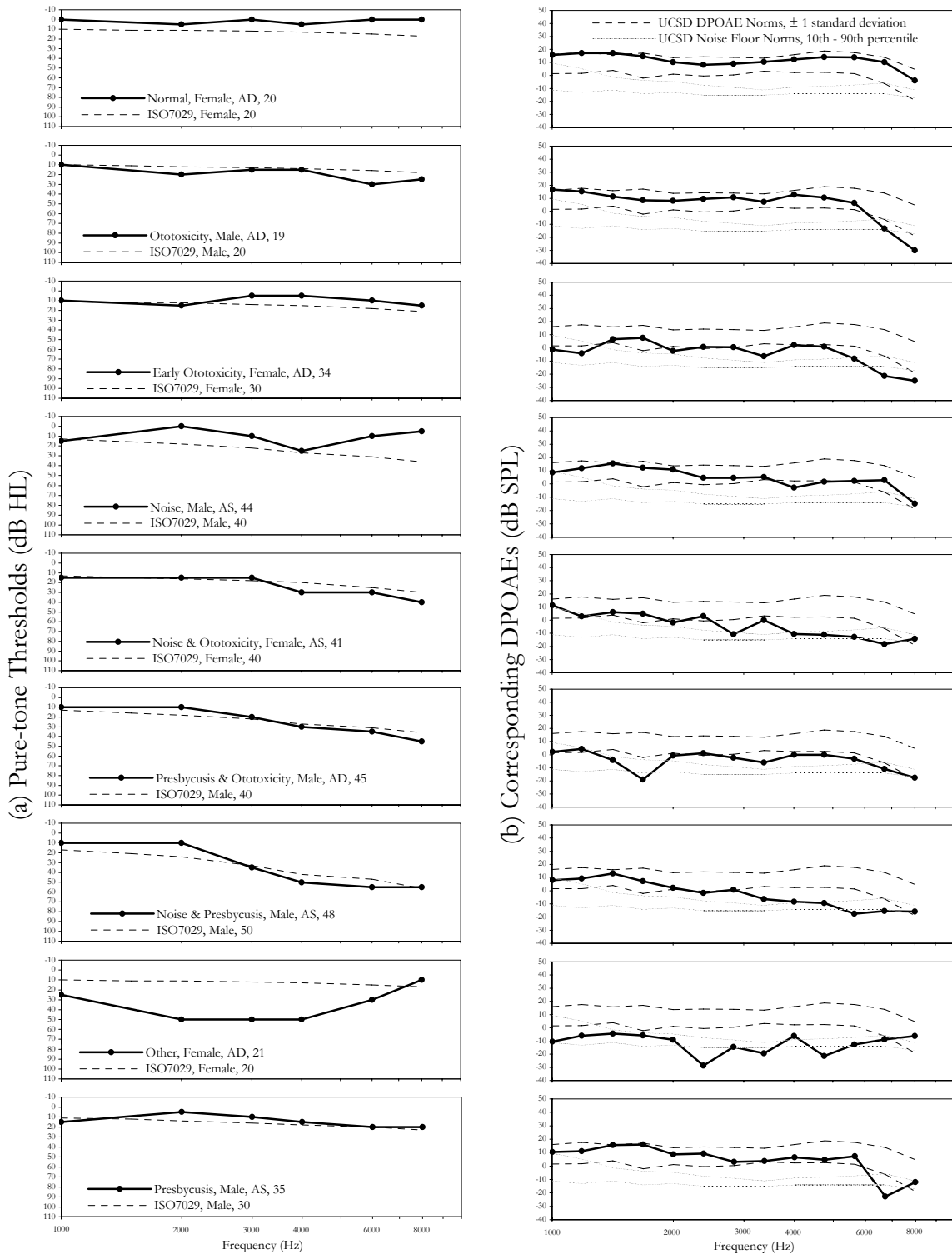


Figure 3. Example (a) pure-tone thresholds and (b) DPOAEs; CF patient data shown for interpretation, gender, ear, age; ISO 7029 95<sup>th</sup> percentile pure-tone norms shown for gender, age; DPOAE norms  $\pm 1$  standard deviation, and noise floor shown for 10<sup>th</sup> - 90<sup>th</sup> percentile.

The calculated sensitivities and specificities of ototoxicity monitoring metrics used in this study are shown in Table II. Sensitivity is herein defined as the percentage of those with a positive ototoxicity interpretation who also have an abnormal test result. Likewise, specificity is defined as the percentage of those with a negative ototoxicity interpretation who also have a normal test result. Of patients ultimately diagnosed with ototoxicity, 68% had abnormal pure-tone air conduction thresholds and 100% had abnormal DPOAEs. Of patients not having an ototoxicity interpretation, 67% had normal DPOAEs and pure-tone thresholds.

Table II. Sensitivities and specificities of metrics used in ototoxicity monitoring of CF adults.

Metric	Sensitivity (%)	Specificity (%)
Abnormal Pure-tone Air Conduction Thresholds	68	67
Abnormal DPOAEs	100	67
Subjective Tinnitus	45	56
Subjective Dizziness	17	85
Abnormal Pure-tone Air Conduction Thresholds or Subjective Tinnitus or Dizziness	85	41

Further analysis of the CF patient data revealed tinnitus and dizziness (the latter assumed to be associated with vestibulotoxicity) incidences of 44.5 and 16.4%, respectively. Coincidentally, 45 and 17% of patients ultimately diagnosed with cochleotoxicity and vestibulotoxicity, respectively, also reported tinnitus and dizziness, respectively, at the time of at least one test (Table II). Moreover 31.6% of patients having an early ototoxicity diagnosis (19 patients with abnormal DPOAEs and normal pure-tone thresholds illustrated in Figure 2) reported tinnitus and/or dizziness at the time of at least one test. If the ototoxicity metric is, therefore, defined as abnormal pure-tone thresholds *and/or* subjective complaint of tinnitus or dizziness, then the sensitivity is found to be 85% for this population

(Table II). Note that the reported sensitivity and specificity of subjective dizziness should be interpreted with caution owing to a relatively small sample size ( $n = 55$ ) for this metric.

### *Survey Data*

Twenty-six (26) CF care facilities participated in the online survey, which is 25.7% of the 101 facilities that were contacted for participation in the study and 19.3% of the 135 CFF-accredited facilities that treat adults. A summary of survey data is shown in Table III, and complete survey data are provided in Appendix Table A-Ia through A-Ic. High percentages, namely 96.2 and 61.5%, of survey respondents noted suspected cases of ototoxicity-related hearing loss and dizziness, respectively, among their patients. In addition, 42.3 and 30.8% of survey respondents reported monitoring for cochleotoxicity and vestibulotoxicity, respectively, but 81.8% (9 out of the 11 currently monitoring) of those do not follow a protocol. All responding clinics that monitor for vestibulotoxicity also monitor for cochleotoxicity.

Table III. Summary of survey data from CF care facilities.

CF clinics reporting:	Respondents (N = 26)	
	n	%
No suspected cases of ototoxicity	1	3.8
Suspected cases of cochleotoxicity	25	96.2
Suspected cases of vestibulotoxicity	16	61.5
Currently monitoring for cochleotoxicity	11	42.3
Currently monitoring for vestibulotoxicity (& cochleotoxicity)	8	30.8
Ototoxicity monitoring but not following a protocol	9	81.8

Figure 4 illustrates that survey responses were obtained from CF care facilities serving anywhere from 25 to over 300 patients; clinics with 25 to 49, 50 to 74, and 150 to 199 patients were each represented by 6 survey responses. Additionally Figure 4 shows the number of clinics within each size range that reported currently monitoring for ototoxicity.

Calculation of the Pearson product moment correlation coefficient (0.132) revealed there is not a significant correlation between the size of the clinic and whether or not it is currently monitoring for ototoxicity.

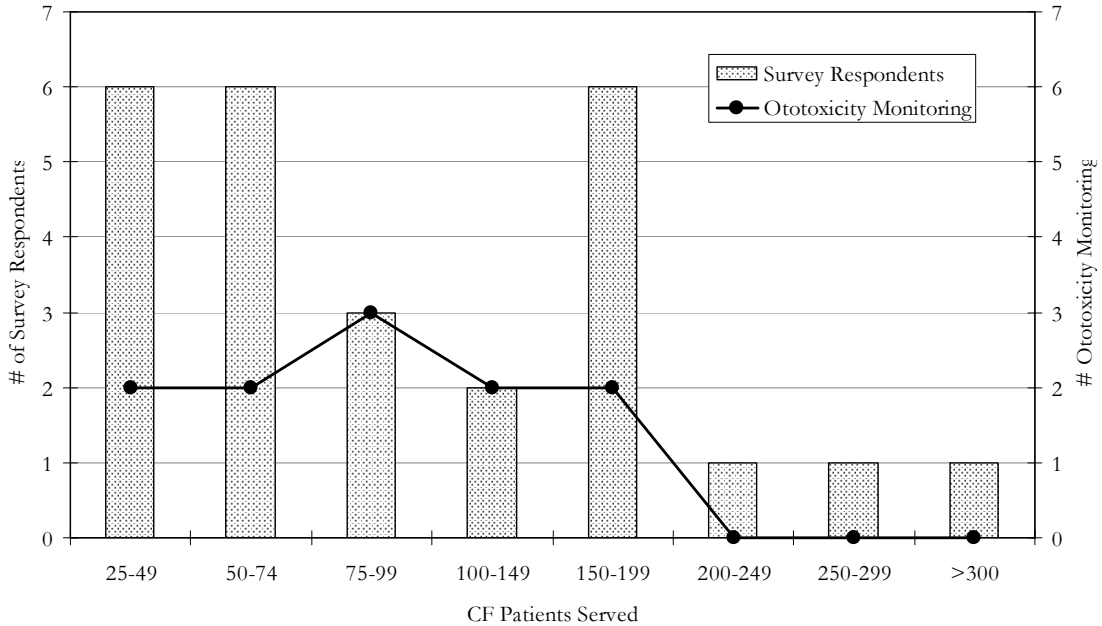


Figure 4. Distribution of clinic sizes among 26 survey respondents.

The data as shown in Figure 5 reveal a wide variety of monitoring methods being used by the CF care facilities. For both outpatients and inpatients, however, pure-tone audiometry at  $\leq 8,000$  Hz and patient questionnaire are most often used in ototoxicity monitoring; for example, 72.7% (8) of those who monitor outpatients for cochleotoxicity (11 noted in Table III) do so using pure-tone audiometry at  $\leq 8,000$  Hz. Figure 6 shows that an audiologist administers the monitoring at only 54.5% (6 out of 11) of facilities; note that one facility reported using both physicians and nurses to conduct monitoring. Only one of these facilities reported using DPOAEs, and the ototoxicity monitoring at that facility is administered by an audiologist.

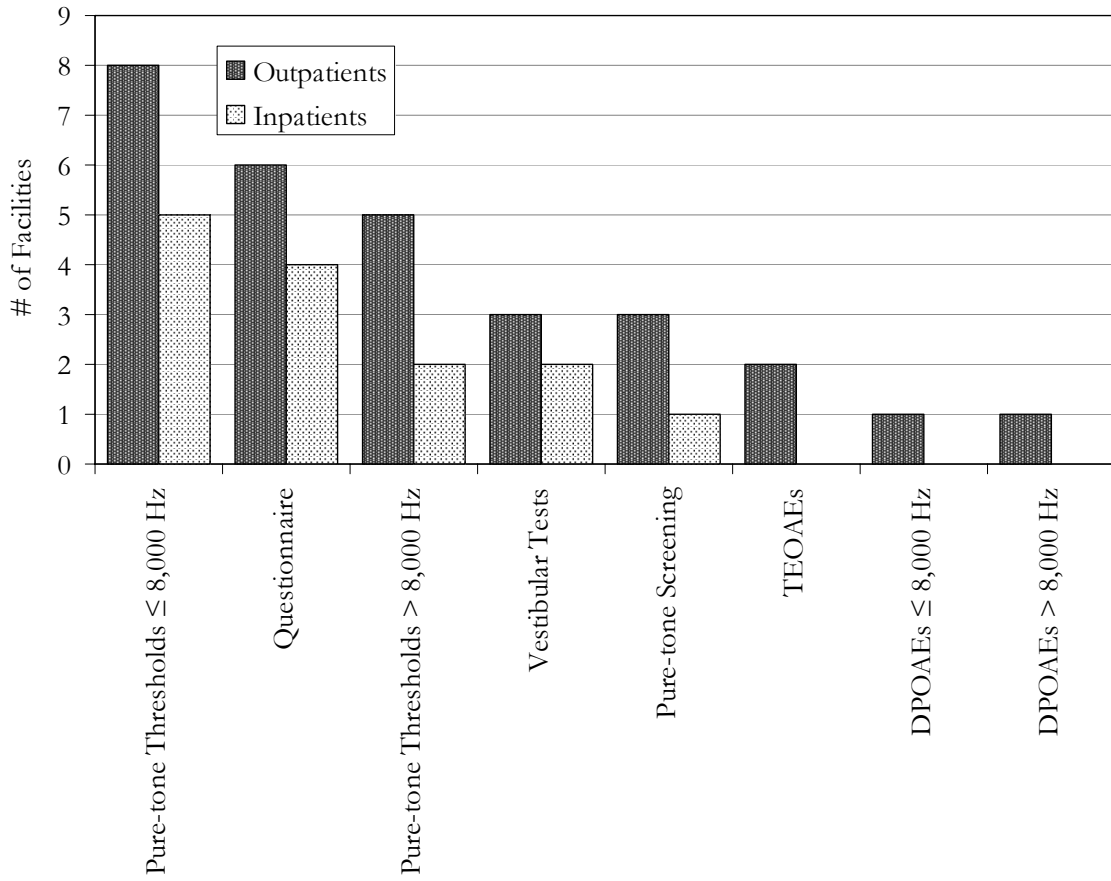


Figure 5. Reported ototoxicity monitoring methods used at adult CF care facilities.

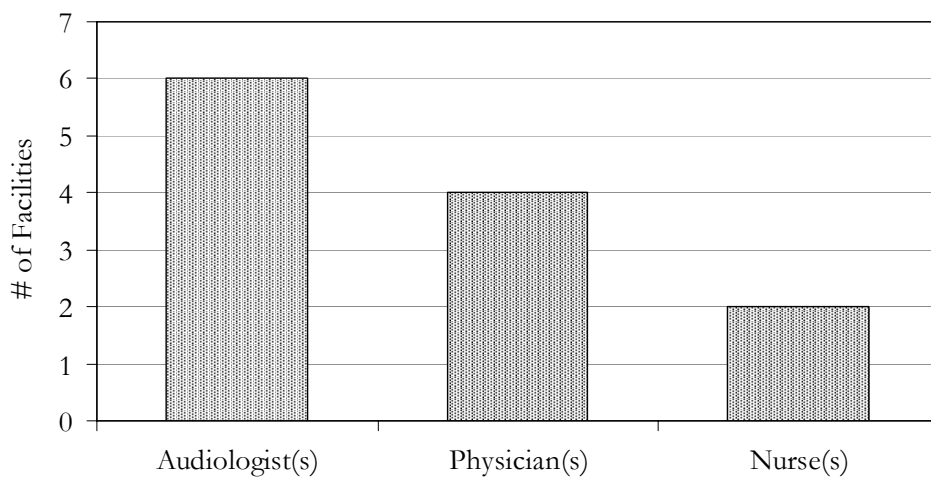


Figure 6. Reported ototoxicity monitoring staff used at adult CF care facilities.

## DISCUSSION

These patient data suggest incidences of cochleotoxicity (52.6%) and vestibulotoxicity (16.4%) for adults with CF are higher than reported by Govaerts et al. (1990) who calculated cochleotoxicity and vestibulotoxicity incidences of 14 and 3%, respectively based on review of the literature. Data reviewed by those authors were obtained with various non-CF populations (ranging from children to older adults) and using various criteria for ototoxicity not including DPOAEs, which may account for the higher incidences observed in the present study. The population of adults with CF may also have one or more ototoxicity risk factors not present in other populations.

The sensitivity and specificity data described in this paper imply that among adult patients with CF and ototoxicity there is 68% probability of abnormal pure-tone thresholds at  $\leq 8,000$  Hz as well as a 100% chance of abnormal DPOAEs. In addition, there is 85% probability that patients with CF and ototoxicity will have abnormal pure-tone air conduction thresholds at  $\leq 8,000$  Hz or subjective tinnitus or dizziness. DPOAEs are more sensitive to cochleotoxicity than are pure-tone thresholds at  $\leq 8,000$  Hz, but they are equally specific. Because the manifestation of cochleotoxicity may be confused with noise-induced hearing loss, presbycusis or other disorders, it is important to obtain subjective data to facilitate ototoxicity diagnosis.

Data obtained via survey of the CFF-accredited adult care facilities indicate the following: CFF adult care facilities have identified possible cases of ototoxicity; most care facilities do not monitor; when performed monitoring usually involves only patient questionnaire and/or pure-tone air conduction audiometry at  $\leq 8,000$  Hz and not per a specified protocol; and monitoring often is not conducted by an audiologist. So, ototoxicity is perceived to be a problem, but many of the care centers are not monitoring perhaps due

to financial and/or logistical constraints. A simple, cost-effective ototoxicity monitoring protocol is needed that can be implemented by the CF care centers to expedite patient care.

Pure-tone air conduction audiometry at  $\leq 8,000$  Hz in combination with patient questionnaire is a feasible and cost-effective means of audiotically monitoring the adult CF population since it requires a minimal amount of equipment that is already available at many CF clinics and minimal personnel training; DPOAEs and pure-tone threshold testing at  $>8,000$  Hz require relatively costly equipment and more extensive training. Based on the CF patient data and survey data, a minimum ototoxicity monitoring protocol is proposed in Figure 7.

Following counseling of the patients regarding the ototoxicity risks of their medications, cerumen management is performed if necessary. A patient questionnaire follows, minimally including questions regarding noise exposure and symptoms of tinnitus, hearing loss, dizziness and oscillopsia (the sensation that stationary objects are visually moving back and forth). If the patient has tinnitus or vestibular symptoms, they should be referred for a complete audiologic evaluation. In addition, however, these patients as well as those without tinnitus and vestibular symptoms should be evaluated using the ototoxicity monitoring protocol. This protocol includes measurement of pure-tone air conduction thresholds bilaterally at 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 Hz. These new data should be compared with serial data if available to facilitate data interpretation. If ototoxicity is suspected, the pure-tone threshold procedure should be repeated immediately and the equipment should be checked. If, after ruling out test-retest variability, equipment malfunction, and tester error, ototoxicity is still suspected, the physician should be notified. The results should be documented and testing should be repeated at least once per week

during aminoglycoside treatment. Testing should be further repeated at one week, three months and six months following cessation of treatment.

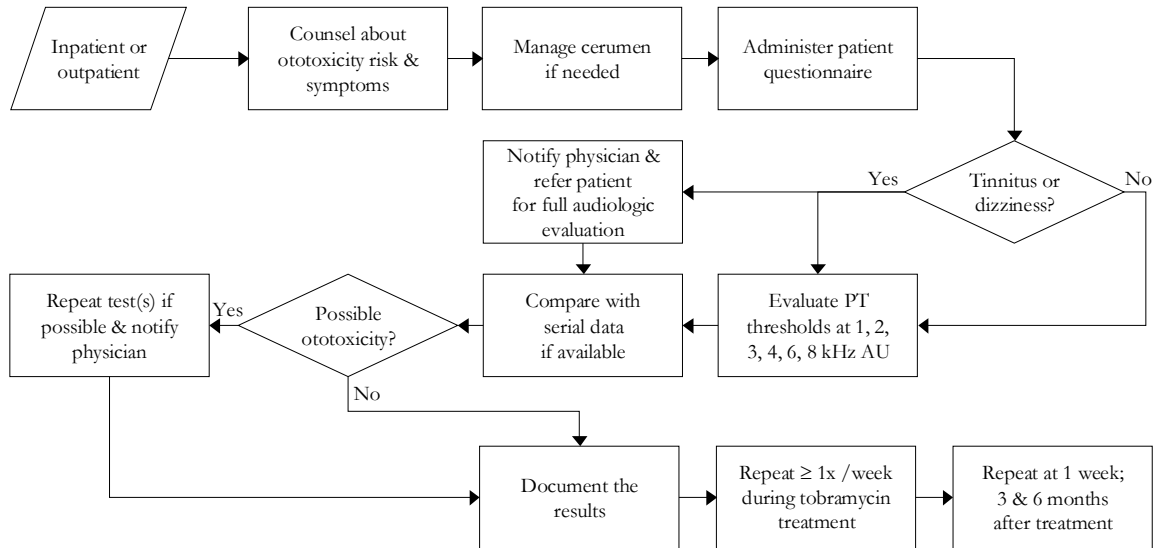


Figure 7. Proposed minimum ototoxicity monitoring protocol for CF adults.

As described earlier in this document there is a large body of literature that recommends the use of DPOAEs or pure-tone thresholds at >8,000 Hz for earlier detection of ototoxicity. Figure 8, therefore, describes a more thorough ototoxicity monitoring protocol for implementation at CF care facilities with resources to implement DPOAE and ultra-high frequency pure-tone testing and data management. The protocol is similar to the minimal one except that pure-tone thresholds at 8,000 to 18,000 Hz and DPOAE amplitudes are measured in both ears with the goal of identifying cochleotoxicity early and quickly affecting the tobramycin regimen before effects are noticeable to the patient; once again frequencies below 1,000 Hz are not evaluated due to variable background noise present in the physician’s office/clinic. Pure-tone audiometry  $\leq$  8,000 Hz is still used since a specific criterion for cochleotoxicity does not currently exist based on DPOAEs. DPOAEs,

however, might provide an earlier indication of ototoxicity (Arnold, Lonsbury-Martin, & Martin, 1999) and serve to both corroborate the pure-tone results and help identify patients who require more frequent audiologic assessment. The measurement of DPOAE latencies and/or growth function thresholds should be considered in the future if additional published data support the results of Katbamna, Homnick, and Marks (1999) who showed that DPOAE latencies and growth function thresholds may be earlier indicators of ototoxicity than are DPOAE amplitudes.

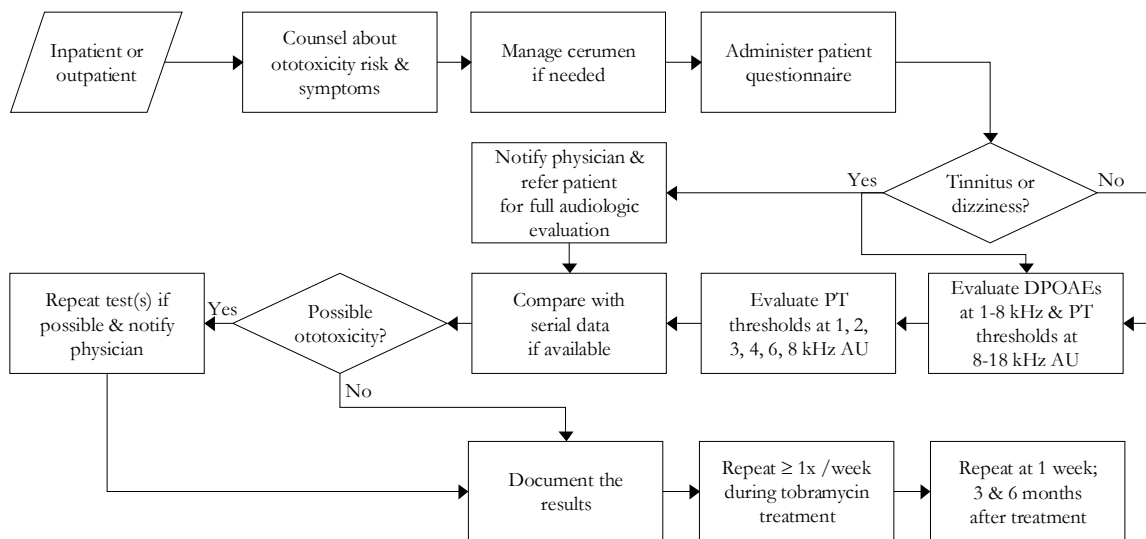


Figure 8. Proposed extended ototoxicity monitoring protocol for CF adults.

Based on the proposal from ASHA (1994), criteria for cochleotoxicity are as follows: a 20 dB poorer pure-tone threshold at one frequency, a 10 dB poorer threshold at two adjacent frequencies, or absent patient responses at the limits of the audiometer at three adjacent frequencies for which responses were previously obtained. If DPOAE amplitudes are measured, then patients showing levels more than one standard deviation lower than the clinical norms should be closely monitored for ototoxicity. Ideally ultra-high frequency pure-tone thresholds can be measured and compared with clinical norms and/or patient-specific

baseline data to provide corroborative evidence of ototoxicity in the event of abnormal DPOAEs. At frequencies where pure-tone threshold changes exceed 10 dB, threshold testing should be repeated after removing and replacing the headphones as well as otherwise verifying instrument functionality. Likewise DPOAE amplitude measurement should be repeated if results are suggestive of cochleotoxicity. The criterion for vestibulotoxicity is a positive report of dizziness, oscillopsia and/or imbalance with medication-induced onset, although patient vestibular complaints should be verified using a complete audiologic assessment.

Timely identification of patients to be monitored is the first step in successful implementation of the protocol. Candidate patients are those who are beginning a regimen of intravenous or inhaled tobramycin either at home or in the hospital, as well as those whose tobramycin regimens are being modified. Patients with advanced age (Gatell et al., 1987) or renal impairment (Black & Pesznecker, 1993) might be particularly susceptible to the ototoxic effects of tobramycin and should be prioritized accordingly. Candidate patients are counseled regarding cochleotoxicity and vestibulotoxicity risks as well as a possible synergism of cochleotoxicity and noise. A baseline audiologic evaluation should be scheduled for completion prior to or within 72 hours of initiating treatment (ASHA, 1994).

At the time of every audiologic assessment, otoscopy is performed first followed by completion of a patient questionnaire. Otoscopy helps identify any obvious factors such as cerumen or middle ear fluid that might affect the test results. In the event of occluding cerumen, the patient is counseled regarding cerumen management. During the subsequent interview, the patient is queried regarding unilateral and bilateral tinnitus since this can be the first reported symptom associated with cochleotoxicity (Black & Pesznecker, 1993), as well as perceived changes in hearing sensitivity, dizziness, oscillopsia, imbalance, and noise

exposure. As mentioned before, loud noise and ototoxic medications have a synergistic effect (Bhattacharyya & Dayal, 1984), which makes it important to ask patients about both occupational and recreational noise exposure, and to counsel patients regarding identification of noisy environments and use of hearing protection (Rabinowitz, 2000).

A baseline audiologic evaluation is performed that includes the following if possible: patient history taking, pure-tone (500 to 18,000 Hz if possible) and speech audiometry, tympanometry, word recognition testing, acoustic reflex threshold and decay testing, and DPOAE amplitude measurement. Minimally the baseline evaluation includes history taking, pure-tone threshold measurement and DPOAE amplitude measurement (if available) for comparison with subsequent ototoxicity monitoring data. Following baseline testing, pure-tone thresholds and DPOAE amplitudes (if available) are monitored at least once per week regardless of the inpatient/outpatient status. However, testing may be performed as often as once per day (Lerner & Matz, 1979) if the patient exhibits ototoxic effects and/or is advanced in age, has renal impairment, or has possible noise induced hearing loss. Testing is performed within one week after cessation of the tobramycin regimen then repeated once every three months for six months thereafter (ASHA, 1994). Referrals for more complete evaluation of hearing and/or balance are provided as necessary based on results from any of the serial monitoring evaluations.

#### *Research Limitations and Areas for Future Study*

There are several limitations in this study. Audiologic interpretation of the patient data is subjective. However, the presence of both pure-tone threshold data and DPOAE data increases confidence in audiologic interpretations. These data are inherently skewed because the determination of ototoxicity ultimately rested on DPOAE results. If a patient had normal pure-tone thresholds but low DPOAEs in the 4,004 to 7,996 Hz range, the

interpretation was “early ototoxicity” assuming the patient had a history of aminoglycoside exposure, even though there may be other etiologies. Since DPOAEs below 8,000 Hz may reflect pure-tone thresholds above 8,000 Hz (Arnold, Lonsbury-Martin, & Martin, 1999), ultra-high frequency pure-tone threshold testing may be used to corroborate DPOAE results especially in the case of an early ototoxicity interpretation; in this research the DPOAE results were not confirmed using other tests. Additionally since most adult CF patients have a long history of treatment with aminoglycosides and other potentially ototoxic drugs, the concept of a baseline audiometric examination is misleading. In this case it is important to use the patient as their own control and to compare their audiologic data with normative values.

Survey responses may not be an unbiased representation of the CFF-accredited adult care facilities. Those CF care facilities participating in the survey may have done so because they are already sensitive to the issue of ototoxicity among the adult CF population. Their responses, therefore, may not be indicative of all care facilities. Such a sampling bias would indicate in a higher prevalence of suspected cochleotoxicity and/or vestibulotoxicity among the CF care facilities than actually exists. Such a bias may also, however, imply that even fewer CF care facilities are monitoring for ototoxicity than suggested by the survey data.

Future study is warranted to further optimize the ototoxicity monitoring protocol for adults with CF. Ultra-high-frequency (>8,000 Hz) pure-tone audiometry is more sensitive to cochleotoxicity than audiometry at  $\leq 8,000$  Hz, but research must be done to determine whether it has acceptable specificity or its use must be limited to intra-patient data comparison. Since the inception of this doctoral project, the UCSD Adult CF Center has begun recording ultra-high frequency pure-tone thresholds. Even more sensitive may be ultra-high frequency DPOAEs, but the requisite equipment is rare. DPOAE latencies or

DPOAE growth functions (Katbamna, Homnick, & Marks, 1999) might be more practical than ultra-high frequency DPOAE amplitudes for early identification of cochleotoxicity among adults with CF and should be investigated since they can be measured using conventional DPOAE equipment.

Additional future study should focus on identification of vestibulotoxicity among the adult CF patients. Vestibular testing can currently be performed as needed when patients report subjective vestibular symptoms, but this testing is logistically cumbersome. A bedside screening for vestibulotoxicity, such as the dynamic visual acuity test, may provide objective data to substantiate symptoms and, therefore, reduce the number of referrals for full vestibular evaluations. Likewise such bedside testing may result in improved identification of vestibulotoxicity if it is performed even on those patients who do not report vestibular symptoms.

A validated ototoxicity monitoring questionnaire is needed to ensure consistent collection and interpretation of subjective data. Such a questionnaire should address hearing and balance, as well as tinnitus and lifestyle topics like noise exposure. These subjective data may be used in combination with objective data to assess the long-term health effects of changes to medication regimens based on ototoxicity monitoring data. Moreover these data may be used to better understand how ototoxicity monitoring ultimately affects quality of life.

## CONCLUSIONS

Patients with CF are typically treated with intravenous or inhaled tobramycin to fight bacterial respiratory infections and prolong life. Since tobramycin is a known cochleotoxic and vestibulotoxic aminoglycoside, it is important to monitor the hearing and balance of patients receiving the medication. Patient risk factors including advanced age, renal

impairment, genetics and noise exposure are critical considerations when identifying specific patients and schedules for ototoxicity monitoring. Ototoxicity monitoring data support early identification of cochlear and vestibular effects of tobramycin thereby allowing modification of the tobramycin regimen when possible and hopefully maximization of quality of life.

The incidence of ototoxicity found in this population of adults with CF is much greater than reported in the literature, emphasizing a need for increased awareness among the CFF-accredited adult care facilities. Minimally ototoxicity monitoring of adult CF patients should include pure-tone air conduction thresholds at standard frequencies and a patient questionnaire. Implementation of this protocol appears feasible and cost effective for the CFF-accredited adult care facilities. However, if possible DPOAEs and ultra-high frequency pure-tone audiometry also should be used for monitoring for even earlier identification of ototoxicity.

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## APPENDIX

OTOTOXICITY MONITORING OF ADULT PATIENTS  
WITH CYSTIC FIBROSIS

University of California, San Diego &amp; San Diego State University

## Statement of Informed Consent

Aaron Jones, a doctoral student, is conducting a research study to determine to what extent the adult care centers certified by the Cystic Fibrosis Foundation (CFF) are monitoring for ototoxicity-related hearing loss and dizziness. You have been asked to participate because you are the representative of a CFF-accredited care center. There will be approximately 100 participants in the study.

This research study is being conducted to partially fulfill the requirements for a Doctor of Audiology degree from the joint doctoral program in audiology at San Diego State University (SDSU) and the University of California, San Diego (UCSD). Based on survey results, analysis of CF patient audiologic data obtained at UCSD, and review of academic and clinical literature, a universal ototoxicity monitoring protocol may be proposed for use nationwide at the adult CF care centers.

As the representative of a CFF-accredited care center, you are invited to participate in the survey portion of this study. The 10-question online survey is intended to be completed by the CFF-accredited care center administrator or his/her delegate. It is expected that completion of the survey will take approximately 15 minutes. Survey responses are limited to once per care center, of which there are approximately 100.

There are no known risks associated with this research study. Participation in this survey is entirely voluntary. All responses to this survey are anonymous and no protected health information is collected. You may refuse to participate or withdraw at any time.

Since this research is not funded, no incentive/compensation for participation is being offered. There will be no direct benefit to participants for involvement in this study.

Questions regarding details of this research can be directed to Aaron Jones who is a Doctor of Audiology student in the School of Speech, Language, and Hearing Sciences at SDSU, (858) 752-1987. Questions regarding your rights as a participant in this research can be directed to the SDSU IRB at (619) 594-4109 and/or the UCSD Human Research Protections Program at (858) 455-5050.

Research records will be kept confidential to the extent provided by law.

Please keep this consent document for your records.

Your initiation and/or completion of the survey indicate that you agree to participate.

Figure A-1. Ototoxicity monitoring Statement of Informed Consent.

**Ototoxicity Monitoring of Adult Patients with Cystic Fibrosis**

**1. Untitled Page**

The goal of this brief survey is to determine to what extent the adult care centers certified by the Cystic Fibrosis Foundation are monitoring for ototoxicity-related hearing loss and dizziness. Please answer all applicable questions to the best of your ability. This survey is intended to be completed by the CF care center administrator or his/her delegate. Please limit survey responses to once per care center. All responses to this survey are anonymous. Thank you for your participation!

**1. What is your role in the CF adult care center?**

Physician     Nurse     Audiologist     Other Clinician     Other

**2. How many adult CF patients are treated by your care center?**

0     1-24     25-49     50-74     75-99     100-149     150-199     200-249     250-299     >300     Don't Know

**3. Has your CF adult care center identified patients with possible ototoxicity-related hearing loss and/or dizziness? Check ALL that apply.**

Yes Hearing Loss  
 No Hearing Loss  
 Yes Dizziness  
 No Dizziness  
 Don't Know

**4. Is your CF adult care center CURRENTLY monitoring patients for ototoxicity-related hearing loss and/or dizziness? Check ALL that apply.**

Yes Hearing Loss  
 No Hearing Loss  
 Yes Dizziness  
 No Dizziness  
 Don't Know

**5. If your center is NOT monitoring patients for the effects of ototoxicity, have you ever considered conducting such monitoring? Check ALL that apply.**

Yes Hearing Loss  
 No Hearing Loss  
 Yes Dizziness  
 No Dizziness

Page 1

Figure A-2a. Ototoxicity monitoring survey page 1.

**Ototoxicity Monitoring of Adult Patients with Cystic Fibrosis**

Don't Know  
 We Are Currently Monitoring

**2. If your center is NOT monitoring for the effects of ototoxicity, SKIP numbe...**

**6. If your center DOES monitor for the effects of ototoxicity, do you currently follow a specific ototoxicity monitoring protocol?**

Yes       No       Don't Know       Not Monitoring

**7. If your center DOES monitor for the effects of ototoxicity, what team member(s) is/are currently administering your ototoxicity monitoring program?**

Physician(s)     Nurse(s)       Audiologist(s)     Other Clinician(s)     Don't Know

**8. If your center DOES monitor for the effects of ototoxicity, how often on average is each adult CF INPATIENT tested? Select the BEST answer.**

Once Per Day     At Least Once Per Week     Bi-weekly     Once During the Inpatient Stay     Rarely / Only as Needed     Never / No Inpatients at This Facility

**9. If your center DOES monitor for the effects of ototoxicity, what test(s) are you currently conducting for ototoxicity monitoring of CF INPATIENTS? Check ALL that apply.**

Patient Questionnaire/Interview  
 Pure-tone Screening  
 Pure-tone Audiometry (<=8000 Hz)  
 High-frequency Pure-tone Audiometry (>8000 Hz)  
 Distortion Product Otoacoustic Emissions (<=8000 Hz)  
 High-frequency Distortion Product Otoacoustic Emissions (>8000 Hz)  
 Transient Otoacoustic Emissions  
 Vestibular Test(s)  
 No Inpatients at This Facility  
 Other (please specify)

**10. If your center DOES monitor for the effects of ototoxicity, what test(s) are**

Figure A-2b. Ototoxicity monitoring survey page 2.

**Ototoxicity Monitoring of Adult Patients with Cystic Fibrosis**

**you currently conducting for ototoxicity monitoring of CF OUTPATIENTS? Check ALL that apply.**

- Patient Questionnaire/Interview
- Pure-tone Screening
- Pure-tone Audiometry (<=8000 Hz)
- High-frequency Pure-tone Audiometry (>8000 Hz)
- Distortion Product Otoacoustic Emissions (<=8000 Hz)
- High-frequency Distortion Product Otoacoustic Emissions (>8000 Hz)
- Transient Otoacoustic Emissions
- Vestibular Test(s)
- No Outpatients at This Facility
- Other (please specify)  
\_\_\_\_\_

Page 3

Figure A-2c. Ototoxicity monitoring survey page 3.

Table A-Ia. Ototoxicity monitoring survey response data.

What is your role in the CF adult care center?		
Answer Options	Response Percent	Response Count
Physician	73.1%	19
Nurse	26.9%	7
Audiologist	0.0%	0
Other Clinician	0.0%	0
Other	0.0%	0
	answered question	26
	skipped question	0

How many adult CF patients are treated by your care center?		
Answer Options	Response Percent	Response Count
0	0.0%	0
1-24	0.0%	0
25-49	23.1%	6
50-74	23.1%	6
75-99	11.5%	3
100-149	7.7%	2
150-199	23.1%	6
200-249	3.8%	1
250-299	3.8%	1
>300	3.8%	1
Don't Know	0.0%	0
	answered question	26
	skipped question	0

Has your CF adult care center identified patients with possible ototoxicity-related hearing loss and/or dizziness? Check ALL that apply.		
Answer Options	Response Percent	Response Count
Yes Hearing Loss	96.2%	25
No Hearing Loss	0.0%	0
Yes Dizziness	61.5%	16
No Dizziness	23.1%	6
Don't Know	0.0%	0
	answered question	26
	skipped question	0

Is your CF adult care center CURRENTLY monitoring patients for ototoxicity-related hearing loss and/or dizziness? Check ALL that apply.		
Answer Options	Response Percent	Response Count
Yes Hearing Loss	42.3%	11
No Hearing Loss	57.7%	15
Yes Dizziness	30.8%	8
No Dizziness	61.5%	16
Don't Know	0.0%	0
	answered question	26
	skipped question	0

Table A-Ib. Ototoxicity monitoring survey response data.

If your center is NOT monitoring patients for the effects of ototoxicity, have you ever considered conducting such monitoring? Check ALL that apply.		
Answer Options	Response Percent	Response Count
Yes Hearing Loss	56.0%	14
No Hearing Loss	4.0%	1
Yes Dizziness	12.0%	3
No Dizziness	32.0%	8
Don't Know	0.0%	0
We Are Currently Monitoring	36.0%	9
	answered question	25
	skipped question	1

If your center DOES monitor for the effects of ototoxicity, do you currently follow a specific ototoxicity monitoring protocol?		
Answer Options	Response Percent	Response Count
Yes	9.5%	2
No	42.9%	9
Don't Know	0.0%	0
Not Monitoring	47.6%	10
	answered question	21
	skipped question	5

If your center DOES monitor for the effects of ototoxicity, what team member(s) is/are currently administering your ototoxicity monitoring program?		
Answer Options	Response Percent	Response Count
Physician(s)	33.3%	4
Nurse(s)	16.7%	2
Audiologist(s)	50.0%	6
Other Clinician(s)	0.0%	0
Don't Know	0.0%	0
	answered question	12
	skipped question	14

If your center DOES monitor for the effects of ototoxicity, how often on average is each adult CF INPATIENT tested? Select the BEST answer.		
Answer Options	Response Percent	Response Count
Once Per Day	0.0%	0
At Least Once Per Week	0.0%	0
Bi-weekly	0.0%	0
Once During the Inpatient Stay	7.1%	1
Rarely / Only as Needed	92.9%	13
Never / No Inpatients at This Facility	0.0%	0
	answered question	14
	skipped question	12

Table A-Ic. Ototoxicity monitoring survey response data.

If your center DOES monitor for the effects of ototoxicity, what test(s) are you currently conducting for ototoxicity monitoring of CF INPATIENTS? Check ALL that apply.		
Answer Options	Response Percent	Response Count
Patient Questionnaire/Interview	33.3%	4
Pure-tone Screening	8.3%	1
Pure-tone Audiometry ( $\leq 8000$ Hz)	41.7%	5
High-frequency Pure-tone Audiometry ( $> 8000$ Hz)	16.7%	2
Distortion Product Otoacoustic Emissions ( $\leq 8000$ Hz)	0.0%	0
High-frequency Distortion Product Otoacoustic Emissions ( $> 8000$ Hz)	0.0%	0
Transient Otoacoustic Emissions	0.0%	0
Vestibular Test(s)	16.7%	2
No Inpatients at This Facility	16.7%	2
Other	41.7%	5
	answered question	12
	skipped question	14

If your center DOES monitor for the effects of ototoxicity, what test(s) are you currently conducting for ototoxicity monitoring of CF OUTPATIENTS? Check ALL that apply.		
Answer Options	Response Percent	Response Count
Patient Questionnaire/Interview	46.2%	6
Pure-tone Screening	23.1%	3
Pure-tone Audiometry ( $\leq 8000$ Hz)	61.5%	8
High-frequency Pure-tone Audiometry ( $> 8000$ Hz)	38.5%	5
Distortion Product Otoacoustic Emissions ( $\leq 8000$ Hz)	7.7%	1
High-frequency Distortion Product Otoacoustic Emissions ( $> 8000$ Hz)	7.7%	1
Transient Otoacoustic Emissions	15.4%	2
Vestibular Test(s)	23.1%	3
No Outpatients at This Facility	0.0%	0
Other	30.8%	4
	answered question	13
	skipped question	13