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Pediatric Ototoxic Monitoring

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PEDIATRIC OTOTOXIC MONITORING

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ABSTRACT

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The prevalence of children living with cancer is estimated to be 129,221 in the United States (National Cancer Institute, 2022). The chemotherapy treatment that these children receive can cause ototoxicity, especially when platinum-based chemotherapy agents are used. Ototoxic monitoring is beneficial for patients undergoing chemotherapy treatment as it allows for treatment modification, dosage modification, early intervention, or auditory rehabilitation to take place based on the patient's hearing status. This is especially important due to the effect hearing loss may have on children's development and quality of life. There are several objective and behavioral auditory tests that can be used to assess hearing status. Behavioral audiometry, specifically pure tone testing, is the gold standard for assessing the hearing status of a patient. Behavioral results can be obtained for pure-tone audiometry and extended high-frequency audiometry conducted either conventionally, via conditioned play audiometry, or via visual reinforcement audiometry. However, young children require different tests in order to obtain reliable responses. The objective tests that may be used for these younger children include otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs). The results of auditory testing are then assessed using a grading scale in order to provide objectivity and consistency when interpreting the data, and in order to make the results more accessible to non-audiologist medical professionals. In order to provide more consistency, there should be standardized pediatric ototoxicity monitoring protocols aligned with the type of chemotherapy administered.

This manuscript will provide a literature review on these topics, generate protocol suggestions for pediatric ototoxicity monitoring, and discuss the research needs and future directions needed for evidence-based audiology practices.

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ALL	Acute Lymphocytic Leukemia
ABRs	Auditory Brainstem Responses
AML	Acute Myeloid Leukemia
ANSI	American National Standards Institute
ASHA	American Speech-Language-Hearing Association
dB	Decibel
DP	Distortion Product
EEG	Electroencephalogram
CHOP	Children's Hospital of Philadelphia
DPOAEs	Distortion Product Otoacoustic Emissions
EHFA	Extended High-Frequency Audiometry
FDA	Food and Drug Administration
HL	Hearing Level
Hz	Hertz
ISO	International Organization for Standardization
OAEs	Otoacoustic Emissions
MPANLs	Maximum Permissible Noise Levels
MPASPLs	Maximum Permissible Ambient Sound Pressure Levels
NCI	National Cancer Institute

NCI-CTCAE	The National Cancer Institute Common Terminology Criteria for Adverse Events
SEER	Surveillance, Epidemiology, and End Results program
SIOP	The International Society of Pediatric Oncology Boston Ototoxicity Scale
SNHL	Sensorineural Hearing Loss
TEOAEs	Transient Evoked Otoacoustic Emissions
VRA	Visual Reinforcement Audiology

CHAPTER 1

LITERATURE REVIEW

Audiologists provide ototoxicity monitoring services to patients receiving ototoxic chemotherapy treatments across the lifespan. Ototoxicity monitoring in pediatric patients has its own unique considerations and needs. This chapter will review the epidemiology of children with cancer, ototoxicity and the rationale for pediatric ototoxicity monitoring, pediatric auditory tests, and grading scales in use. This will serve as the foundation for Chapter 2, which will discuss the considerations for audiologists when implementing ototoxicity monitoring in young patients.

Epidemiology of Children with Cancer

As of January 1, 2019, there was an estimated 129,221 children living with cancer in the United States (National Cancer Institute, 2022). According to the Surveillance, Epidemiology, and End Results program, or the SEER, which is a program of the National Cancer Institute, incidence rates for 2015-2019 for children under the age of 20 years were 18.7 per 100,000 for females, and 20.2 per 100,000 for males (National Cancer Institute, 2022). Ward et al. (2014) estimated that by 2016, a child in the United States would have a .35% chance of developing cancer before they were 20 years old. This would represent one in every 285 children. Children under the age of 1 year have the highest incidence of cancer, with a rate of 27.0 per 100,000 children (National Cancer Institute, 2022). The next highest group would be 15 to19 year-olds with a rate of 25.3 per 100,000, followed by 1- to 4-year-olds at a rate of 23.0 per 100,000.

Generally, there is a higher incidence of cancer in males than females, although this varies by the type of cancer. According to the National Cancer Institute (NCI), 2022 the ten most common childhood cancers are leukemia, brain and other nervous system cancers, non-Hodgkin lymphoma, Hodgkin lymphoma, thyroid cancer, testicular cancer, soft tissue cancer, bone and joint cancer, ovarian cancer, and kidney and renal pelvis cancer. The incidence for each type of pediatric cancer does vary by age and by sex.

Leukemias

For children aged 0-14 years acute lymphocytic leukemia, or ALL, is the most common cancer making up about 26% of new cases of cancer in this age group (Ward et al., 2014). It is the most common type of childhood leukemia as it makes up about 80% of childhood leukemia cases (Caughey & Michels, 2009). Between 2003 and 2009, the 5-year survival rate for children with ALL was 90% (Ward et al., 2014). This means that 90% of children living with this cancer have not died due to their cancer five years or more after being diagnosed.

While treatments for ALL may vary between patients, common regimens for children and young adults include an induction chemotherapy regimen consisting of a combination of vincristine, an anthracycline, a corticosteroid, and L-asparaginase (Brown et al., 2020). These are typically administered over a four-to-six-week treatment regime (Inaba & Mullighan, 2020). After this, a consolidation phase, that may last several months, is implemented to get rid of any leukemic cells remaining. This phase will consist of similar drugs used in the induction phase and may also include methotrexate, cytarabine, 6-mercaptopurine, cyclophosphamide, and thioguanine (Brown et al., 2020; Inaba & Mullighan, 2020). Then, maintenance or continuation therapy will be completed to decrease the chance of relapse. This phase will likely last two to three years and integrate a daily dose of 6-mercaptopurine and a weekly dose of methotrexate

with or without vincristine and steroid pulses as well (Brown et al., 2020; Inaba & Mullighan, 2020). Throughout all of these phases, central nervous system directed therapy will likely be performed in order to clear leukemic cells from sites past the blood-brain barrier (Brown et al., 2020; Inaba & Mullighan, 2020). This therapy can also be incorporated into the other phases as cranial irradiation, intrathecal chemotherapy which is injected between the layers of tissue that cover the brain and spinal cord, or systemic chemotherapy that has central nervous system effects (Inaba & Mullighan, 2020).

Children ages 15-19 more commonly develop acute myeloid leukemia, or AML, rather than ALL. AML makes up about 4% of new cancer cases in this age group (Ward et al., 2014). The long-term survival rate for AML is about 70% (Rasche et al., 2018). Treatment is similar to that of ALL, although prophylaxis is less often required and higher doses of anthracycline may be given (Ward et al., 2014). The induction therapy phase should include cytarabine and anthracycline or mitoxantrone (Rubnitz & Kaspers, 2021). The consolidation phase will include more chemotherapy. However, higher-risk patients will undergo an allogenic hematopoietic stem cell transplant as soon as they are in a state of remission after the induction phase, and when a suitable donor is identified (Rubnitz & Kaspers, 2021).

Brain and Central Nervous System Cancers

Brain and other nervous system cancers make up about 21% of new cases in children ages 0-14, and about 10% in children ages 15-19 (Ward et al., 2014). From 2012 to 2018, the five-year relative survival rate for children aged 0-19 was 74.9% (National Cancer Institute, 2022). The three most common categories of central nervous system tumors are astrocytomas, medulloblastomas, and ependymomas (Ward et al., 2014). A recognized cause of brain tumors is high-dose therapeutic radiation. Thus, children who have been treated with cranial irradiation for

ALL or other types of cancers are at an increased risk of developing a brain tumor. Treatment depends on a variety of factors, but surgery is utilized whenever possible to remove as much of the tumor as possible. Then, chemotherapy and, or radiation therapy may be used. However, since radiation therapy may cause neurocognitive deficits, chemotherapy with reduced or delayed radiation is often utilized for children under three years of age. The chemotherapeutic agents used may include cisplatin, cyclophosphamide, etoposide, vincristine, carboplatin, and thiotepa (Thorarinsdottir et al., 2007).

Lymphomas

Non-Hodgkin lymphoma makes up about 6% of new cases in children ages 0-14 and 8% in children ages 15-19 (Ward et al., 2014). From 2012 to 2018, the five-year relative survival rate for children aged 0-19 was 90.4% (National Cancer Institute, 2022). The most common subtypes for children and adolescents are Burkitt lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, and anaplastic lymphoma (Ward et al., 2014). The incidence for each type of lymphoma varies around the world. Lymphomas account for around half of all childhood cancer cases in equatorial Africa, with a very high incidence of Burkitt lymphoma. In Africa, Burkitt lymphoma most commonly occurs in the jaw or around the eyes. Whereas in the United States, Burkitt lymphoma most commonly occurs in the abdomen. For most subtypes of non-Hodgkin lymphoma multiagent chemotherapy is the most common treatment (Ward et al., 2014). The multiagent chemotherapy used will commonly consist of cyclophosphamide, high-dose methotrexate, cytarabine, and intrathecal chemotherapy (Hochberg et al., 2009).

Hodgkin lymphoma is the most common cancer in children ages 15-19, making up about 15% of new cases in this age group and about 4% of new cases in children ages 0-14 (Ward et al., 2014). From 2012 to 2018, the five-year relative survival rate for children aged 0-19 was

98.1% (National Cancer Institute, 2022). Hodgkin lymphoma is sensitive to radiation therapy (Ward et al., 2014). However, radiation therapy is not a preferred treatment for children and adolescents because of the pulmonary and cardiac toxicity that it can cause. The most common treatment approaches combine multiple cycles of chemotherapy and radiation therapy (Diehl et al., 2004). Commonly used chemotherapy agents for treatment of Hodgkin lymphoma include doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide, and dacarbazine (Kahn & Kelly, 2018).

Thyroid Cancer

Thyroid cancer is more prevalent in children ages 15-19 than in other age groups, making up about 11% of new cases in this age group (Ward et al., 2014). From 2012 to 2018, the five-year relative survival rate for children aged 0-19 was 99.8% (National Cancer Institute, 2022). The most common treatment is a total thyroidectomy (Mancino & Kim, 2017; Paulson et al., 2019). This will likely be followed up by radioiodine therapy. Radioiodine therapy, which is a type of radiation therapy that consists of radioactive iodine, is utilized to kill off any remaining cancer cells post-surgery.

Testicular Cancer

Testicular cancer is more prevalent in children ages 15-19 than in other age groups, making up about 8% of new cases in this age group (Ward et al., 2014). From 2012 to 2018, the five-year relative survival rate for children aged 0-19 was 96.4% (National Cancer Institute, 2022). Cases of testicular cancer occur in all age groups but there is peak in incidence rates that occurs before children are three years old and at the post pubertal period (Ciftci et al., 2001). The primary treatment for testicular cancers is orchiectomy, or surgical removal of the testicles, which may be followed by radiation if necessary (Goldfarb & Fischer, 2017). Later-stage cancers

may also require chemotherapy, or adjuvant chemotherapy may be used as a preventative measure consisting of cisplatin, vinblastine, bleomycin, cyclophosphamide, and dactinomycin (Leonard et al., 1991).

Bone Tumors

Bone tumors make up about 7% of new cases in children ages 15-19 and 4% of new cases in children ages 0-14 (Ward et al., 2014). From 2012 to 2018, the five-year relative survival rate for children aged 0-19 was 71.3% (National Cancer Institute, 2022). The most common types of bone tumors found in pediatric patients are osteosarcomas and Ewing sarcomas (Ward et al., 2014). Osteosarcoma incidence increases with age in pediatric patients, and it is uncommon for it to develop in children who are younger than five years old. Previous radiation treatment is a risk factor for developing osteosarcoma. Treatment commonly consists of preoperative chemotherapy, surgical removal of the tumor, and postoperative chemotherapy (Luetke et al., 2014). Most chemotherapy regimens used to treat osteosarcomas consist of high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide (Luetke et al., 2014). Ewing sarcoma incidence rates are higher for older children and adolescents rather than for younger children as well (Ward et al., 2014). Treatment commonly includes induction chemotherapy, then surgical removal or radiation therapy, followed by postoperative chemotherapy. The chemotherapy agents commonly used include vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (Cripe & Yeager, 2015).

Ovarian Cancer

Ovarian cancer is most prevalent in children ages 15-19 than in other age groups, making up about 2% of new cases in this age group (Ward et al., 2014). From 2012 to 2018, the five-year relative survival rate for children aged 0-19 was 91.4% (National Cancer Institute, 2022). There

are fewer cases for girls younger than 15 years old than girls aged 15-19 (Ward et al., 2014). The primary treatment is surgery. However, patients who have nonlocalized disease will also receive chemotherapy. The chemotherapy regimens that are most commonly used to treat this type of cancer are known to cause possible hearing loss and kidney toxicity. These regimens commonly consist of carboplatin, etoposide, and bleomycin (Mann et al., 2000; Newton et al., 2019).

Ototoxicity

Ototoxicity is a pharmacological reaction that causes damage to the inner ear or to the auditory nerve (Ganesan et al., 2018). This can cause cochlear dysfunction resulting in hearing loss, or vestibular dysfunction resulting in balance issues. Ototoxicity is associated with many drugs such as platinum-based chemotherapeutic agents, aminoglycoside antibiotics, loop diuretics, macrolide antibiotics, and antimalarials (Ganesan et al., 2018; Landier, 2016). Symptoms may include hearing loss, tinnitus, and vertigo which may develop gradually or rapidly (Ganesan et al., 2018). Platinum chemotherapy agents such as carboplatin and cisplatin are known ototoxic drugs that can cause permanent, progressive hearing loss which is attributed to cochlear outer hair cell death (Clemens et al., 2017; Freyer et al., 2019; Waissbluth et al., 2018). Patients treated with these ototoxic drugs may experience tinnitus as well (Waissbluth et al., 2018).

Rationale for Pediatric Ototoxicity Monitoring

Ototoxic monitoring allows for the start and progression of a hearing loss to be observed during and after the course of pharmacological treatment of cancer. Having this knowledge may allow for treatment modification before severe auditory damage has developed (Landier, 2016). Treatment modification in these situations has often been done by reducing the dosage of chemotherapeutics changing the dosing schedule or changing the agent being used for an agent

known to be less ototoxic (Minasian et al., 2018). For example, cisplatin may be substituted with carboplatin (Minasian et al., 2018). The problem with this approach is that it can jeopardize the effectiveness of treatment. Thus, the prescribing physician or oncologist will need to decide about any change in treatment with all factors in mind. The audiologist's role is to support the physician by providing audiological data to be utilized in this decision making (Fligor, 2019). Even if there is no reasonable alternative treatment available, ototoxic monitoring would allow for early intervention and auditory rehabilitation for the patient (Landier, 2016). Anticipating audiologic interventions and counseling for the patient and their family would be a secondary role for the audiologist (Fligor, 2019).

In the future, audiologists may be involved in hearing loss prevention using otoprotectants as an emerging way to potentially protect auditory structures from damage caused by toxins. Currently, only one otoprotectant is approved by the U.S. Food and Drug Administration (FDA). Sodium thiosulfate was approved in September of 2022 to be used in order to reduce the risk of ototoxicity that is associated with cisplatin for pediatric patients being treated for localized, non-metastatic solid tumors (U.S. Food and Drug Administration, 2022). The PEDMARK® sodium thiosulfate injection is to be given intravenously and is approved for children older than one month of age. A limitation of sodium thiosulfate is that the safety and efficacy has not been determined when it is administered after cisplatin infusions longer than six hours (U.S. Food and Drug Administration, 2022).

Other otoprotectant clinical trials are underway for testing antioxidant molecules such as tiopronin, vitamin E, curcumin via both the transtympanic route, which means injected into the tympanic membrane, and via systemic administration (Romano et al., 2020; Waissbluth, 2020). Amifostine and D-methionine are other substances that are being tested (Romano et al., 2020).

However, there is a possibility for these compounds to interfere with the chemotherapy efficacy when taken systemically (Romano et al., 2020). N-acetylcysteine, steroids, and vitamin E have been found to have good auditory protection capacity when administered via the transtympanic route according to Riga et al. (2013). Ototoxicity monitoring for pediatric patients will likely evolve to include monitoring the hearing status outcomes for both ototoxic drugs and otoprotectant treatments in the future.

Consequences of Pediatric Hearing Loss

Hearing loss can have a dramatic effect on young children because they are in critical developmental phases of life. Younger children are developing speech, language, and fluency, which are skills that they will need to utilize for the rest of their lives. If hearing loss occurs from birth to any time before these skills are developed it is considered a prelingual hearing loss (Fligor, 2019; Nance et al., 2006). Hearing loss that occurs at birth is called congenital hearing loss and can be caused by genetic factors, environmental causes, or an unknown etiology (Hema Bindu & Reddy, 2008).

Prelingual hearing loss puts children at risk for developing speech and language delays (Fligor, 2019). This is because children learn by overhearing the speech models from people around them. However, very young children with a hearing loss will not be able to hear all that is said to, or around them and thus will not be able to utilize learning by overhearing the same way that their normal hearing peers can. Language and communication are vital for psychosocial development, cognition, learning, and literacy (Freyer et al., 2019; Gurney et al., 2007; Schreiber et al., 2014).

The severity of the hearing loss may also have an impact on the child's development. However, even children with mild to moderate hearing losses have lower language levels as

compared to normal hearing peers (Tomblin et al., 2015) Children with more minimal hearing losses tend to experience difficulty understanding speech in noisy environments (Bess et al., 1998).The children in the Tomblin et al. (2015) study who were fit with amplification earlier, showed better language development. This suggests that there are better outcomes for children receiving early intervention.

It has also been found that older children's educational achievements, social-emotional development, and quality of life can be negatively affected by hearing loss (Clemens et al., 2017; Fligor, 2019). Indirect effects on the child and family may include family tension due to breakdowns in family communication and social isolation (Bess et al., 1998).

Children who develop a hearing loss rather than being born with a hearing loss are considered to have acquired hearing loss. An acquired hearing loss can be the result of ototoxic medications, contraction of a bacterial or viral infection (otitis media, meningitis; cytomegalovirus), trauma (skull fracture, tympanic membrane puncture, ossicular chain discontinuity) or a variety of other disorders (Clemens et al., 2017; Freyer et al., 2019; Ganesan et al., 2018; Hema Bindu & Reddy, 2008; Landier, 2016;). The consequences resulting from acquired hearing loss can be mitigated by early intervention and if possible, prevented in the first place. The focus of this manuscript will be on acquired hearing loss due to ototoxicity.

Pediatric Auditory Tests

There are many different ototoxic monitoring protocols. However, uniformity is essential in the clinical setting (Fligor, 2019). If the outcomes are not uniform, there is no ability to compare data across clinical trial sites or across studies. Once the audiological data is collected, a grading scale is used to interpret the data in a way that is easy for the oncologist to quickly

understand. The oncologist can then utilize that information in their decision making. Below is an overview of common audiological tests that may be used for ototoxic monitoring.

Pure Tone Audiometry

The standard method for hearing assessment in older children is pure-tone audiometry which is a subjective test as it requires a behavioral response from the patient (American Speech-Language-Hearing Association, 2005; Bass & Bhaget, 2014; Landier, 2016). This assessment determines the lowest level that a person can detect a stimulus 50% of the time, known as their hearing threshold (HL), and it is measured at discrete frequencies. As mentioned previously, the hearing threshold is determined as the lowest level of intensity in decibels (dB) that a patient behaviorally responds to at least 50% of the time. Pure tones are the sound stimuli used because they are frequency specific. According to the American Speech-Language-Hearing Association (ASHA) Guidelines for Manual Pure Tone Audiometry (2005), air conduction measurements should be conducted at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. Bone-conduction measurements should be conducted at octave intervals from 250 to 4000 Hz and at 3000 Hz as well (ASHA, 2005). Hearing thresholds are considered to be in the normal hearing range at values 15 dB HL or less for children (Northern & Downs, 2014). Hearing thresholds between 16 and 30 dB HL would be considered a mild hearing loss, 31-50 dB HL would be a moderate hearing loss, 51-70 would be a severe hearing loss, and greater than 71 dB HL would be a profound hearing loss (Northern & Downs, 2014).

Pure-tone audiometry is typically done in an acoustically treated sound booth as standard practice (ASHA, 2005). However, developments in boothless audiometry enable pure-tone audiometry to be performed outside of a sound-booth. In order to effectively do this, the American National Standards Institute (ANSI) Maximum Permissible Ambient Noise Levels

(MPANLs) for Audiometric Test Rooms provided in the ANSI S3.1-1999 R2018 standard must be applied (Lord, 2019; Margolis & Madsen, 2015; Meinke & Martin, 2023). ANSI S3.1 provides the maximum sound pressure levels of ambient noise that can be tolerated in the test environment in order to test to 0 dB HL (Meinke & Martin, 2023). In order to determine allowable levels, the attenuation that the transducers provide should also be accounted for (Margolis & Madsen, 2015; Meinke & Martin, 2023). When testing outside of a sound booth the ambient noise levels must be monitored continually as they can be variable (Meinke & Martin, 2023).

Conventional pure-tone audiometry is performed by presenting tonal stimuli to a listener using a variety of transducers including insert earphones, supra-aural headphones or circumaural headphones so that ear specific information can be obtained. The patient may respond in several ways such as clicking a button or raising their hand when the stimuli is heard. Familiarization to the response task is recommended by ASHA (2005). This is accomplished by first presenting a signal at an intensity high enough to elicit a clear response. A common method of familiarization is using a 1000 Hz tone that is continuously on but completely attenuated and increasing the intensity level of the tone until a response occurs (ASHA, 2005). Familiarization may also be done by presenting a tone at 30 dB HL and then proceeding to obtain hearing threshold measurements if a clear response occurs, or by raising the intensity level to 50 dB HL if a response to 30 dB HL is not elicited. Presentation levels are increased by additional 10 dB steps if needed until a clear response is obtained (ASHA, 2005).

Determining the hearing threshold is most often done using the Hughson-Westlake method in which the stimuli is presented at an audible level and if the patient responds to the stimuli, decreasing the intensity by 10 decibels (ASHA, 2005). If the patient does not respond

when the stimuli is presented, the level will be raised five decibels and presented again. This process (up 5 dB if no response, down 10 dB if a response) is repeated until the lowest decibel level at which responses are given at least half of the time is found (ASHA, 2005). The test can be done using either an automatic or manual technique when testing adults and most children over the age of five (Kelly, 2009). Pure-tone audiometry may be difficult due to short attention spans and cognitive development possibly being a limiting factor (Yeung et al., 2013).

Conditioned Play Audiometry

Conditioned play audiometry can be used for children with developmental ages of two to five years, and possibly for older children who require more interactive testing to keep their attention (American Academy of Audiology, 2020). This is a variation of pure-tone audiometry that utilizes play reinforcement techniques as the child is taught how to give a play response to the stimulus (Hodgson, Chapter 32, 1985). The difference between conditioned-play audiometry and conventional audiometry is the way in which the patient is responding (American Academy of Audiology, 2020). When using conditioned-play audiometry the child will give a conditioned play response such as throwing a block into a bucket or changing a picture on the screen every time they hear the stimulus (Sabo, 1999). Conditioning is done by giving the child a brief training session in which the clinician is ensuring the child understands the task (American Academy of Audiology, 2020). The conditioning stimuli should be at a level that is easily audible to the child. The child should be able to respond at least two times in a row to the stimuli, unprompted before hearing threshold estimation should begin.

One of the earliest examples of play audiometry was developed by Dix and Hallpike (1947) and termed the peep-show technique. In this technique, the child was taught to press a button when both a sound and light stimulus were presented simultaneously. After pushing the

button, the child would see a picture illuminated. Eventually, when the child was responding well, the auditory stimulus would be presented alone, and each appropriate response would be reinforced. This process would then be repeated until hearing thresholds were obtained. Since the peep-show technique was developed, many similar procedures have been developed. Currently, the term conditioned play audiometry refers to any audiological testing that incorporates a play response that is taught to the child in response to the stimulus (Hodgson, Chapter 32, 1985).

Visual Reinforcement Audiometry

For children around six months to three years of age, visual reinforcement audiometry (VRA) techniques can be used (Widen & O'Grady, 2002). Visual reinforcement audiometry was introduced by Lidén and Kankkunen (1969) as a variation to the Conditioned Orientation Reflex developed by Suzuki and Ogiba (1960). Since VRA has been introduced the term has become more of a general term that describes any technique that utilizes a visual reinforcer when testing hearing. When using this technique, the desired response is the child turning towards the direction from which the sound originates (the source). When the child does this, reinforcement is given by a momentary lighting up and activation of a motorized toy (Sabo, 1999; Widen & O'Grady, 2002). Visual reinforcement is given in order to maintain the head-turn response of the child who instinctively searches for the sound source (Sabo, 1999). In practice, this means that a sound is played through a transducer (soundfield speaker, earphone) and when the child turns toward the sound source, the visual reinforcement is given. Visual reinforcement audiometry is commonly conducted through speakers in a sound-treated room (soundfield).

Visual reinforcement audiometry may also be performed using insert earphones or headphones, if the child will tolerate wearing them (Sabo, 1999; Weiss et al., 2016). If VRA is done using the soundfield speakers, the information obtained is not ear specific. Weiss et al.,

demonstrated that insert earphones can be useful during VRA testing in order to obtain ear specific information, especially for 18 to 24 month old children (2016). Children younger than six months old are not sufficiently developed to be able to respond to pure-tone audiometry testing and thus would need to be evaluated using objective test methods such as auditory brainstem response (ABR) testing or otoacoustic emission (OAE) testing which will be discussed in later sections. Some of the methods previously mentioned can also be utilized to complete extended high-frequency audiometry testing.

Extended High-Frequency Audiometry

Extended high-frequency audiometry (EHFA) measures hearing thresholds at frequencies between 9000 and 20,000 Hz (Rodríguez Valiente et al., 2016). Testing is conducted the same way as pure-tone audiometry and in the same testing environments, either in an acoustically treated sound booth or utilizing boothless audiometry techniques (ASHA, 2005). However, calibrated high-frequency circumaural headphones should be used as the transducer when performing this EHFA. Ototoxic agents initially affect the sensory cells that correlate with higher frequencies. Thus, testing these frequencies would indicate auditory damage before conventional pure-tone audiometry (Knight et al., 2017). An earlier study by Knight et al. (2007) found that ototoxic changes were first seen in EHFA, then in DPOAEs, and then in conventional pure-tone audiometry. The extended high frequencies tested in the study were 9000, 10000, 11200, 12500, 14000, and 16000 Hz. The DPOAE frequencies tested in the study were 11 log-spaced f2 frequencies between 1453 and 8438 Hz, and the conventional pure-tone audiometry frequencies tested were 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. However, it is difficult to obtain extended high-frequency hearing thresholds in younger children (Knight et al., 2007). The most common reason audiologists give for not conducting extended high-frequency audiometry is not

having the equipment for this test (Knight et al., 2007). However, more recently, audiometers have become equipped with extended high-frequency transducers and allow for EHFA capabilities as part of a standard instrumentation package. Of note, most existing ototoxicity grading scales do not acknowledge the presence of hearing loss in extended high frequencies (Ganesan et al., 2018).

Otoacoustic Emissions

Otoacoustic emissions, or OAEs, are an objective test of auditory function. This means that the patient is not required to behaviorally respond for the test to be conducted. Which makes OAE testing ideal for infants and non-responsive adults. For this test, a probe that has both a speaker for the stimuli to be played through and a microphone to pick up the evoked response is placed in the patient's ear. The stimulus is then repeatedly played, and the probe microphone detects and records the low-level response emitted from the cochlea. OAEs may be more sensitive to initial ototoxic damage than conventional pure-tone audiometry (Knight et al., 2017). Otoacoustic emissions are not a measure of hearing level, but rather they are a measure of hair cell functionality within the cochlea. Otoacoustic emissions evaluate the outer hair cells which are one of the first structures in the inner ear to be damaged by ototoxins.

However, it is important to note that OAE testing is also sensitive to middle ear pathologies, or any conductive hearing losses as this will block the OAE from being measured in the ear canal. Middle ear pathologies, such as otitis media, are common in the pediatric population, and especially in those children who are immunocompromised due to ototoxic agents (Ganesan et al., 2018). These middle ear pathologies can cause OAEs to be undetectable because they prevent the evoked auditory emission from traveling backwards from the cochlea through the middle ear to the ear canal where the measurement microphone is positioned. Currently,

OAEs cannot be used individually for ototoxic monitoring because there is no grading scale that incorporates this data (Fligor, 2019).

There are multiple types of OAEs, and the tests are named based on the stimuli used to evoke them (Dhar & Hall, 2018, p. 115-153; Northern & Downs, 2014). There are distortion product OAEs (DPOAEs), transient evoked OAEs (TEOAEs), and spontaneous OAEs. Spontaneous OAEs can be recorded in some individuals without any explicit stimulation but do are not universally present in all ears. However, DPOAEs and TEOAEs are types of OAEs used routinely in the clinical setting.

Distortion Product Otoacoustic Emissions

Distortion product OAEs are the most commonly used type of OAE testing performed in the clinic setting. This test puts two stimulus sounds that are a tonal pair into the ear known as $f1$ and $f2$ and measures the distortion that is produced in the cochlea and detected in the ear canal using sensitive microphones in the OAE probe. The distortion product (DP) is the response to the stimuli that a healthy cochlea generates and emits (Northern & Downs, 2014). This acoustic response is composed of tonal signals with frequencies that are arithmetically related to the frequencies of the stimuli tones. The frequencies of the responses are determined by the $f1$ and $f2$ stimuli tones and can be at frequencies $2f_1$-$2f_2$, $2f_2$-$2f_1$, or $3f_1$-$2f_2$ (Lonsbury-Martin & Martin, 1990). The $2f_1$-$2f_2$ is the most commonly used clinical DPOAE measurement for both adults and pediatrics.

Decreased distortion product amplitude levels correspond to outer hair cell damage. Results of the DPOAE test are plotted on a DP-gram with the amplitude displayed as a function of the stimulus frequency (Northern & Downs, 2014). If DPOAEs are present, the patient has hearing thresholds better than approximately 50 to 60 dB HL (Reavis et al., 2011) In the Reavis

et al. (2011) study, the DPOAE responses are considered present if the amplitude is greater than -20 dB SPL and the DPOAE amplitude was 6 dB or greater than the noise floor. Currently, if changes in DPOAEs are seen, they should be compared to behavioral hearing threshold changes, as there is not a standard for what is considered a significant ototoxic related DPOAE change (Reavis et al., 2011). Cisplatin exposures have been associated with changes in DPOAE responses for children and adults (Knight et al., 2007; Reavis et al., 2011).

Transient Evoked Otoacoustic Emissions

Otoacoustic emissions that are evoked by using brief click (broadband) or tone-burst stimuli are referred to as click-evoked or transient evoked OAEs (TEOAEs). In order to determine the physiologic condition of the test ear, the response to the stimulus is compared to the noise floor and analyzed in narrow frequency bands (Northern & Downs, 2014). Since a broadband stimulus is used, TEOAEs emit a wide frequency response ranging from 500 to 4000 Hz. The clicks or tone-pip stimuli are brief and repeatedly presented in order to average the responses. The TEOAE response typically occurs four to fifteen milliseconds after the stimuli is presented. Responses can typically be measured in ears that have hearing thresholds better than approximately 30 to 40 dB HL. If hearing thresholds are poorer than this, TEOAE responses will be absent. When TEOAEs are used as a hearing screening tool, responses must be present and at least 5 dB above the noise floor. Studies have shown that TEOAEs are sensitive enough to detect aminoglycoside-induced ototoxicity (Hotz et al., 1994; Naeimi et al., 2009)

Auditory Brainstem Response

An ABR test is an objective test used to evaluate the integrity of the auditory system (Crumley, 2011). The test measures auditory function via neuronal activity measured up to the level of the brainstem (Fria, 1985). Since it is an objective test measuring neuronal activity, there

is no subjective response to the stimuli required from the patient. However, to obtain reliable test results the patient must be still and quiet so that muscle artifact and other noise is minimized when obtaining the response. Therefore, the patient must be cooperative, asleep or sedated. Auditory brainstem responses are created by using acoustic stimuli (clicks or tones) to trigger a synchronous neural depolarization that travels from the auditory nerve to the cerebral cortex (Crumley, 2011). Neural activity is measured using three to four surface electrodes placed on the surface of the skin on the head (Crumley, 2011). The measured response is recorded onto a graph known as the ABR waveform. This waveform consists of waves labeled I through V which are representative of neural generators occurring over time along the auditory pathway (Jacobson & Hyde, 1985). Wave I is associated with the distal part of the auditory nerve, wave II with the proximal part of the auditory nerve, wave III with the cochlear nucleus, wave IV with the midline brainstem structures, and wave V with the lateral lemniscus (Scherg & Von Cramon, 1985). Once the waveform is plotted, it can be interpreted by the audiologist based on latency and amplitude. The hearing threshold can be estimated in the context of the minimal sound level that an ABR response is recorded.

There are two main stimulus types utilized for conducting ABRs, a click stimulus and a tone burst stimulus. The stimuli can be presented through supra-aural headphones or insert earphones, typically starting at a high presentation level around 75-85 dB HL and then reducing this to find threshold (Levit et al., 2018). Using a tone burst allows frequency specific information to be obtained which is not available if a click stimulus is used. The click has spectral energy that broadly stimulates the cochlea resulting in responses representative of the 2000 Hz to 4000 Hz range of hearing (Gorga et al., 1985). According to Sininger (1993), the ABR thresholds are within 10 dB HL of the average mid frequency (500-4000 Hz) audiometric

thresholds when using a click stimulus. When using tone bursts, there is a high correlation between ABR thresholds and psychophysical hearing thresholds of the same nominal frequency (Stapells et al., 1995). This shows that the ABR is a valid test of auditory function and valid for use of obtaining hearing thresholds for children who are too young to respond behaviorally. Infants four to six months old are known to be tested successfully in their natural sleep state but older children may require sedation to have the optimal test condition (Crumley, 2011). It is helpful to have the patient in a sleep state as this lowers the background electroencephalogram which improves the signal to noise ratio, allowing the small ABR signal to be more easily detected (Levit et al., 2018).

The three electrodes used are called the ground electrode, non-inverting electrode, and inverting electrode (Jacobson & Hyde, 1985). There are multiple electrode montages or placements that can be used when conducting an ABR. A commonly used electrode montage for infant ABR testing would include placing the non-inverting electrode at Cz or Fz which is toward the top and center of the head (Atcherson & Stoody, 2012b, Chapter 2). The inverting electrode is placed at Mi or Ai which is on the mastoid or earlobe. The ground electrode is placed at Mc or Ac which corresponds to the opposite mastoid or earlobe of where the inverting electrode was placed (Atcherson & Stoody, 2012b, Chapter 2). The electrodes are then connected to a preamplifier which increases the gain or amplitude of the signal before it is analyzed. This is important for the response to be analyzed because of how small the auditory brainstem response is. Filters, summation, and averaging are then applied to the responses before they are analyzed (Jacobson & Hyde, 1985).

The responses are recorded on an electroencephalogram, or EEG, which displays neurophysiologic or brain activity (Atcherson & Stoody, 2012a, Chapter 1). The waveform

responses are evaluated based on timing, latencies, and morphology (Jacobson & Hyde, 1985). While ABRs can be used in the detection of cochlear pathologies, they can also be affected by outer or middle ear pathologies (Joint Committee on Infant Hearing, 2007). The latencies, or timing of responses can be interpreted by referencing normative values based on age and sex. However, national standards for the calibration of ABR instrumentation do not currently exist. Therefore, audiologists are encouraged to obtain normative data for the specific instruments and protocols that they are using (Joint Committee on Infant Hearing, 2007). Generally, for adults, normal wave latencies occur at approximately 2 msec for wave I, and 6 msec for wave V (Northern & Downs, 2014). For children, these wave latencies occur later due to the maturation differences in younger children (Issa & Ross, 1995). While ABRs can be used for physiologic hearing threshold estimation, there is no universally accepted criteria to define ototoxicity using ABRs and thus research in this area is limited (Ganesan et al., 2018)

Grading Scales

A grading scale is a tool that aims to capture when ototoxicity occurs and in most cases the degree of impairment (King & Brewer, 2018). These scales are used to provide objectivity and consistency when interpreting auditory data. They also tend to use a metric that makes the results more accessible to medical professionals who are not audiologists. Use of a grading scale allows the medical team to evaluate changes in hearing quickly and easily, recognize how the changes will impact daily life, and whether a therapeutic change will be necessary. Many grading scales for pediatric ototoxic monitoring are meant to be used to evaluate pure tone audiometry results. There are two main types of assessment criteria used for ototoxicity, those that rely on a change in hearing levels from baseline, or those that measure absolute hearing thresholds (Brock et al., 2012).

Brock Scale

The Brock scale was developed to evaluate high-frequency hearing loss in children induced by cisplatin (Brock et al., 1991). The authors propose a grading system of hearing loss that ranges from zero to four. The grade increases as more frequencies are affected (Crundwell et al., 2016). It is recommended that alternative chemotherapy should be considered if grade two ototoxicity has developed (Brock et al., 1991). Grades two through four include moderate to severe high-frequency hearing loss. This scale does not distinguish between normal hearing and a mild hearing loss as changes below 40 dB HL are not taken into consideration (Crundwell et al., 2016). Pre-existing hearing loss is also not taken into consideration. If there is an asymmetrical loss, the protocol is to report results of the better ear.

Chang Scale

The Chang grading system used the Brock scale as a starting point and then modifications were made (Chang & Chinosornvatana, 2010). This scale was created to provide immediate and accurate reflections of a patient's audiological status in regard to the type of intervention that they would need. The Chang scale incorporates functional deficits that are caused by hearing loss levels that are less than 40 dB HL, as these would not be incorporated by the Brock scale.

The International Society of Pediatric Oncology Boston Ototoxicity Scale

The International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Scale was introduced by Brock et al. in 2012. The scale utilizes absolute hearing threshold levels and thus a baseline test is not required. The SIOP scale was created with the intended use of being for patients at the end of their clinical trial. It specifies that the hearing thresholds must indicate a sensorineural hearing loss (SNHL) rather than a conductive hearing loss. It is also sensitive to

high-frequency losses that may result in reduced audibility of frequencies in the average speech spectrum.

The National Cancer Institute Common Terminology Criteria for Adverse Events

The most current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) is version 4 (National Cancer Institute, 2009). This scale was designed to outline unfavorable symptoms or diseases that are temporarily associated with certain medical treatments or procedures (Crundwell et al., 2016). This scale has grades one through four that are based on hearing threshold change, the number of frequencies that are affected, and the indications for intervention. Pediatric sub-groups have been created for all grades which are new to version four. With this scale, grading without a baseline test is available as the currently available absolute hearing thresholds are used as the assessment criteria rather than an earlier test (Brock et al., 2012).

Between these four grading scales, there are differences in what grades are used, as not all of them utilize a grade zero category. The frequencies that need to be affected also vary in determining what grade a hearing loss would be given. Some of the scales use the most current thresholds to grade a hearing loss, whereas others may use a comparison of hearing thresholds to the baseline testing. Table 1.1 provides a comparison of these four different grading scales.

Table 1.1

Ototoxic Grading Scales

Grade	NCI-CTCAE[1]	Brock Scale[2]	SIOP Ototoxicity Scale[3]	Chang Scale[4]
0	Not defined	< 40 dB at all frequencies	≤ 20 dB at all frequencies	≤ 20 dB at 1, 2, and 4 kHz
1	Threshold shift or loss of 15-25 dB relative to baseline average at two or more contiguous frequencies in at least one ear; or a subjective change in the absence of a grade 1 threshold shift	≥ 40 dB at 8 kHz	> 20 dB SNHL above 4 kHz	**1a** ≥ 40 dB at any frequencies 6-12 kHz **1b** > 20 dB and < 20 dB at 4 kHz
2	Threshold shift or loss of > 25-90 dB average at two contiguous frequencies in at least one ear	≥ 40 dB at 4 kHz and above	> 20 dB SNHL at 4 kHz and above	**2a** ≥ 40 dB at 4 kHz and above **2b** > 20 and < 40 dB at any frequency below 4 kHz
3	For pediatrics: A hearing loss sufficient enough to indicate therapeutic intervention including hearing aids (≥ 20 dB bilateral hearing loss in the speech frequencies, ≥ 30 dB unilateral loss and requiring additional speech language related services	≥ 40 dB at 2 kHz and above	> 20 dB SNHL at 2 or 3 kHz and above	≥ 40 dB at 2 or 3 kHz and above
4	For pediatrics; Audiologic indication for a cochlear implant and requiring additional speech language related services	≥ 40 dB at 1 kHz and above	> 40 dB SNHL at 2 kHz and above	≥ 40 dB at 1 kHz and above

Sources. [1](National Cancer Institute, 2009) [2](Brock et al., 1991). [3](Brock et al., 2012). [4](Chang & Chinosornvatana, 2010).

Summary

The prevalence of children living with cancer is high, at an estimated 129,221 children living with cancer in the United States (National Cancer Institute, 2022). The chemotherapy treatment that these children receive can cause ototoxicity, especially platinum-based chemotherapy agents. Ototoxic monitoring is beneficial as it allows for treatment modification, dosage modification, early intervention, or auditory rehabilitation to take place based on the patient's hearing status. This is especially important due to the drastic negative effect on children that hearing loss may have on development and quality of life. There are several objective and behavioral auditory tests that can be used to assess hearing status. Behavioral audiometry, specifically pure tone testing, is the gold standard for assessing the hearing status. Behavioral results can be obtained for pure-tone audiometry and extended high-frequency audiometry conducted conventionally, via conditioned play audiometry, or via visual reinforcement audiometry. However, young children require different tests in order to obtain reliable responses. The objective tests that may be used for these younger children include OAEs and ABRs. The results of auditory testing are then assessed using a grading scale in order to provide objectivity and consistency when interpreting the data, and in order to make the results more accessible to non-audiologist medical professionals. In order to provide more consistency, there should be standardized protocols on what testing to do when conducting pediatric ototoxic monitoring.

CHAPTER 2

CLINICAL APPLICATION

Pediatric Ototoxic Monitoring Considerations

When implementing pediatric ototoxic monitoring, there are many factors that need to be considered such as the child's age and development, responsiveness, financial constraints, the logistics of scheduling, and a plethora of other challenges a family may face. The approach taken in determining age-appropriate protocols for this manuscript was achieved by contacting three major pediatric hospitals in the U.S., one of which allowed for their protocol to be included in this manuscript (Appendix A). The other two protocols that were shared allowed the content to be incorporated in the text, but permission was not given to allow reproduction of the actual hospital protocol within this manuscript.

Age of the Child

As discussed in previous sections, the age of the child determines which hearing tests are able to be completed. While pure-tone audiometry is the gold standard for evaluating the hearing status of a patient it is not always possible to obtain these results (American Speech-Language-Hearing Association, 2005). For obtaining pure tone audiometry results in younger children, other methods such as visual reinforcement audiometry and conditioned play audiometry can be utilized. Visual reinforcement audiometry is typically used for children six months to three-years-old and conditioned play audiometry can be utilized for children ages two to five-years-old (American Academy of Audiology, 2020; Widen & O'Grady, 2002). If behavioral results cannot be obtained, conducting an ABR or OAEs would be an option as well.

Responsiveness of the Patient

Another consideration when assessing a patient's hearing is the responsiveness of the patient. This will determine whether a subjective test can be completed or if an objective test is necessary to obtain reliable results. If subjective tests cannot be completed due to unresponsiveness of the patient, the ASHA 1994 guidelines for treatment of patients receiving cochleotoxic drug therapy encourages the use of objective measures (American Speech-Language-Hearing Association, 1994). The subjective tests mentioned previously are pure tone audiometry as well as extended high-frequency audiometry. The objective tests that are available mentioned previously are ABR and OAE testing. However, it is important to realize that OAEs only measure the functionality of a portion of the auditory system rather than the whole system, and they are sensitive to middle ear pathologies which may make them absent (Ganesan et al., 2018). Auditory brainstem responses are recorded when a patient is in a quiet, cooperative state, or asleep. If there are difficulties obtaining a pediatric ABR because of a patient's inability to be in a sleep state, conducting an ABR while the patient is sedated or under general anesthesia can be scheduled with a physician consultation.

Financial Constraints

Patient finances need to be considered in the implementation of ototoxic monitoring as well as this can be a significant burden on the patient's family whether directly or indirectly. These patients likely have many other health bills accumulating in relation to their chemotherapy treatment and other health conditions requiring medical care. Typically, ototoxic monitoring would be covered by insurance with a physician referral, but this is dependent on the insurance carrier and whether the family is able to commute to an in-network provider. In addition, there may be non-medical related expenses such as travel to and from the patient's appointments. A

study by Boyden et al. (2022), found that of the 601 parents of children with serious illnesses, over 65% of the parents reported some level of financial burden. Other studies have found that financial toxicity affects many cancer survivors in the U.S., even if they have health insurance (Ver Hoeve et al., 2021). There are studies that have analyzed out of pocket costs for cancer patients and their families with costs often segmented into three different categories; psychosocial, indirect, and direct costs (Iragorri et al., 2021; Pisu et al., 2010). In the Iragorri et al. (2021) study, it was found that the estimated out of pocket cost was highest for pediatric cancer families, at an estimated $800.00 U.S. dollars per month.

Scheduling Considerations

Logistically, scheduling can be a factor in providing care for these patients as well. These patients have a plethora of other medical appointments they need to go to often ranging from other preventative appointments, diagnostic tests, and chemotherapy treatment appointments. Often the chemotherapy treatments leave the patient feeling unwell which makes it difficult for them to be able to attend their other appointments, including audiology appointments. Many patients may feel that the preventative appointments are less important as they are not the main concern at the time of treatment and thus these are the first appointments to be omitted from their schedule when they are feeling unwell.

Ototoxicity Monitoring Protocols

As stated previously, three major pediatric hospitals in the U.S. were contacted, one of which, Boston Children's Hospital allowed for their protocol to be included in this manuscript (Appendix A). Consequently, Boston Children's Hospital will be referred to by name throughout the rest of the manuscript. The other two protocols that were shared are incorporated in the text. The Children's Hospital of Philadelphia (CHOP) verbally provided information for this project

but did not provide a document. This information was provided via personal communication with Jenn Ruths, an audiologist at CHOP (J. Ruths, personal communication, June 27, 2023). When mentioning this protocol, the acronym CHOP will be utilized. The third hospital will be referred to as Hospital #3 as this hospital agreed to provide de-identified protocol information.

Birth to Six Months

A baseline hearing test should be completed before the patient's first ototoxic chemotherapy treatment or within 24 hours of the first treatment. During the baseline audiometric evaluation, it is important to first acquire a case history for all patients. For children treated with chemotherapy, it is necessary to obtain information of past treatment(s) and treatment cycles as well as any newborn hearing screening results. All of the children's hospital protocols reviewed recommended performing a visual examination and otoscopy if possible. If a patient is in the birth to six months age range, and they are not able to respond behaviorally, thus objective tests will need to be completed. One of the protocols that were reviewed recommend measuring DPOAEs at conventional frequencies as well as extended high-frequencies above 8000 Hz (DeFonzo et al., 2015). The CHOP procedures state that DPOAEs should be conducted from 1500 Hz to 10,000 Hz for children in this age group. While the Boston ototoxic monitoring protocol is not broken into age groups, it states that ABR threshold testing may be warranted for patients who are unable to complete behavioral audiometry testing. The Boston ototoxic monitoring protocol recommends that "ear specific ABR testing should include thresholds in this order; 8000 Hz, 4000 Hz, 2000 Hz and 1000 Hz" (DeFonzo et al., 2015). The CHOP procedures recommend performing a diagnostic ABR as a baseline, testing from 500 Hz to 4000 Hz using tonebursts. If tympanometry is performed, a 1000 Hz probe tone should be used since infants have a mass dominated system in the middle ear (Hoffmann et al., 2013). The CHOP procedures

call for DPOAEs to be relied upon as the baseline test only if an ABR cannot be conducted. At follow-up audiological evaluations, conducted throughout the patient's chemotherapy treatments, otoscopy should be performed again if possible as well as tympanometry in order to rule out conductive hearing loss as a reason for change in hearing thresholds which may confound detection of a sensorineural change. The CHOP procedures call for monitoring to be conducted utilizing DPOAEs. A repeat diagnostic ABR should be conducted if DPOAEs are not present at 4000 Hz or lower. If there has been a change in the higher frequencies (>4000 Hz), it is still important to let the medical team know, but a new diagnostic ABR is not deemed necessary. The Boston ototoxic monitoring protocol also recommends DPOAEs be conducted at follow-up appointments (DeFonzo et al., 2015). According to the CHOP protocols, follow-up evaluations should be completed before every treatment if the patient is being given cisplatin only or if they are being given cisplatin and carboplatin simultaneously. If the patient is only being given carboplatin, audiometric follow-ups should be completed after two cycles of chemotherapy have been administered, and before a third cycle is administered. According to the Hospital #3 protocols, follow-up evaluations for all age groups should be completed before the administration of every dose of chemotherapy.

After the patient has completed the chemotherapy treatment, follow-up monitoring is still recommended as it may take many years for all of the chemotherapeutic agents to leave the body and stop having potential effects on the patient's health. For all ages, the Boston protocol recommends that if follow-up assessments are not specified by the medical team, they should be completed six months post-treatment and annually after that for the next three years (DeFonzo et al., 2015). For the birth to six months age group, the CHOP protocols recommend a follow-up evaluation one-month post-treatment and then annually until the child is three years post-

treatment or until the child is five years old, whichever has a longer duration. However, if the patient's treatment regimen included both cisplatin and carboplatin the timeline of annual hearing evaluations is extended to five years post-treatment instead of three years post-treatment. Hospital #3 protocols for all children treated with a platinum-based chemotherapy, specify that an audiologic follow-up should be completed no later than one-month post-treatment and then again at three months, six months, one year, and two years post-treatment. For children under six years of age who are 2 years post-treatment, evaluations should be completed annually.

Six Months to Five Years

As stated previously, at the baseline audiometric evaluation, it is important to acquire a case history, especially to obtain information of past treatment and treatment cycles as well as any newborn hearing screening results. For older children in this age group, it is also important to attempt to gain information on tinnitus and vestibular related symptoms. Also, otoscopy should be completed at all baseline appointments if possible. Tympanometry should be completed as well. However, starting at six ~~mo~~nths old, a 226 Hz probe tone should be used rather than a 1000 Hz probe tone as the child's ear should have further developed and become a stiffness dominated system rather than a mass dominated system (Carmo et al., 2013). Utilizing the Boston ototoxic monitoring protocols, the ABR and DPOAE testing procedures would be the same in this age group as they were for the birth to six months age group (DeFonzo et al., 2015). However, for the six months to 5-year age group, behavioral responses for hearing testing can start to be obtained. Thus, the CHOP protocol recommends pure tone thresholds are obtained at 1500 Hz through 8000 Hz as well as in the extended high frequencies at 10,000 Hz, 12,500 Hz, and 16,000 Hz. If a hearing loss is evident, bone conduction testing is recommended. In each ear, if possible, word recognition scores and speech recognition scores should be completed at the

baseline test with the Boston protocol recommending speech recognition be obtained at 50 dB HL (DeFonzo et al., 2015; J. Ruths, personal communication, June 27, 2023). For air conduction pure tone testing, the Boston protocol states that behavioral testing should be completed from 250 Hz to 16,000 Hz. A bone conduction threshold should be obtained at 4000 Hz in order to help detect a conductive or mixed hearing loss and at any other frequencies as warranted by the air conduction results.

At the follow-up appointments for continued monitoring, otoscopy and tympanometry should be obtained again if possible. The Boston protocol states that pure tone threshold testing should be completed following the same procedure used when obtaining the baseline testing and that speech audiometry should be completed if there is a change in sensorineural hearing thresholds (DeFonzo et al., 2015). It is recommended that the patient's medical team be made aware of test results when a significant change in hearing thresholds is evident. A significant change is classified as a decrease of 15 dB or greater at one frequency or a worsening of 10 dB or greater at two adjacent frequencies when the monitoring test is compared to the baseline hearing test. A significant change in DP amplitude is considered to be 6 dB poorer or greater when compared to baseline DP amplitudes.

Since the Boston protocol follow-up evaluation recommendations are the same for all ages it is recommended that if follow-up assessments post-treatment are not specified by the medical team, follow-up assessments should be completed six months post-treatment and annually after that for the next three years (DeFonzo et al., 2015). The CHOP protocols recommend follow-up evaluations every three months for the first-year post-treatment. After the first year, an annual evaluation should be completed until the child is three years post-treatment or five years old, whichever is longer. However, if the patient's treatment regimen included both

cisplatin and carboplatin the follow-up evaluation timeline is extended to five years post-treatment. Although, if the pure tone results are considered normal below 8000 Hz and DPOAEs are absent, it is recommended that evaluations are conducted every six months. If there are abnormalities in the pure tone thresholds, follow-up hearing tests should be completed every four to six months post-treatment based on the stability of these results. For this age group, Hospital #3 protocols recommend follow-up evaluations at one month, three months, six months, one year, and two years post-treatment and then annually thereafter.

Five Years Old and Older

As with the younger age groups, a case history should be obtained for the baseline appointment and otoscopy should be completed. Tympanometry should be completed using a 226 Hz probe tone. For this age group, an ABR would not typically be warranted unless the child is unable to be tested utilizing behavioral responses. The Boston protocols state that pure tone testing and DPOAE testing would be the same in relation to the frequencies being obtained (DeFonzo et al., 2015). For this age group, the CHOP protocol for air conduction and bone conduction pure tone testing is the same as for the 6 months to five-year-old category. Since the baseline testing is the same for this age group as the 6 months to five-year olds, the follow-up appointment is also going to be the same. However, after finishing treatment the frequency of follow-up appointments according to the CHOP procedures are every three years.

Since the Boston protocol follow-up evaluation recommendations are the same for all ages, if follow-up assessments are not determined by the medical team, they should be performed six months post-treatment and annually after that period for the next three years (DeFonzo et al., 2015). The CHOP protocols recommend follow-up evaluations every three months for the first-year post-treatment. After the first year, an annual evaluation should be completed until the child

is three years post-treatment unless they were treated with both cisplatin and carboplatin. If this is the case, annual evaluations should be completed until five years post-treatment. The exception being, if pure tone results are considered normal below 8000 Hz and DPOAEs are absent, follow-up DPOAE testing should be completed every six months. If there are abnormalities in the pure tone thresholds, follow-up hearing tests should be completed every four to six months post-treatment based on the stability of these results. The Hospital #3 protocols are the same for all age groups in relation to timing of follow-ups evaluations for the first two years. However, children who are younger than six years old are recommended to receive annual evaluations starting two years post-treatment. For children who are six to twelve years old it is recommended that hearing evaluations are conducted every other year. For patients older than twelve years the period for follow-up examinations are extended to every five years.

Reporting Results: Communication with Physicians

When reporting results to physicians, it is important to provide information pertinent to the patient's treatment regimen in a way that is accessible to the physician. That is why grading scales, like the ones mentioned in chapter one, have been developed for reporting hearing evaluation results to physicians. The audiologist report will likely be communicated to both the primary care physician and the oncologist, and if necessary, any of the patient's additional medical team members. When deciding which grading scale should be referenced when reporting the outcomes from ototoxicity monitoring testing, it is important to consider whether the scale takes pre-existing hearing loss into consideration or not. A challenge that lies with ototoxic monitoring protocols that compare hearing thresholds with the baseline test rather than using absolute thresholds, is that a baseline test is not always completed due to a variety of circumstances. Scales that utilize absolute thresholds allow for the grading levels to better

correlate to the functional hearing challenges that the patient may face. Whereas grades that are based on changes from baseline may not correlate to the patient's functional listening ability if there was a previous hearing loss.

Of the four grading scales discussed in chapter one, the SIOP Boston Ototoxicity Scale is recommended for grading and reporting results to physicians. This scale utilizes absolute thresholds and thus is able to be used to report results even if a baseline test is not available for comparison. Since absolute thresholds are used, the grades also have a correlation to the degree of hearing loss. Since test frequencies above 4000 Hz are taken into consideration, this scale is sensitive to high-frequency hearing losses that can cause reduced audibility of frequencies that are in the average speech spectrum. The SIOP grading scale also specifies that the hearing thresholds used for grading should indicate a SNHL rather than a conductive hearing loss.

Reporting Results: Communication with Parents

As the parents or caretakers are the responsible party for the child's overall health, it is vital to keep them informed of their child's hearing test results. It is also vital to work with the child's medical team to have unity amongst the team with regard to the options moving forward. However, it is ultimately the audiologist's responsibility to communicate the results of the ototoxicity monitoring outcomes to the patient and their family. It is important to begin educating patients regarding the test techniques and how the results are reported at the baseline exam. As soon as the testing is complete, results should be explained to the parents. It is important to counsel the parents regarding the changes, if any, in the hearing thresholds. If the hearing thresholds have worsened, the topic of hearing loss should be approached with sensitivity. Parents should be allowed space to ask questions and process their emotions as this news can initiate an emotional response. It is important not to overwhelm the parent with

information but rather be flexible regarding how much information they would like with respect to the next steps and resources for care and support. Any changes in hearing should be retested to confirm the change before determining the need for rehabilitative strategies. If a hearing loss is permanent, it is important to connect parents with an educational audiologist and offer information regarding parent support groups such as “Hands and Voices.”

CHAPTER 3

CRITICAL APPRAISAL OF THE RESEARCH AND FUTURE DIRECTIONS

Assessment of the Literature and Gaps in the Literature

Ototoxicity in children receiving chemotherapeutic medications is a widely researched area and the body of literature is growing. However, there are still gaps in the existing research that need further investigation. As far as the epidemiology of pediatric patients with cancer is concerned, it can be difficult to obtain a generalizable sample of children from existing studies because each patient's situation can be vastly different. The factors that vary across patients include age, severity of the cancer, concomitant pharmacological and radiation treatments, not to mention the genetic and physiological factors that differ on an individual level. There are pediatric cancer patients who could be currently treated with chemotherapy agents that are not known to be ototoxic but have been treated with ototoxic medications in the past and thus it is important to know the child's treatment regimen throughout the entire duration in order to determine if an ototoxic chemotherapy agent was ever used previously. It is also important that as new treatment regimens are created in the rapidly evolving area of cancer treatment, that the new treatments are monitored to know if ototoxicity will be a concern.

Audiologic Testing

For ototoxic monitoring there is no defined minimum test battery (Neuwelt & Brock, 2010). This minimum test battery should include which tests should be obtained first as well as the critical test frequencies that should be attempted to be obtained first for cases in which testing is limited due to illness, inattention, or lack of cooperation (Bass & Bhagat, 2014; Neuwelt &

Brock, 2010). Overall, since there is no gold standard for measuring ototoxicity specificity and sensitivity cannot be calculated until there is a standard in place (Knight et al., 2007). In addition, without an international standard for reporting ototoxicity, results across different diseases and studies cannot be compared if the same method of reporting is not used (Ganesan et al., 2018; Knight et al., 2017). Lack of universally accepted criteria to define ototoxicity using DPOAEs and ABRs would prevent these tests from being included in a minimum test battery (Ganesan et al., 2018).

Vestibulotoxicity

Throughout this manuscript, auditory ototoxicity is covered but vestibulotoxicity is not discussed, even though both are forms of ototoxicity (Crundwell et al., 2016). Vestibulotoxicity is damage to the balance system which is housed in the inner ear. Thus, vestibulotoxicity is another possible side effect of chemotherapy treatment, specifically platinum chemotherapy treatment. There are no widely accepted guidelines for monitoring of vestibulotoxicity even though it is well established that certain aminoglycosides are vestibulotoxic (Ganesan et al., 2018). However, there are difficulties in this area as symptoms are likely only apparent if the patient is mobile. Symptoms may also be attributed to the patient's debilitated state. Currently, there is not any single test that can identify vestibulotoxicity and thus a test battery would be needed to monitor patients for vestibulotoxicity which would be difficult for patients with a compromised health status (Ganesan et al., 2018).

Grading Scales

A major gap in the literature is that there is a lack of a standardized universal grading scale, which means there is no standardized way to report pediatric ototoxic test results for each age group or test procedure (Bass & Bhagat, 2014; Crundwell et al., 2016; Ganesan et al., 2018;

Knight et al., 2017) Having age appropriate standards is especially important for children in critical speech and language development (Crundwell et al., 2016). Of the grading scales that do exist, behavioral hearing test results are the criterion used for grade determination. However, as discussed previously in the manuscript, young children cannot perform subjective tests but rather results would come from objective tests such as OAEs and ABRs, and there are no grading scales incorporating objective tests (Bass & Bhagat, 2014; Ganesan et al., 2018; Knight et al., 2007; Knight et al., 2017). As discussed previously, it may be difficult to obtain a full audiologic data set from children undergoing chemotherapy and thus a grading scale would need to be able to assign a grade without the full audiologic set, otherwise children without a full data set may be overlooked (Bass & Bhagat, 2014; Neuwelt & Brock, 2010).

Research Challenges

Since the population discussed is specialized, research related to hearing loss specific to children undergoing chemotherapy is more limited than studies in which the population of children include those administered any ototoxic drug including but not limited to chemotherapy, radiation, aminoglycoside antibiotics, and loop diuretics. This population commonly has other comorbid conditions and medications being administered which can make it difficult to isolate the specific cause of ototoxicity in these patients.

As discussed previously in the manuscript, it can be difficult to get reliable hearing test results for young children. A child that is six months old or younger, cannot respond to EHFA testing as you cannot place the EHFA supra-aural headphones on them and expect responses to testing in a child that young. Typically, testing using soundfield would be a good option for young children, but it cannot be done for EHFA and using soundfield would cause detection of an asymmetrical hearing loss to be missed (Bass & Bhagat, 2014). Using DPOAEs in research,

extended high frequencies can be tested up to around 16,000 Hz. The high frequency limits of clinical ABR equipment are only up to around 14,000 Hz and not readily available on all instruments. So, in practice, many young children may not be sufficiently monitored to provide the earliest indication of ototoxicity. In addition, there are no national standards for the calibration of ABR or OAE instrumentation which causes a lack of uniform performance standards (Joint Committee on Infant Hearing, 2007).

Even if the child is old enough to be able to provide behavioral responses, they are dealing with a chronic illness and may not feel well enough to undergo subjective testing. Based on the cooperation of the child, it may take multiple visits to get a complete data set whether subjective or objective tests are being used (Bass & Bhagat, 2014). This limits the timeliness of the intervention if needed.

Future Research Directions

There are many clinical needs in the area of pediatric ototoxic monitoring. There is a need for a standardized protocol for each age-group of children, especially very young children. Having standardized protocols will help with consistency in what hearing tests are being conducted in pediatric ototoxic monitoring programs. Standardized protocols would also help to ensure age appropriateness in the hearing tests being completed for ototoxic monitoring in pediatric patients. Not only is this helpful clinically, but it would allow more consistency when analyzing data for research purposes. Once standardized protocols are in place, there is an ability to build a grading scale that can incorporate all of the standardized procedures for reporting of ototoxic monitoring results. This would be important to do as OAE and ABR results are not integrated into any of the currently used grading scales. Another clinical need is for the ASHA 1994 guidelines for treatment of patients receiving cochleotoxic drug therapy to be updated.

These guidelines are outdated as there has been much progress in hearing test measures since they were created, especially in the area of DPOAE and ABR testing capabilities. Additionally, the ASHA 1994 guidelines were not specifically written with the consideration of pediatric ototoxic monitoring in mind. Thus, an updated version of these guidelines considering pediatric ototoxic monitoring is a professional need. In the meantime, audiologists are encouraged to build their own standardized protocols within their practice settings and stay on top of the evolving nature of research in this area.

Summary

Since there is such a high prevalence of children living with cancer, estimated to be around 129,221children in the United States that have received chemotherapeutic treatments that can be ototoxic, there is a need for pediatric ototoxic monitoring (National Cancer Institute, 2022). If a hearing change is detected during the ototoxic monitoring process, there are multiple options of how to proceed such as treatment modification, dosage modification, early intervention, or auditory rehabilitation if needed, especially if this is occurring during the critical speech-language developmental periods. It is vital that children and families receive the support they need in order to provide them with the ability for successful developmental outcomes and to preserve their quality of life. While behaviorally based pure-tone audiometry is the gold standard for assessing a patient's hearing status, objective tests are often needed for the pediatric population. Grading scales based upon pure-tone audiometry are then used to make ototoxicity monitoring results accessible to non-audiologist medical professionals, and to provide objectivity and consistency in data interpretation.

When creating a pediatric ototoxic monitoring protocol, there are many factors that need to be taken into consideration such as the child's age, the responsiveness of the patient, financial

constraints, and scheduling considerations. The protocol should be organized by age groups as there are developmental differences in a child's abilities and needs in relation to conducting hearing evaluations. Of the four grading scales based on pure-tone audiometry, the SIOP Boston Ototoxicity Scale is recommended for grading and reporting results to physicians. The SIOP Boston Ototoxicity Scale is preferred because it allows for results to be reported even if a baseline test was not able to be obtained, because the grade levels have a correlation to the degree of hearing loss, and it is sensitive to high-frequency hearing losses. Audiologists have a responsibility to use evidence-based approaches when creating ototoxicity monitoring protocols for pediatric patients and there is a need for professional guidance in this area of practice.

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APPENDIX A

BOSTON OTOTOXIC MONITORING PROTOCOL

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Ototoxic Monitoring

Purpose

Ototoxic medications have the potential to damage structures of the inner ear, frequently resulting in permanent hearing loss. Hearing loss has a negative impact on the communication, education and social-emotional wellbeing of children especially when identification is delayed. It is essential to establish an audiologic protocol to assess hearing sensitivity in pediatric patients who are currently receiving treatment or are post treatment with potentially ototoxic medications. Vigilant monitoring of hearing acuity and outer hair cell function of the cochlea allows for early detection, intervention, and habilitation of permanent hearing loss.

Audiologic monitoring in this pediatric population is critical as young children are acquiring speech and language skills. Identification of ototoxicity is crucial in children receiving cancer treatments because of the impact that acquired hearing loss has on their social and educational outcomes (Bass & Bhagat, 2014). Their age and illness pose challenges to their participation in many audiologic procedures. For some children, complete audiologic profiles may only be obtained over a series of appointments.

Populations Intended

Patients who undergo treatment with potentially ototoxic medications, including cisplatin, carboplatin, aminoglycoside antibiotics, loop diuretics, and nonsteroidal anti-inflammatory agents (see Appendix 1 for list of ototoxic medications). Patients who may have kidney disease or who receive radiation therapy or bone marrow transplants are at an increased risk of hearing loss and may also be included in ototoxicity monitoring.

Expected Outcome

By following a standardized audiometric protocol for children undergoing treatment with ototoxic agents, we may increase the early identification and habilitation of hearing loss.

Procedures

Baseline Audiologic Evaluation

Baseline test battery, prior to any treatment, should *optimally* include the following:

- Visual Otoscopy
- Tympanometry
- Separate ear pure tone hearing thresholds
    - Behavioral Testing: 250-16,000 Hz
    - Auditory Brainstem Response (ABR) Testing: 500-8,000 Hz Thresholds should be completed in the following order of importance alternating between ears for ototoxicity measurement:
    - 8,000 Hz, 4,000 Hz, 6,000 Hz, 3,000 Hz, 2,000 Hz
- Bone conduction threshold at 4000 Hz, as SIOP determination of Grade is dependent on that information in the presence of abnormal middle ear status or suspected conductive or mixed hearing loss. Other bone conduction thresholds as needed.
- Speech audiometry (SRT/SAT and word recognition at 50 dB HL, when possible)
- Distortion product otoacoustic emissions (DPOAE) using ototoxicity protocol (optional protocol on Biologic Scout and Interacoustics Titan see Appendix 3 for specific protocol and parameters)

Audiologic evaluations of young or sick children depend on the child's state of cooperation and compliance. Audiologists should have realistic expectations for this cohort and should customize the evaluations to obtain the most important information starting with the high frequency regions. It may be appropriate to condition in a lower frequency region and then move to the higher frequencies once a conditioned response is established. If frequency specific data is not forthcoming via behavioral audiometry or DPOAEs, repeat sessions should be considered.

It is important to measure ultra-high frequency hearing thresholds or otoacoustic emissions at baseline testing and when 8000 Hz is documented to be normal. A decrease in thresholds or otoacoustic emissions above 8000

Hz will not affect the SIOP grading system and may not affect speech and language acquisition, but is evidence of ototoxic effects in the auditory system.

For patients who are unable to participate in behavioral audiometry, auditory brainstem response (ABR) threshold testing may be warranted. Pending patient sleep state, ear specific ABR testing should include thresholds in this order: 8000 Hz, 4000 Hz, 2000 Hz and 1000 Hz. Should difficulties with patient sleep state arise, consult with the patient's medical team to discuss options for ABR testing while under sedation or general anesthesia.

Evaluation During Ototoxic Treatments

Audiologic monitoring is requested by the medical team per the designated patient protocol. The audiologist can recommend interim evaluations to confirm and monitor thresholds using their clinical judgment.

The assessment will include:

- Otoscopy
- Tympanometry
- Pure tone threshold testing following baseline procedure
- DPOAE

If there is a change in sensorineural hearing thresholds, speech audiometry should be performed.

The patient's medical team (nurse practitioner, oncologist, attending) should be informed of test results when a significant change in hearing threshold is noted. **A significant change in sensory hearing thresholds is a change of 15 dB or more at one frequency or a change of 10 dB or more at two adjacent frequencies. A significant change in DPOAE amplitude is 6 dB or more.**

The audiologist should counsel the family regarding confirmatory threshold testing, amplification, and/or communication strategies to be used by family members and care givers.

Evaluations Following Ototoxic Treatments

If follow-up assessments are not specifically dictated by the medical team after the completion of treatment and the patient's hearing remains unaffected, the audiologist should recommend monitoring thresholds in 6 months and then annually for 3 years.

Audiometric Changes and Grade Determination

The department of audiology at Boston Children's Hospital adopted the 2012 International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Scale as a grading system for audiologic results during treatment with ototoxic agents (Appendix 2). This system is specifically written for children and measures absolute hearing levels to define grade rather than a change from baseline.

Following each audiologic evaluation, results are uploaded via AudioHub to Power Chart. These results should include the ototoxic agent administered and previous Grade if available. The medical team then determines the current Grade and determines any treatment changes based on hearing. Typically there is no direct communication between audiologist and oncologic team; however, if the audiologist notes threshold shifts that amount to a Grade change, phone communication is initiated. Soft findings such as change in DPOAEs should also activate a phone call.

Reporting Requirements

- The medical diagnosis requiring ototoxic treatment is entered in the "Other" section of the patient's history.
- The name of the potentially ototoxic medication and where in the course (e.g., "baseline", "first cycle of five", "post-treatment monitoring") is entered in the "Other" section of the patient's history. • Distortion product otoacoustic emissions results are photographed in Audiohub in the Results section and interpreted under the "Other Test Findings" section.
- SIOP Ototoxicity Grade is entered in the "Comments and Recommendations" section.
- Stability or significant changes in threshold are described in the "Comments and Recommendations" section.

For patients with a diagnosed hearing loss, the audiologist will use their clinical judgment to determine if a formal report is necessary. The audiogram is found under the Diagnostic Studies tab of PowerChart. Narrative reports are found under the Clinical Documents tab of PowerChart.

ICD-10 Coding

- If normal hearing:
  - Medical diagnosis (e.g., C80.1 – malignant neoplasm)
  - Hearing status (e.g., Z01.10 – normal findings)
- If ototoxic hearing loss identified; note that a significant change in pure tone threshold or DPOAE amplitude qualifies as ototoxic hearing loss:
  - Medical diagnosis (e.g., C80.1 – malignant neoplasm)
  - Ototoxic agent (e.g., T45.1X5D – adverse effect of chemotherapy, subsequent)
  - Hearing status (e.g., H91.03 – bilateral ototoxic hearing loss).

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Appendix 1

Ototoxic Medications

Aminoglycosides [T36.5X6 (A/D/S)]

Streptomycin
Neomycin
Kanamycin
- Amikacin
- Tobramycin

Spectinomycin
Paromomycin
Gentamicin
Verdamicin
Astromicin
Ampicillin
- Antihelminthics
- Chloramphenicol
- Chlorhexidine

Vancomycin

Antineoplastic Agents [T45.1X5 (A/D/S)]

- Cisplatin
- Carboplatin

Loop Diuretics [T50.1X5 (A/D/S)]

Furosemide
- Lasix
- Fusid
- Frumex

Bumetanide
- Bumex
- Burinex

Ethacrynic acid
- Edecrin

Torasemide
- Demadex
- Diuver
- Examide

Etozoline
- Diulozin
- Elkapin
- Etopinil

Piretanide
- Arelix
- Eurelix
- Tauliz

Bendroflumethiazide
Bumetadine
Chlorthalidone
Ethacrynic Acid

Appendix 2

SIOP Boston Ototoxicity Scale

Grade	Parameters
1	> 20 dB HL (i.e., 25 dB HL or greater) SNHL above 4 kHz (i.e., 6 or 8 kHz)
2	≤ 20 dB HL at all frequencies (2 – 8 kHz)
3	more) SNHL at 2 kHz and above _ SNHL at 4 kHz and above
4	> 20 dB HL SNHL at 2 kHz or 3 kHz and above > 40 dB HL (i.e., 45 dB HL or

Scale is based on sensorineural hearing thresholds in dB hearing level (HL; bone conduction or air conduction with a normal tympanogram). Bone conduction thresholds are used to determine the grade in the case of abnormal tympanometry and/or suspected conductive or mixed hearing loss. Even when the tympanogram is normal, bone conduction is strongly recommended at the single frequency that is determining the ototoxicity grade to fully confirm that the hearing loss at that frequency is sensorineural. Temporary, fluctuating conductive hearing loss due to middle ear dysfunction or cerumen impaction is common in the pediatric population, and decreases in hearing thresholds that include conductive hearing losses do not reflect ototoxicity to the cochlea.

Appendix 3

Biologic Scout DPOAE Collection Protocol Parameters

Protocol Name: 1.5-10 kHz Ototoxic Test (Standard and High Noise)

Frequencies and Levels	
Frequency Begin (Hz):	10,000
Frequency End (Hz):	1,500
F2/F1 Ratio:	1.22
Points Per Octave:	4
L1 Level dB:	65
L2 Level dB:	55

Stopping Crite ia	
Min DP Amplitude (dB):	-5
Noise Floor (dB):	-17
S/N Ratio (dB):	8
Point Time Limit (sec):	20

Interacoustics Titan DPOAE Collection Protocol Parameters

Stimulus	
Frequency Range (Hz)	500-10,000
Nominal Frequency	F_2
Frequency Step	25 Hz
Level	30-80 dB SPL (75 dB SPL for 6 kHz, 65 dB SPL for 8-10 kHz)
Level Step	1 dB
Transducer	IOW Probe auto detection, auto calibrated

Recording	
Analysis Time	Minimum 2 seconds to unlimited time
A/D Resolution	24 bit, 5.38 Hz resolution
Artifact Rejection System	-30 to +30 dB SPL or off
Stimulus Tolerance	Adjustable between 1 and 10 dB
SNR Criteria	Adjustable between 3 and 25 dB
Probe Check Window	256 points frequency response of the ear canal due to a click stimulus
DP- Response Window	4096 points
Residual Noise	A RMS average measurement in DP- bin frequency area (26 bins at frequencies < 2500 Hz & 60 bins > 2500 Hz)

