PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS (PIHL)

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Editorial

OTOTOXICITY: A MAJOR CAUSE OF ACQUIRED HEARING LOSS

In the US military, noise is the most obvious and most cited cause for hearing loss. Weapons, even small arms, can fire at impulse levels exceeding 140 dB SPL. Craft – be it on land, in the water, or in the air – can expose personnel to hours of loud noise. These hazards are well known and precautions have been put in place through regulations, such as the DoD Design Criteria Standard Noise Limits MIL-STD-1474E (2015), and implementation of hearing conservation programs through DoD Instruction 6 055.12 (2010). Advances in these areas can be seen through the acquisition of quieter ships by the US Navy as well as the development and implementation of new types of hearing protection devices, such as the US Army's Tactical Communication and Protective Systems (TCAPS). Unfortunately, acquired hearing loss and tinnitus can still occur. Is this a failure of the regulatory system? Or are there other causes to consider?

Our committee of the Pharmaceutical Interventions of Hearing Loss (PIHL) Working Group has been discussing ototoxicity as one possible cause for hearing loss and tinnitus, as well as vestibular deficits, in military personnel. While ototoxicity is mostly considered a medical concern (e.g., from medications), it is also an occupational hazard (e.g., from exposures to solvents, noxious gases, etc.). Public health centers within the DoD have identified over 20 common potentially ototoxic agents readily encountered by the military. Crucially, exposures to ototoxins do not occur separately from noise exposures and their combined effects must often be considered as additive or synergistic assaults on the Warfighters' hearing and vestibular senses. According to USAPHC Fact Sheet 51-002-0713 Occupational Ototoxins (Ear Poisons) and Hearing Loss, the following activities frequently combine noise and ototoxic exposures: painting; printing; boat building; construction; furniture making; manufacturing metal, leather, and petroleum products; fueling vehicles and aircraft; firefighting; weapons firing; radiator repairing; and pesticide spraying. To best protect the hearing of all military personnel, we must first know which toxins can affect hearing and how.

Over 200 medicines induce dose-dependent ototoxicity. Many are lifesaving treatments, and medical providers must balance the odds of saving a life with the risk of degraded hearing and vestibular performance. This increasingly common scenario emphasizes the importance of developing effective ototoxicity monitoring programs. Within such programs, including those being developed within the DoD and VA, clinical decisions

become more evidence-based to implement appropriate early invention strategies when hearing loss is identified. Hypothesis-driven research continues to elucidate the mechanisms of ototoxicity and provides growing insight to when and how interventions can occur, and how protective measures can be best utilized.

The primary role of this Ototoxicity committee (composed of 30+ contributors) is to raise the visibility of the inherent risks of ototoxicity in the military environment and develop strategies to better mitigate those risks. Reducing the risks of ototoxicity will benefit both military personnel, and also civilian populations. Improved hearing and vestibular health throughout military and civilian populations will improve our nation's health and national security, to paraphrase the late Senator for Oregon, Mark. O. Hatfield.

This newsletter introduces an overview of ototoxicity monitoring programs, and also highlights a recently-recognized risk factor – inflammation – that can exacerbate both ototoxicity, and also noise-induced hearing loss. The Ototoxicity committee of PIHL will extend its activities with two forthcoming special journal editions, one on ototoxicity monitoring and another on biomedical mechanisms of ototoxicity. We will continue to share our collective knowledge to appropriate audiences to raise awareness of what ototoxicity is, it's etiology, how it can be monitored, along with current and new strategies to prevent ototoxicity.

~ Kelly Watts, AuD and Peter Steyger, PhD

MEDICATION-INDUCED OTOTOXICITY MONITORING

Amy Boudin-George, AuD, Kelly King, AuD, PhD, and Dawn Konrad-Martin, PhD

Ototoxic medications have the potential to damage auditory or vestibular structures and/or functions. They are administered, typically, as life-saving measures by physicians (American Academy of Audiology [AAA], 2009; American Speech-Language Hearing Association [ASHA], 1994). The most commonly used ototoxic medications include various aminoglycoside antibiotics for the treatment of tuberculosis and advanced bacterial infections, and platinum-based antineoplastic therapies used to treat a variety of cancers (AAA, 2009). Audiologists can monitor hearing and/or balance throughout a patient's treatment with an ototoxic medication, identify and attempt to address changes to these systems that could affect quality of life, and inform therapeutic decision-making as ototoxicity can be dose limiting.

Previously published guidelines outline general protocols for ototoxicity monitoring, allowing some flexibility for each audiologist to build programs that suit his or her facility. Despite the existence of these guidelines, ototoxicity monitoring does not appear to occur routinely, suggesting that there are other important considerations for successfully implementing an ototoxicity monitoring program. Further, pharmacological interventions to prevent ototoxicity have been slow to materialize. These issues spurred development of The Ototoxicity Monitoring Program Committee, a subgroup of the Department of Defense (DoD) Hearing Center of Excellence (HCE) Pharmaceutical Interventions for Hearing Loss (PIHL) Ototoxicity Committee. This group is comprised of audiologists and researchers who are subject matter experts familiar with ototoxic medications, their pharmacological and clinical effects on patients, audiometric techniques, and the requirements of monitoring programs.

Among other endeavors that will be made by this group to expand ototoxicity monitoring efforts, members are developing two papers that specifically inform the present report and will be featured in a special edition of the International Journal of Audiology. The first paper, by Carmen Brewer and Kelly King at the National Institutes of Health (NIH), will review the many grading systems for ototoxic hearing loss. The second paper, led by Dawn Konrad-Martin at the Department of Veterans Affairs (VA) National Center for Rehabilitative Auditory Research and with co-authors Kathleen Campbell, Marilyn Dille, Jennifer Hopper, Candice Ortiz, and Gayla Poling, will highlight the challenges to guideline-adherent ototoxicity monitoring and offer strategies for overcoming them. The paper will also provide an overview of the tools and methods available for clinical audiologists to implement successful ototoxicity monitoring programs exemplified within the DoD, VA, NIH, and private sector care settings.

As a Clinical Audiologist for the HCE and member of The Ototoxicity Monitoring Program Committee, the first author of this report conducted a preliminary retrospective analysis of data pulled from the DoD Military Health System (MHS) to gain insight into ototoxicity monitoring practices for the armed services. Ototoxic medications, to include tobramycin, amikacin, gara/gentamycin, streptomycin, kanamycin, carboplatin, and cisplatin, are used at 46 Military Treatment Facilities (MTFs) throughout the DoD, 42 of which house Audiology Clinics. Data pulled from these clinics indicate that of the 2860 patients treated with ototoxic medications between 2011 and 2015, only 244 or approximately 9% of patients received audiologic evaluations within one month prior to beginning or during treatment. Only 6% received baseline audiograms prior to beginning treatment. As expected, based on discussions within the committee regarding service gaps within civilian, DoD and VA settings, few adult patients appear to be receiving these services based on this cursory evaluation. This indicates a significant service opportunity for the audiology community.

In terms of implementing an ototoxicity monitoring program, audiologists may need to know where to start. The ASHA guidelines (1994) for audiologists working with patients receiving ototoxic medications is an 18-page document outlining the following: the need for ototoxicity monitoring programs, which medications require monitoring, criteria

indicating change in hearing, ideal monitoring procedures, and post-treatment aural rehabilitation options. This document was produced to provide audiologists with a framework for the requirements in a monitoring program and, with this in mind, was further developed in a guidance document created by a group of subject matter experts in 2009 (AAA, 2009). The AAA guidelines go on to define the role of audiologists in the treatment care team (as well as the roles of other team members), describe the testing of pure tone thresholds near each patient's high frequency hearing limit in a screening method called the Sensitive Region of Ototoxicity (SRO), and provide an overview of tests used for monitoring vestibulotoxicity.

Operational definitions of ototoxicity can and should vary based on the personalized needs of the patient, the facility, and the stakeholders involved. However, there is also a need for consistent reporting of ototoxic hearing loss so clinical data can be more effectively synthesized for the benefit of improving care. Numerous grading scales have been developed to capture ototoxicity, many of which are designed to identify functional change in hearing, and all have limitations. Understanding the unique needs and goals of a given monitoring program is essential before selecting the most appropriate scale to capture ototoxic change. Using operationally defined scales provides consistency and objectivity to interpretation, and usually involves a metric that is approachable to the non-audiologist. Furthermore, these scales are critical in clinical trial development and implementation; they allow an audiologist to objectively rank or grade the degree of hearing loss, provide government agencies with data to judge drug safety, and assess the efficacy of otoprotection interventions.

Examples of existing grading schemes include one proposed by ASHA, which is sensitive to early detection of ototoxic change, but which is binary in outcome (yes/no) and does not capture the degree of change; NCI Common Terminology Criteria for Adverse Events (CTCAE), which grades adverse events, hearing change, and/or therapeutic needs associated with an intervention; and both Brock's Hearing Loss Grades and the International Society of Pediatric Oncology (SIOP), neither of which require a baseline, thus, presume a population without preexisting hearing loss (e.g., pediatric). These are just some examples of available grading schemes, and, ultimately, the individual clinician or researcher must pick a metric that is most appropriate for their population and goals. There is no perfect and universal scale to capture ototoxicity, and it is critical that the pros and cons of each are considered *a priori*. It is also important that all of the stakeholders understand each other's "language", or at least are well-versed in each other's ototoxicity terminology.

Treatment care providers in specialties such as oncology, infectious disease, pulmonology, and neonatology may need to be made aware of the potential ototoxic effects of therapies they utilize and strategies available to address the damage. Although extending or saving life is a paramount consideration for these providers, the established importance of hearing and equilibrium for maintaining quality of life must be considered. If a patient is unable to communicate or remain mobile in his or her life after treatment, this can negatively affect the ability to work, participate in school, and enjoy social

interactions (ASHA, 1994; Anderson & Matkin, 2007). Significant hearing loss is associated with depression, anxiety, feelings of isolation, and feelings of anger, as well as decreased access to and utilization of medical care despite having a greater incidence of co-morbid conditions than people with normal hearing (Ebert & Heckerling, 1995; Barnett & Franks, 1999; Kochkin & Rogin, 2000).

In order for an audiologist to work with patients who are receiving ototoxic medications effectively, acceptance, support, and input are required from the entire treatment care team. Not only do the referrals for baseline testing and monitoring ideally come from these treatment care providers, an understanding of how the providers' will make use of audiological evidence to inform treatment is also paramount for the monitoring program to be effective. With the support of treatment care providers, audiologists can ensure the information they provide is actionable for the purposes of the entire treatment team.

The audiologist's role is as an ally in the treatment process: To monitor for early signs of hearing and balance dysfunction, and educate the patient and treatment care providers about these important toxicities. The audiologist can also contribute information to the therapeutic decision-making process regarding the risk-benefit ratio of intervention (e.g, chemotherapy). Regular monitoring and early detection of loss of function allows proactive treatment planning, rapid therapy adjustment when possible, and timely re/habilitation when needed. When hearing loss is unavoidable, the audiologist is able to provide augmentative interventions to improve communication and balance outcomes for the patient. In addition to hearing aids, audiologists can offer communication strategies and other assistive technologies. The audiologist's role also includes post-treatment re/habilitation and counseling support. As one important example, the audiologist can help to distinguish some symptoms of hearing loss – withdrawal, isolation, and confusion – from those of depression or dementia.

Ideally, an ototoxicity monitoring program will allow the early detection and identification of hearing loss and vestibular dysfunction by evaluating the patient *before* treatment is initiated and at pre-determined intervals using the methods found in the aforementioned clinical practice guidelines. However, patients or treating physicians typically request Audiology services only *after* they become symptomatic, and clinics may struggle to accommodate the rapid availability and extensive monitoring schedule that some of these diagnoses and treatments require. Furthermore, there is a dearth of clear research data identifying incidence and prevalence of ototoxicity related to many interventions; this represents a gap in the knowledge base, which, once filled, could help inform appropriate monitoring schedules and reduce barriers to clinical trials evaluating otoprotection and rescue.

Considering the audiological evaluations, counseling, education of patients, families and providers, and the rehabilitation and management for hearing loss, a successful ototoxicity monitoring program can be a time-intensive endeavor. It may be necessary to flag patients for monitoring, or for monitoring more intensely, who may be vulnerable to ototoxicity based on the presence of certain risk factors. These include, but are not

limited to high cumulative dose of the ototoxic drug, co-administration of radiation or additional medications that may act synergistically to increase ototoxicity, poor renal function, and older age (Vermorken et al, 1983; Kopelman et al, 1988; Hallmark et al, 1992; Mencher et al, 1995; Seligmann et al,1996; Bokemeyer et al, 1998; Ress et al, 1999; de Jongh et al, 2003; Bertolini et al, 2004; Li et al, 2004; Biro et al, 2006; Marshall et al, 2006; Bhandare et al, 2007; Rybak, 2007; Truong et al, 2007; Dille et al., 2012).

The audiologist who can arm him/herself with State of the Science information on ototoxic medications will add substantial value to the treatment care team. They should be aware of the types and effects of ototoxic medications, as well as develop and maintain an understanding of the State of the Science for PIHL prophylaxis/treatment options for the prevention of medication-induced ototoxicity to share with treatment providers, separate fact from fiction, and best direct patient care.

Directions of the PIHL Ototoxicity Monitoring Program Committee

The Committee has several lanes of outreach planned for the coming year to make information and resources available to all clinicians. In August 2016, two Committee members gave an overview of ototoxicity monitoring for DoD and VA audiologists via a webinar. In November 2016, members of this committee will present as part of a mini-series on ototoxicity during the ASHA Convention. In 2017, the International Journal of Audiology will publish a special edition titled "Ototoxicity – Special Topics in Clinical Monitoring". This special edition, directed by members of this Committee, will discuss adult ototoxicity monitoring, as described earlier in this report. The monitoring of pediatric and neonatal populations will also be discussed with perspective articles from several treatment provider specialties and will include information regarding the future of ototoxicity, its monitoring and prevention.

The Committee will create a tool-kit, which will be available through the HCE website, to allow an easy transition of their compilation of ideas into ototoxicity program management. The tool-kit will include: a) a breakdown of existing guidelines to offer the minimum program requirements to clinicians in a digestible format, b) patient and provider resources (e.g., handouts, presentations) that can be modified to fit each clinic's needs, and c) a framework for the creation of clinical standard operating procedures. Within the DoD, audiologists can use templates created by members of this Committee in the electronic medical record to streamline reporting, with an explanation of test results and action needed, if any, based on those results.

Conclusion

The daunting tasks of influencing important medical treatment decisions, managing the logistics of an ototoxicity monitoring program, and maintaining an ever-changing knowledge base have the potential to hinder success before an ototoxicity monitoring program even begins. By gathering the subject matter experts in ototoxicity monitoring and using their knowledge base to put accurate and useful information at audiologists'

fingertips, this Committee aims to increase the numbers of patients able to receive guideline-adherent ototoxicity monitoring as a routine part of therapeutic treatment with potentially ototoxic medications. This can mean better quality of life for patients being treated with ototoxic medications; as one committee member noted, "quality of life impacts survivorship; the two can never be completely disentangled."

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INFLAMMATORY THREATS TO OPTIMAL HEARING HEALTH

Peter Steyger, PhD

Throughout our lives, and especially as children, we can become infected by bacteria, viruses, fungi or parasites. Most frequently, our bodies mount specific systemic inflammatory response pathways to counter these infections and recover good health. When a systemic infection is particularly severe, we can feel extremely sick – with fever, chills, lethargy, and decreased cognitive function - as the inflammatory response intensifies to combat the infection. Yet, at the same time, our acute sense of hearing (and vision) is rarely considered dysfunctional, except in cases of localized infections such as middle ear infections or labyrinthitis (see below). As such, the inner ear (the cochlear and vestibular systems) has been considered an immunologically-privileged site (Oh et al., 2012), as few components of the inflammatory response (e.g., immune cells, antibodies) were present within the inner ear, excluded by the blood-labyrinth barrier that is akin to the blood-brain barrier. This immunologically-isolated view of the inner ear has been overthrown in recent years by several pioneering studies that show the inner ear actively participating in classical local and systemic inflammatory mechanisms, with unexpected and unintended consequences.

Middle ear infections degrade the ability to hear low level sound, primarily through impaired conductive transmission of acoustic stimuli. Recent studies show that middle ear infections trigger intra-cochlear inflammatory responses, disrupting cochlear homeostasis, and initiate cochlear tissue remodeling, all of which can transiently or permanently impact auditory function (Trune et al., 2015). Middle ear inflammation increases the permeability of the round window to macromolecules, enabling pro-inflammatory signals and bacterial endotoxins to penetrate through the round window into the perilymphatic scala tympani of the cochlea (Ikeda et al., 1990; Kawauchi et al., 1989). Spiral ligament fibrocytes lining the scala tympani respond to these immunogenic signals, releasing inflammatory chemokines that attract immune cells to migrate across the blood-labyrinth barrier into the inner ear (Kaur et al., 2015b; Oh et al., 2012). Inner ear recruitment of systemic immune cells is also evident after selective hair cell death (Kaur et al., 2015a; Kaur et al., 2015b) {see companion article by Tejbeer Kaur, this issue}. In addition, macrophage-like cells are localized adjacent to blood vessels (perivascular macrophages) within the inner ear (Zhang et al., 2012), and supporting cells in the organ of Corti exhibit glial-like (anti-inflammatory) properties by phagocytosing cellular debris following sensory hair cell death (Monzack et al., 2015). These data raised the notion that inner ear tissues can mount a local response to inflammatory signals similar to that accomplished systemically following sterile induction, e.g., after a crushing injury resulting in necrotic cell death (Rock et al., 2010), and more specifically, by noise-induced cochlear cell death (Fujioka et al., 2014; Hirose et al., 2005) {see also companion article by K. Prasad, this issue}.

Three meningeal membranes envelop cerebrospinal fluid (CSF) that protect the brain and spinal cord, and are nourished by the highly-vascularized blood-brain barrier. Infection of the meningeal membranes - meningitis - has long been known to induce labyrinthitis, cochlear fibrosis and ossification that can impair optimal cochlear implantation procedures (Caye-Thomasen et al., 2012). Strikingly, meningogenic bacteria migrate from CSF through the cochlear aqueduct into the perilymphatic scala tympani at the base of the cochlea (Takumida and Anniko, 2004), and can induce temporary (when treated rapidly with non-ototoxic antibiotics) or permanent hearing loss (Bhatt et al., 1993; Perny et al., 2016; Richardson et al., 1997). Over time, bacteria spread through perilymph via the helicotrema to the basal region of the scala vestibuli before entering cochlear endolymph and the vestibular apparatus, inducing widespread inflammation (Takumida and Anniko, 2004). Preclinical models with untreated meningitis frequently develop hearing loss, and this was closely correlated with rapid elevation of markers for inflammation markers in CSF (Bhatt et al., 1993; Perny et al., 2016). Local infusion of bacterial endotoxin into the cochlea also induced a dose-dependent increase in inflammatory infiltrates and hearing loss (Darrow et al., 1992; Tarlow et al., 1991).

In contrast to these direct inflammatory challenges to the cochlea, systemic infections or inflammation do not generally modulate auditory function, and has been shown experimentally (Hirose et al., 2014b; Koo et al., 2015). Nonetheless, systemic inflammation changes cochlear physiology. Systemic administration of immunogenic stimuli (bacterial lipopolysaccharides, LPS) triggered cochlear recruitment of mononuclear phagocytes into the spiral ligament over several days (Hirose et al., 2014b). While LPS and inflammation typically vasodilate blood vessels, facilitating greater extravasation of plasma and immune cells into the interstitial fluids, the tight junctions between endothelial cells of cochlear capillaries generally remain intact (unpublished data, manuscript in preparation). Yet, systemic LPS-induced inflammation altered the permeability of the blood-perilymph barrier, with a 2-3 fold increase in fluorescein in perilymph (Hirose et al., 2014a). Similarly large systemic LPS-induced increases in cochlear levels of inflammatory markers also occurred (Koo et al., 2015; Quintanilla-Dieck et al., 2013). This is particularly significant as substantially higher levels of individual cytokines (e.g., IL-1β; IL-10) in serum was not replicated in cochlear tissues, suggestive of a general paucity of paracellular flux between the tight junction-coupled endothelial cells comprising the blood-labyrinth barrier of the cochlear lateral wall (Koo et al., 2015). This phenomenon was further emphasized at later time points, when cochlear tissues expressed higher levels of individual cytokines (e.g., IL-6, IL-8; MIP-1α) while serum levels returned to very low baseline levels, suggestive of local, cochlear (parenchymal) production of cytokines. This was confirmed by upregulation of mRNA for these cytokines in cochlear tissues (Koo et al., 2015). Thus, the cochlea contributes to inflammatory responses induced by systemic, as well as cochlear, immunogenic stimuli originating from bacteria, or other sources of inflammation, e.g., cellular debris.

Severe bacterial infections, such as bacteremia, meningitis or sepsis, are often treated with aminoglycosides antibiotics, despite their well-known ototoxic effects, due to their broad-spectrum bactericidal activity. Most prior studies of aminoglycoside-induced ototoxicity, including those from this laboratory, have been conducted in healthy preclinical models. Given the background above, we then examined how these inflammation-induced changes in cochlear physiology, and particularly the blood-labyrinth barrier, affected cochlear uptake of aminoglycosides and subsequent ototoxicity. Low systemic dosing with LPS to induce inflammation, without altering serum levels of aminoglycosides, increased cochlear uptake of aminoglycosides, particularly in the stria vascularis (Koo et al., 2015). There was also a lack of paracellular flux between endothelial cells of dilated cochlear capillaries in the strial vascularis and spiral ligament, suggestive of transcellular trafficking of aminoglycosides (Koo et al., 2015). Potential cell-regulated mechanisms to traffic aminoglycosides across the endothelial cells forming the blood-labyrinth barrier include transcytosis, ion channel flux, and transporters. Once aminoglycosides traversed the cochlear blood-labyrinth barrier, they preferentially enter hair cells from endolymph via the mechanoelectrical transduction channels located on hair cell stereocilia (Alharazneh et al., 2011; Li and Steyger, 2011; Marcotti et al., 2005).

Induction of systemic inflammation also synergistically potentiated aminoglycoside-induced ototoxicity. The frequency range of auditory threshold shifts and the degree of hair cell death induced by aminoglycosides was greater than in preclinical models without inflammation (Koo et al., 2015). Inflammation also potentiated cisplatin-induced ototoxicity (Oh et al., 2011). Interestingly, significant auditory threshold shifts occur in cochlear regions where hair cells appear morphologically intact following ototoxic drug administration (Koo et al., 2015; Nicol et al., 1992). Recent studies now show that aminoglycosides can, in specific situations, induce cochlear synaptopathy, disrupting the synapses between inner hair cells and their innervating afferent nerve fibers as well as decreased neuronal density in the spiral ganglion of the cochlea (Oishi et al., 2015). Remarkably, experimental meningitis and the consequent inflammatory response also induced cochlear synaptopathy and significantly decreased spiral ganglion density (Perny et al., 2016). Thus, cochlear synaptopathy may contribute to the greater degree of cochlear dysfunction observed relative to that suggested by actual hair cell loss.

Thus, the inflammatory response in the inner ear is highly modulated compared to systemic tissues due to the blood-labyrinth barrier preventing rapid entry of immune cells and antibodies. Nonetheless, cochlear tissues are capable of mounting sustained cellular inflammatory responses to both local and systemic immunogenic stimuli. Typically, these would be, presumably, evolutionarily beneficial for preserving inner ear function, but they can have unexpected consequences such as potentiating the ototoxicity of specific medications developed in recent decades. Thus, much further work is required to unravel the implications of cochlear and systemic inflammation on cochlear physiology as well as cochlear responses to acoustic trauma, infections of the middle ear, meninges or CSF, as well as, ototoxic medications.

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OTOTOXICITY: OXIDATIVE STRESS, INFLAMMATORY, AND IMMUNE RESPONSES

Tejbeer Kaur, PhD

Certain therapeutic agents are known to cause damage to the ear that can result in hearing loss and balance disorders. These drugs, which include aminoglycoside antibiotics and chemotherapeutics such as cisplatin, are considered ototoxic and include medicines critical for treating serious infections and cancers. Hearing and balance problems caused by these drugs can sometimes be reversed when the drug therapy is discontinued. However, the damage is often severe and irreversible leading to permanent hearing loss.

Ototoxicity from the aminoglycoside antibiotic, gentamicin, is the most common single cause of bilateral vestibulopathy (balance disorder), accounting for 15 to 50% of all cases, and also causes cochleotoxicity (or hearing loss) in 5 to 10% of treated patients (http://american-hearing.org/). Over 60% of pediatric patients treated with cisplatin develop irreversible hearing loss. Pediatric hearing loss is particularly problematic since it delays educational fulfillment and social development (Knight et al., 2005).

Although these drugs are widely used clinically in both developed and developing countries, the ototoxic side effect remains the major clinical limitation. Therefore, it is imperative to understand the molecular and cellular mechanisms of drug-induced ototoxicity in order to develop treatments and protective strategies.

Ototoxic drugs primarily cause death of the sensory hair cells within the cochlea and vestibular system. Some studies suggest that these drugs can also damage the cochlear lateral wall, resulting in a dysfunctional blood-labyrinth barrier (Laurell et al., 2000 and 2007), and also cause delayed cochlear neuronal degeneration (Oesterle et al., 2009). Several cellular injury mechanisms have been proposed using *in vitro* and *in vivo* models. Below, I discuss some of the identified molecular and cellular mechanisms of ototoxicity.

Oxidative stress and inflammation

Several studies have concluded that the generation of reactive oxygen species (ROS) are linked to ototoxicity (Chen et al., 2007, Rybak and Ramkumar et al., 2007, Rybak et al., 2007, Mukherjea et al., 2010, Mukherjea et al., 2011). Ototoxic drugs are thought to enter hair cells through the mechanotransduction channels and form complexes that are highly reactive, resulting in the production of an ROS-like superoxide, hydrogen peroxide, hydroxyl radical (Lesniak et al., 2005, Clerici et al., 1995, 1996; Kopke et al., 1997). Toxic levels of ROS are believed to promote apoptotic and necrotic cell death by various downstream mechanisms (reviewed by Rybak et al., 2007). Although the role of oxidative stress in inner ear damage is well established, the sources of ROS are less clear. Recently studies show that expression of superoxide-generating nicotinamide-adenine

dinucleotide phosphate (NADPH) oxidase isoform (NOX3) in the organ of Corti of the cochlea (Banfi et al., 2004), and vestibular organs (Paffenholz et al., 2004), is up-regulated ~2 fold following cisplatin exposure, leading to increased levels of superoxide and sensory hair cell apoptosis (Mukherjea et al., 2006). Superoxide anion may be generated from other cochlear sources besides NOX3, including NOX1 and NOX4, and their expression is also increased with cisplatin treatment (Kim et al., 2010). Suppression of these NOX enzymes by pretreatment with small interfering RNA (siRNA) or small molecule inhibitors reduced cisplatin ototoxicity, with preservation of hearing thresholds and hair cells.

Oxidative stress is also considered a major contributing factor to noise-induced cochlear injury. Noise exposure in Wistar rats has been shown to upregulate cochlear expression of NOX1 and dual oxidase2 (DUOX2, another member of NADPH oxidase family); whereas, NOX3 was down-regulated (Vlajkovic et al., 2013). This study demonstrated that noise exposure has an opposite effect to cisplatin on NOX3 expression. Such noise-induced downregulation of NOX3 may suggest an endogenous protective mechanism to reduce the production of superoxide in a noise-damaged cochlea. Recently, a human genome-wide association study identified the gene for NOX3 as critical since it is associated with susceptibility to NIHL (Lavinsky et al., 2015).

Another source for ROS generation due to ototoxic drug exposure is the transient receptor potential vanilloid 1 (TRPV1) channel, which is expressed in the organ of Corti and auditory neurons. Cisplatin treatment co-activates TRPV1 and NOX3, and induction of these proteins is dependent on ROS generation, leading to hair cell death. Cisplatin-mediated ROS generation via NOX3 was shown to be crucial to the activation and induction of TRPV1 (Mukherjea et al., 2008). Crucially, the generation of ROS induced by cisplatin in sensory hair cells is dependent on TRPV1. Furthermore, inhibition of TRPV1 suppressed NOX3 expression, ROS generation, and is associated with decreased cisplatin-induced apoptosis and hearing loss. Similar studies show that aminoglycosides induce the expression of TRPV1 in both auditory and vestibular ganglia of mice (Kitahara et al., 2005; Ishbashi et al., 2009). Inhibition of TRPV1 or NOX enzymes offers a novel pathway for therapeutic management of sensorineural hearing loss due to ototoxic drugs and noise.

Inflammation has also been implicated in cisplatin-induced cell death. Many pro-inflammatory genes such as transcription factor nuclear factor kappa B (NFκB) and inducible nitric oxide (iNOS) are up regulated in the stria vascularis and spiral ligament of the cochlea of cisplatin treated mice (Watanbe et al., 2002; So et al., 2007). Inhibition of NFκB seems to decrease cell death due to cisplatin *in vitro* (Chung et al., 2008). Pro-inflammatory cytokines like TNF-α, IL-1β and IL-6 are also up regulated in the vestibular organs and cochlea by cisplatin treatment (So et al., 2007; Kim et al., 2008; So et al., 2008). Inhibition of TNF-α signaling with etanercept can be otoprotective (So et al., 2008). Inflammatory transcription factor, signal transduction and transcription factor 1 (STAT1) also mediates cell death following exposure to ROS, TNF-α and DNA damage (Stephanou et al., 2001; Townsend et al., 2004; De Vries et al., 2004). Cisplatin treatment also induces STAT1 activation in both the utricle (Schmitt et al., 2009) and cochlea (Kaur et al., 2011).

The cisplatin-induced activation of STAT1 was mediated by ROS generation via NOX3. Activation of STAT1 increased the expression of downstream pro-inflammatory genes TNF-a, iNOS and COX2, ultimately leading to inflammation and hair cell death in the cochlea. This evidence suggests that inhibition of either STAT1 or TNF-a is sufficient to suppress cisplatin-induced hair cell apoptosis and hearing loss. Another recent study demonstrated that absence of STAT1 attenuates both cisplatin and aminoglycoside-mediated hair cell death (Levano and Bodmer 2015). Together these studies highlight STAT1 as a central player in ototoxicity in ROS generation and inflammation that lead to hair cell death and hearing loss. Recently, it has also been demonstrated that cisplatin can activate STAT1 via mitogen-activated protein kinases (MAPKs) such as ERK1/2, p38 and JNK. Inhibition of these kinases reduces cisplatin-induced inflammatory STAT1 phosphorylation (Kaur et al., 2016). Although, the source of MAPK activation is currently unknown, targeting MAPKs (probably locally) is another potential target to prevent ototoxicity.

Emerging evidence has implicated cochlear Inflammation as a major contributor of noise-induced cochlear injury. Several studies have demonstrated an inflammatory response in the cochlea following exposure to traumatic noise that involves an up-regulation of pro inflammatory mediators (cytokines, chemokines and cell adhesion molecules, followed by rapid infiltration and migration of immune cells from the systemic circulation (Discolo et al., 2005, Fujiko et al., 2006, Hirose et al., 2005, Tan et al., 2008, Wakabayashi et al., 2010,Tan et al., 2016). To date, various inflammatory genes and proteins have been tied to cochlear inflammation, yet the precise molecular mechanisms, the time course and the function in the development of cochlear injury remain to be elucidated. {For further discussion on inflammation, please read the companion article by Kedar Prasad, Ph.D.}

Immune response to sterile cochlear injury

The inner ear of the peripheral auditory system was once thought to be an “immune-privileged” organ similar to the brain in the central nervous system. The cochlea seems to have no lymphatic drainage system and the blood-labyrinth barrier is tightly controlled to separate the cochlear microenvironment from circulation. However, within the last decade several studies have demonstrated the presence of immunoresponsive cells within the inner ear under steady state conditions (Hirose et al., 2005; Tornabene et al., 2006; Lang et al., 2006; Okano et al., 2008; Sato et al., 2008; O’Malley et al., 2015). These studies indicated that bone marrow-derived cells of hematopoietic origin can migrate into the cochlear modiolus and lateral wall, and reside as tissue macrophages within the cochlea. Bone marrow-derived cells from the systemic circulation continuously replace these cochlear resident macrophages over several months. However, the exact ontogeny and function of inner ear resident macrophages during steady state remains unclear.

Sterile damage to the sensory epithelium can induce an increase in the number of macrophages within the inner ear, in addition to the resident immune cells. Injury to the

auditory sensory epithelium either by laser or ototoxic drugs induces inflammation characterized by monocytes/macrophage infiltration into the chick basilar papilla (Warchol et al., 1997; Bhave et al., 1998). Inflammatory cells have also been noted in a number of studies that have examined the mammalian cochlea after noise injury (Fredelius 1998; Fredelius and Rask-Anderson, 1990; Hirose et al., 2005; Tornabene et al., 2006). The authors reported a large increase in the number of CD45 and F4/80 positive cells after loud noise exposure in the mouse cochlea. The number of cochlear macrophages is also increased in the spiral ganglion, spiral ligament along with injured sensory epithelium after kanamycin (aminoglycoside) toxicity (Sato et al., 2010). These findings clearly indicate that there is an immune response (evident by increase in the number of macrophages) to sterile cochlear injury. Macrophages may clear up dying hair cell debris by phagocytosis during injury, and be involved in repair of the cochlear sensory epithelium. It seems also likely that macrophages are involved in the degeneration of the cochlear structures (Singh and Wangemann, 2008; Lu et al., 2012). Nevertheless, mechanisms of macrophage infiltration into the cochlea, the contribution of resident versus recruited macrophages and the precise role of cochlear macrophages in an injured cochlea are unclear.

Blockage of pro-inflammatory cytokine IL-6 has been shown to significantly reduce the number of cochlear macrophages during injury (Wakabayashi et al., 2010). Monocyte chemoattractant protein-1 (also known as CCL2) and its primary receptor CCR2 are known effectors of monocyte chemotaxis *in vivo* (Ransohoff 2002). Nevertheless, monocyte migration remained unchanged in the absence of both CCL2 and CCR2 after noise exposure in the cochlea (Sautter et al., 2006). Recent studies by Kaur and colleagues shed light on the role of macrophages during sterile cochlear injury. Selective hair cell loss appears sufficient to recruit macrophages towards the injured sensory epithelium of both vestibular organs (Kaur et al., 2015a) as well as cochlea (Kaur et al., 2015b). The number of macrophages in damaged sensory epithelium increases immediately after hair cell death, and then decreases within a few weeks. Interestingly, the number of macrophages also increased in the spiral ganglia, despite no evident loss of auditory neurons. The number of macrophages in the ganglion remained elevated for longer periods compared to the damaged sensory epithelium (also observed in aminoglycoside and acoustic injury mouse models of hearing loss, *unpublished data*). To investigate the mechanism of macrophage infiltration during cochlear injury, Kaur et al., 2015b have focused on chemokine-fractalkine (CX_3CL1-CX_3CR1) signaling. The ligand CX_3CL1 was reported to be expressed by mature spiral ganglion neurons in the cochlea, while the receptor CX_3CR1 is known to be exclusively expressed by macrophages in the cochlea (Hirose et al., 2005) and monocytes in the vasculature (Jung et al., 2000). Genetic deletion of CX_3CR1 from immune cells reduced the recruitment of macrophages both in the sensory epithelium and the spiral ganglion, suggesting that CX_3CL1-CX_3CR1 signaling is involved in the recruitment of inflammatory cells into the damaged cochlea. Also, disruption in fractalkine signaling by deleting CX_3CR1 resulted in a significant loss of spiral ganglion cells after hair cell death (also observed in aminoglycoside and acoustic

injury mouse models of hearing loss, *unpublished data)*. This suggests that macrophage recruitment towards the spiral ganglion neurons after cochlear injury is required for the long-term survival of cochlear neurons via fractalkine signaling. Another study demonstrated that CX_3CR1-deficient cochlear macrophages exacerbate kanamycin ototoxicity (Sato et al., 2010). The authors reported more functional and structural damage in the organ of Corti in CX_3CR1-null mice compared to control littermates. Collectively, these findings point to an unexpected interaction between the inner ear and innate immune system and suggest that macrophages influence neuronal survival during sterile cochlear injury and have a neuroprotective role in deafened ears. It is necessary to better understand the cellular and molecular mechanisms of this macrophage-mediated neuroprotection and identify targets. This research will be instrumental for the development of therapeutic agents that can promote neuronal survival or axonal regeneration in patients with hearing loss.

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ROLE OF OXIDATIVE STRESS AND INFLAMMATION IN NOISE-INDUCED HEARING LOSS

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Published studies suggest that induced oxidative stress and inflammation play an important role in the initiation and progression of noise-induced hearing loss (NIHL). Noise-induced oxidative damage to hair cells immediately initiates an acute inflammatory reaction that can trigger repair processes at the site of injury. Once healed, the local inflammatory response is turned off. However, if the damage is not repaired due to persistent oxidative damage, chronic inflammation that releases additional free radicals and pro-inflammatory cytokines occurs.

What is the Evidence for Oxidative Stress in NIHL?

Evidence for the role of induced oxidative stress in hearing disorders comes from two sources, directly by measuring the levels of markers of oxidative damage in blood or urine, and indirectly by the use of antioxidants to decrease the degree of hearing loss.

Exposure to high intensity noise decreases the levels of serum total antioxidant capacity and increased nitric oxide in the serum of guinea pigs (Diao et al., 2003). Increased nitric oxide levels form peroxynitrite that can damage cochlear hair cells. Impulse noise also enhances oxidative stress in preclinical studies(Clerici et al, 1995; Henderson et al., 1999; Henderson et al., 2006; Ohlemiller et al., 1999; Van Campen et al., 2002; Yamashita et al., 2004). The levels of nitric oxide, peroxynitrite, oxidative stress, nuclear factor-kappa-beta (NF-kappaB), glutamate receptor (NMDA) (methyl-D-aspartate), and calcium are elevated in hair cells in vitro, or cochlear tissues in vivo, i.e., preclinical (animal) models(Ohlemiller et al., 1999; Yaman et al., 1995; Minami et al., 2004). Noise exposure-induced tinnitus occurs in approximately 21 to 42% of exposed individuals(Neri et al., 2006; Kowalska and Sulkowski, 2001). About 34% of tinnitus patients have post-traumatic stress disorders (PTSDs) (Fagelson, 2007). A review has suggested that increased oxidative stress, chronic inflammation and excitotoxicity are common biochemical defects that participate in the initiation and progression of PTSD, mild traumatic injury (TBI), and penetrating TBI (Prasad, 2015). Since NIHL appears to involve these biochemical abnormalities, it is not surprising that significant number of patients with tinnitus develop PTSD.

NADPH (nicotinamide-adenine dinucleotide phosphate) oxidases (NOXs) transport electrons across the plasma membrane and produce superoxide radicals from oxygen in the cytoplasm. Exposure to moderate or intense noise increases the activity of NOXs in rat cochleae, and inhibition of NOXs with diphenyleneiodonium after noise exposure reduced the degree of hearing loss(Vlajkovic et al., 2013). Pravastatin inhibition of NOX activity also decreased noise-induced hearing loss in mice(Park et al., 2012).

Whole-body exposure to vibration induced chronic stress including oxidative stress in the neutrophils and lymphocytes of albino rats (Dolgushin and Davydova, 2013). This may explain the observation in which the combination of noise and vibration from hand-held tools increased the risk of hearing loss in industrial workers(Pettersson et al, 2014; Turcot et al., 2015). Exposure to bony external canal of guinea pigs to vibration or noise revealed that older animals were more sensitive to vibration-induced inner ear damage than younger animals. In addition, it was found that vibration was more effective than sound in causing damage to inner ear (Zou et al., 2001).

Increased oxidative stress and chronic inflammation are also associated with ageing (Le and Keithley, 2007). D-galactose induces hearing loss that resembles normal aging in rats, and is associated with increased oxidative stress, and an accumulation of mutated mitochondrial DNA in peripheral and central auditory cells(Du et al., 2015; Chen et al, 2010; Zhong et al., 2011). Additional preclinical and clinical studies are needed to substantiate the role of oxidative stress in noise-induced hearing disorders.

Where are the Gaps in the Evidence for Oxidative Stress in NIHL?

In order to establish the role of oxidative stress in initiating, and the progression of, NIHL, additional studies are needed to determine the level of biomarkers for oxidative damage in patients with NIHL, and in individuals exposed to noise without any symptoms of hearing

loss. Measurement of one marker of oxidative damage will not be sufficient to reflect the status of oxidative stress. Biomarkers of oxidative damage should include malondialdehyde (MDA) and 3-nitrotyrosine in plasma, and 8-hydroxyguanosine levels in urine. In addition, the blood levels of antioxidant enzymes, and selected antioxidants, such as vitamin E, vitamin C, and glutathione (in plasma), should also be determined in the same subjects. Similar preclinical studies after noise exposure should also be performed.

What is the Evidence for Inflammation in NIHL?

Noise exposure also induces cochlear inflammation in preclinical models by increasing levels of intracellular adhesion molecules and cochlear recruitment of leukocytes(Shi and Nuttall, 2007; Yamamoto et al., 2009). Intense noise exposure also activated nuclear transcription factor-KappaB (NF-KappaB) and increased the levels of pro-inflammatory products including: intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and inducible nitric oxide synthase (iNOS) in the cochleae of mice(Masuda et al, 2006). Polymorphisms in the gene for interleukin-6 (IL-6) increased the susceptibility of NIHL in individuals over the age of 60 years(Braga et al., 2014). The role of chronic inflammation in NIHL has yet to be adequately studied.

Where are the Gaps in the Evidence for Inflammation in NIHL?

To establish the role of inflammation in initiating, and the progression of, NIHL, additional studies on the levels of biomarkers for inflammation in serum and cochlear tissue are needed. Measurements of multiple markers of inflammation over time during and after exposure will accurately reflect the status of inflammation. At minimum, serum levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), TNF-alpha, and NF-KappaB, and C-reactive protein (CRP), a non-specific marker of inflammation, in individuals with acute NIHL, or exposed to noise without symptoms of NIHL, are needed. Similar studies in preclinical models after noise exposure are also needed. To obtain meaningful data, the levels of biomarkers for (chronic) inflammation and oxidative stress must be determined and correlated in the same subject samples in both humans and animal models exposed to noise.

Improving Prevention and Management of NIHL

A review of several studies suggest that increased oxidative stress and inflammation play a role in initiating, and the progression of NIHL (Prasad, 2011); therefore, reducing these biochemical changes is a rational choice to better prevent and manage these disorders. Excessive release of glutamate plays important roles in the onset of noise-induced tinnitus and neurotoxicity(Puel et al., 1998; Hakuba et al., 2000; Ruel et al., 2005; Brozoski et al., 2013). Therefore, attenuating excess glutamate release is essential to ameliorating noise-induced tinnitus and neurotoxicity. I propose that simultaneously reducing oxidative stress, inflammation, and glutamate release is necessary for improved prevention and management of NIHL.

Individual antioxidants or anti-inflammatory drugs can partially prevent hearing loss in preclinical models and humans (Angeli et al, 2005). However, supplementation with individual antioxidants or glutamate antagonist in humans with idiopathic sudden sensorineural hearing loss, tinnitus and Meniere's disease has had limited benefit(Seidman, 1998; Tepel, 2007; Raponi et al., 2003; Kang et al, 2013; Kapoor et al., 2011). One reason for these limited effects may be that individual antioxidants in highly oxidative environments, such as the noise-exposed cochlea would be oxidized, and then act as pro-oxidants. I propose that supplementation with one antioxidant or glutamate antagonist cannot enhance the levels of antioxidants (enzymes, dietary or endogenous compounds) and simultaneously reduce the release of glutamate and its toxicity. Most clinical studies to date with a single agent have not provided optimal benefits in preventing hearing loss or tinnitus.

To optimally reduce oxidative stress and inflammation, it is essential to simultaneously enhance the levels of antioxidants (Prasad, 2016) as well as the release of glutamate (Chang et al., 2012; Schubert et al., 1992; Yang and Wang, 2009; Hung et al., 2009). I propose that a mixture of micronutrients can simultaneously enhance the levels of cytoprotective enzymes through activation of the Nrf2/ARE (nuclear transcription factor-2/antioxidant response element) pathway, and increase the levels of dietary and endogenous antioxidant compounds be utilized. This mixture of micronutrients can also prevent the release and toxicity of glutamate (Prasad and Bondy, 2016). One review described that antioxidant compounds can activate Nrf2 without the need for ROS stimulation (Prasad and Bondy, 2016).

Nrf2 belongs to the Cap ´N´Collar (CNC) family that contains a conserved basic leucine zipper (bZIP) transcriptional factor. Under physiological conditions, Nrf2 is associated with Kelch-like ECH-associated protein 1 (Keap1), which inhibits Nrf2(Williamson et al., 2012; Itoh et al., 1997 . Antioxidant-activated Nrf2 dissociates itself from the Keap1- Cul-Rbx1 complex and translocates in the nucleus where it heterodimerizes with a small Maf protein, and binds with the ARE (antioxidant response element) leading to increased expression of target genes coding for several cytoprotective enzymes including antioxidative enzymes(Hayes et al., 2000; Chan et al., 2001; Jaramillo and Zhang, 2013).

One proposed mixture of micronutrients contains multiple dietary antioxidant compounds (vitamin A, vitamin C, vitamin E, vitamin D, curcumin, and resveratrol), endogenous antioxidants (alpha-lipoic acid, L-carnitine, and coenzyme Q10), and a synthetic antioxidant N-acetylcysteine (NAC), mineral selenium, omega-3-fatty acids and all B-vitamins.

Future studies

Future preclinical and clinical studies to prevent or to improve the management of NIHL may utilize a mixture of agents that increase the levels of antioxidant enzymes through the Nrf2/ARE pathway, and simultaneously also increase dietary and endogenous antioxidant compounds. Optimally such mixtures would also include compounds that

reduce the synaptic release of glutamate from sensory hair cells and its potential of neurotoxicity/excitotoxicity.

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RECENTLY PUBLISHED LITERATURE

Articles determined to be of particular interest will be listed with full abstract in "Research Highlights" below, followed by the remainder of the "Relevant Literature," all published between January 2015 and September 2016

RESEARCH HIGHLIGHTS

Editors evaluated over 344 article abstracts and full text articles as needed for inclusion in this edition's listing of recently published PIHL-related literature. While the final retention of articles was a subjective decision by the editors, care was taken to ensure that articles met at least a basic criterion of relevance or interest to the PIHL community. Articles which were selected dealt with preclinical or clinical models of ototoxicity, including reviews. Those omitted were those that did not directly focus on one or more ototoxin(s). Searching only PubMed, the following search was conducted:

"Ototoxicity": 344 articles reviewed by abstract; 163 retained

Common variants in ACYP2 influence susceptibility to cisplatin-induced hearing loss.

Xu H, Robinson GW, Huang J, Lim JY, Zhang H, Bass JK, Broniscer A, Chintagumpala M, Bartels U, Gururangan S, Hassall T, Fisher M, Cohn R, Yamashita T, Teitz T, Zuo J, Onar-Thomas A, Gajjar A, Stewart CF, Yang JJ.

Nat Genet. 2015 Mar;47(3):263-6.
doi: 10.1038/ng.3217. Epub 2015 Feb 9.

Taking a genome-wide association study approach, we identified inherited genetic variations in ACYP2 associated with cisplatin-related ototoxicity (rs1872328: P = 3.9 × 10(-8), hazard ratio = 4.5) in 238 children with newly diagnosed brain tumors, with independent replication in 68 similarly treated children. The ACYP2 risk variant strongly predisposed these patients to precipitous hearing loss and was related to ototoxicity severity. These results point to new biology underlying the ototoxic effects of platinum agents.

Achievement of Therapeutic Vancomycin Trough Serum Concentrations with Empiric Dosing in Neonatal Intensive Care Unit Patients.

Ringenberg T, Robinson C, Meyers R, Degnan L, Shah P, Siu A, Sturgill M.

Pediatr Infect Dis J. 2015 Jul;34(7):742-7.
doi: 10.1097/INF.0000000000000664.

BACKGROUND: The recommended goal serum trough concentration for vancomycin has increased to 10 to 20 mcg/mL, with a higher range of 15 to 20 mcg/mL for serious infections due to methicillin-resistant Staphylococcus aureus in children and adults. Although neonatal references have also recommended these higher target concentrations, dosing recommendations remained unchanged. The objective of this study was to assess the percentage of neonates and young infants achieving a serum trough concentration between 10 and 20 mcg/mL with empiric vancomycin dosing based on Neofax® in a neonatal intensive care unit (NICU) population.
METHODS: A multi-institutional retrospective chart review was conducted to identify NICU patients who received a minimum of three doses of intravenous vancomycin and had at least one appropriately drawn trough. Additional outcomes included the duration of vancomycin therapy, number of dose adjustments required to attain goal trough concentrations, time to goal trough, and incidence of nephrotoxicity and ototoxicity.
RESULTS: Of the 171 vancomycin serum trough concentrations included in the primary outcome, only 25.1% achieved a goal trough of 10 to 20 mcg/mL with empiric dosing. Only 44.6% of patients achieved the goal trough of 10 to 20 mcg/mL at any time during their vancomycin therapy. The average gestational age was 28.2 ± 4.1 weeks, average postnatal age at start of vancomycin was 34.1 ± 34.6 days, and average weight of the patients at start of vancomycin was 1602 ± 1014.5 g. The average and median total daily dose in those patients who achieved an initial vancomycin trough of 10-20 mcg/mL were 32.4 mg/kg/day and 30 mg/kg/day, respectively.
CONCLUSION: Dosing of vancomycin based on Neofax® in NICU patients is insufficient in yielding serum trough concentrations of 10 to 20 mcg/mL. Further studies are needed to evaluate the optimal dosing regimen to achieve higher trough concentrations in this patient population.

Aminoglycoside-induced ototoxicity.

Leis JA, Rutka JA, Gold WL.

CMAJ. 2015 Jan 6;187(1):E52.
doi: 10.1503/cmaj.140339. Epub 2014 Sep 15.

Review: Aminoglycoside-induced ototoxicity can profoundly affect quality of life; Aminoglycoside-induced ototoxicity is often preventable; Discontinuation of aminoglycoside therapy at the earliest recognition of ototoxicity may reduce the extent of impairment; Normal laboratory monitoring may provide false reassurance; Patients must be counselled regarding the risks and benefits of aminoglycoside therapy.

High-frequency audiometry reveals high prevalence of aminoglycoside ototoxicity in children with cystic fibrosis.

Al-Malky G, Dawson SJ, Sirimanna T, Bagkeris E, Suri R.

J Cyst Fibros. 2015 Mar;14(2):248-54.
doi: 10.1016/j.jcf.2014.07.009. Epub 2014 Aug 13.

BACKGROUND: Intravenous aminoglycoside (IV AG) antibiotics, widely used in patients with cystic fibrosis (CF), are known to have ototoxic complications. Despite this, audiological monitoring is not commonly performed and if performed, uses only standard pure-tone audiometry (PTA). The aim of this study was to investigate ototoxicity in CF children, to determine the most appropriate audiological tests and to identify possible risk factors.
METHODS: Auditory assessment was performed in CF children using standard pure tone audiometry (PTA), extended high-frequency (EHF) audiometry and distortion-product otoacoustic emissions (DPOAE).
RESULTS: 70 CF children, mean (SD) age 10.7 (3.5) years, were recruited. Of the 63 children who received IV AG, 15 (24%) children had ototoxicity detected by EHF audiometry and DPOAE. Standard PTA only detected ototoxicity in 13 children. Eleven of these children had received at least 10 courses of IV AG courses. A 25 to 85 dBHL hearing loss (mean±SD: 57.5±25.7 dBHL) across all EHF frequencies and a significant drop in DPOAE amplitudes at frequencies 4 to 8 kHz were detected. However, standard PTA detected a significant hearing loss (>20 dBHL) only at 8 kHz in 5 of these 15 children and none in 2 subjects who had significantly elevated EHF thresholds. The number of courses of IV AG received, age and lower lung function were shown to be risk factors for ototoxicity.
CONCLUSIONS: CF children who had received at least 10 courses of IV AG had a higher risk of ototoxicity. EHF audiometry identified 2 more children with ototoxicity than standard PTA and depending on facilities available, should be the test of choice for detecting ototoxicity in children with CF receiving IV AG.

Adenosine A1 Receptor Protects Against Cisplatin Ototoxicity by Suppressing the NOX3/STAT1 Inflammatory Pathway in the Cochlea.

Kaur T, Borse V, Sheth S, Sheehan K, Ghosh S, Tupal S, Jajoo S, Mukherjea D, Rybak LP, Ramkumar V.

J Neurosci. 2016 Apr 6;36(14):3962-77.
doi: 10.1523/JNEUROSCI.3111-15.2016.

Cisplatin is a commonly used antineoplastic agent that produces ototoxicity that is mediated in part by increasing levels of reactive oxygen species (ROS) via the NOX3 NADPH oxidase pathway in the cochlea. Recent studies implicate ROS generation in

mediating inflammatory and apoptotic processes and hearing loss by activating signal transducer and activator of transcription (STAT1). In this study, we show that the adenosine A1 receptor (A1AR) protects against cisplatin ototoxicity by suppressing an inflammatory response initiated by ROS generation via NOX3 NADPH oxidase, leading to inhibition of STAT1. Trans-tympanic administration of the A1AR agonist R-phenylisopropyladenosine (R-PIA) inhibited cisplatin-induced ototoxicity, as measured by auditory brainstem responses and scanning electron microscopy in male Wistar rats. This was associated with reduced NOX3 expression, STAT1 activation, tumor necrosis factor-α (TNF-α) levels, and apoptosis in the cochlea. In vitro studies in UB/OC-1 cells, an organ of Corti immortalized cell line, showed that R-PIA reduced cisplatin-induced phosphorylation of STAT1 Ser(727) (but not Tyr(701)) and STAT1 luciferase activity by suppressing the ERK1/2, p38, and JNK mitogen-activated protein kinase (MAPK) pathways.R-PIA also decreased the expression of STAT1 target genes, such as TNF-α, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and reduced cisplatin-mediated apoptosis. These data suggest that the A1AR provides otoprotection by suppressing NOX3 and inflammation in the cochlea and could serve as an ideal target for otoprotective drug therapy.
SIGNIFICANCE STATEMENT: Cisplatin is a widely used chemotherapeutic agent for the treatment of solid tumors. Its use results in significant and permanent hearing loss, for which no US Food and Drug Administration-approved treatment is currently available. In this study, we targeted the cochlear adenosine A1 receptor (A1AR) by trans-tympanic injections of the agonist R-phenylisopropyladenosine (R-PIA) and showed that it reduced cisplatin-induced inflammation and apoptosis in the rat cochlea and preserved hearing. The mechanism of protection involves suppression of the NOX3 NADPH oxidase enzyme, a major target of cisplatin-induced reactive oxygen species (ROS) generation in the cochlea. ROS initiates an inflammatory and apoptotic cascade in the cochlea by activating STAT1 transcription factor, which is attenuated by R-PIA. Therefore, trans-tympanic delivery of A1AR agonists could effectively treat cisplatin ototoxicity.

Replication of a genetic variant in ACYP2 associated with cisplatin-induced hearing loss in patients with osteosarcoma.

Vos HI, Guchelaar HJ, Gelderblom H, de Bont ES, Kremer LC, Naber AM, Hakobjan MH, van der Graaf WT, Coenen MJ, te Loo DM.

Pharmacogenet Genomics. 2016 May;26(5):243-7.
doi: 10.1097/FPC.0000000000000212.

OBJECTIVE: Irreversible hearing loss is a frequent side effect of the chemotherapeutic agent cisplatin and shows considerable interpatient variability. The variant rs1872328 in the ACYP2 gene was recently identified as a risk factor for the development of cisplatin-induced ototoxicity in children with brain tumors. We aimed to replicate this finding in patients with osteosarcoma.

METHODS: An independent cohort of 156 patients was genotyped for the rs1872328 variant and evaluated for the presence of cisplatin-induced ototoxicity.
RESULTS: A significant association was observed between carriership of the A allele and cisplatin-induced ototoxicity after the end of treatment (P=0.027).
CONCLUSION: This is the first study replicating the association of ACYP2 variant rs1872328 with cisplatin-induced ototoxicity in patients with osteosarcoma who did not receive potentially ototoxic cranial irradiation. Hence, the ACYP2 variant should be considered a predictive pharmacogenetic marker for hearing loss, which may be used to guide therapies for patients treated with cisplatin.

A systematic review and meta-analysis of the efficacy and safety of N-acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB.

Kranzer K, Elamin WF, Cox H, Seddon JA, Ford N, Drobniewski F.

Thorax. 2015 Nov;70(11):1070-7.
doi: 10.1136/thoraxjnl-2015-207245. Epub 2015 Sep 7.

BACKGROUND: Ototoxicity is a severe side effect of aminoglycoside antibiotics. Aminoglycosides are recommended for the treatment of multidrug-resistant TB (MDR-TB). N-Acetylcysteine (NAC) appears to protect against drug- and noise-induced hearing loss. This review aimed to determine if coadministering NAC with aminoglycoside affected ototoxicity development, and to assess the safety and tolerability of prolonged NAC administration.
METHODS: Eligible studies reported on the efficacy of concomitant NAC and aminoglycoside administration for ototoxicity prevention or long-term (≥ 6 weeks) administration of NAC regardless of indication. Pooled estimates were calculated using a fixed-effects model. Heterogeneity was assessed using the I(2) statistic.
RESULTS: Three studies reported that NAC reduced ototoxicity in 146 patients with end-stage renal failure receiving aminoglycosides. Pooled relative risk for otoprotection at 4-6 weeks was 0.14 (95% CI 0.05 to 0.45), and the risk difference was -33.3% (95% CI 45.5% to 21.2%). Eighty-three studies (N=9988) described the administration of NAC for >6 weeks. Abdominal pain, nausea and vomiting, diarrhoea and arthralgia were increased 1.4-2.2 times.
DISCUSSION: This review provides evidence for the safety and otoprotective effect of NAC when coadministered with aminoglycoside. It represents a strong justification for a clinical trial to investigate the effect of concomitant NAC treatment in patients receiving aminoglycosides as part of MDR-TB treatment.

Endotoxemia-mediated inflammation potentiates aminoglycoside-induced ototoxicity.

Koo JW, Quintanilla-Dieck L, Jiang M, Liu J, Urdang ZD, Allensworth JJ, Cross CP, Li H, Steyger PS.

Sci Transl Med. 2015 Jul 29;7(298):298ra118.
doi: 10.1126/scitranslmed.aac5546.

The ototoxic aminoglycoside antibiotics are essential to treat severe bacterial infections, particularly in neonatal intensive care units. Using a bacterial lipopolysaccharide (LPS) experimental model of sepsis, we tested whether LPS-mediated inflammation potentiates cochlear uptake of aminoglycosides and permanent hearing loss in mice. Using confocal microscopy and enzyme-linked immunosorbent assays, we found that low-dose LPS (endotoxemia) greatly increased cochlear concentrations of aminoglycosides and resulted in vasodilation of cochlear capillaries without inducing paracellular flux across the blood-labyrinth barrier (BLB) or elevating serum concentrations of the drug. Additionally, endotoxemia increased expression of both serum and cochlear inflammatory markers. These LPS-induced changes, classically mediated by Toll-like receptor 4 (TLR4), were attenuated in TLR4-hyporesponsive mice. Multiday dosing with aminoglycosides during chronic endotoxemia induced greater hearing threshold shifts and sensory cell loss compared to mice without endotoxemia. Thus, endotoxemia-mediated inflammation enhanced aminoglycoside trafficking across the BLB and potentiated aminoglycoside-induced ototoxicity. These data indicate that patients with severe infections are at greater risk of aminoglycoside-induced hearing loss than previously recognized.

The amikacin research program: a stepwise approach to validate dosing regimens in neonates.

Smits A, Kulo A, van den Anker J, Allegaert K.

Expert Opin Drug Metab Toxicol. 2016 Sep 21:1-10. [Epub ahead of print]

INTRODUCTION: For safe and effective use of antibacterial agents in neonates, specific knowledge on the pharmacokinetics (PK) and its covariates is needed. This necessitates a stepwise approach, including prospective validation.
AREAS COVERED: We describe our approach throughout almost two decades to improve amikacin exposure in neonates. A dosing regimen has been developed and validated using pharmacometrics, considering current weight, postnatal age, perinatal asphyxia, and ibuprofen use. This regimen has been developed based on clinical and therapeutic drug monitoring (TDM) data collected during routine care, and subsequently underwent prospective validation. A similar approach has been scheduled to quantify the impact of hypothermia. Besides plasma observations, datasets on deep compartment PK were also collected. Finally, the available literature on developmental toxicology (hearing, renal) of amikacin is summarized.

EXPERT OPINION: The amikacin model reflects a semi-physiological function for glomerular filtration. Consequently, this model can be used to develop dosing regimens for other aminoglycosides or to validate physiology-based pharmacokinetic models. Future studies should explore safety with incorporation of covariates like pharmacogenetics, biomarkers, and long-term outcomes. This includes a search for mechanisms of developmental toxicity. Following knowledge generation and grading the level of evidence in support of data, dissemination and implementation initiatives are needed.

Serial Monitoring of Otoacoustic Emissions in Clinical Trials.

Konrad-Martin D, Poling GL, Dreisbach LE, Reavis KM, McMillan GP, Lapsley Miller JA, Marshall L.

Otol Neurotol. 2016 Sep;37(8):e286-94.
doi: 10.1097/MAO.0000000000001134.

The purpose of this report is to provide guidance on the use of optoacoustic emissions (OAEs) as a clinical trial outcome measure for pharmaceutical interventions developed to prevent acquired hearing loss secondary to cochlear insult. OAEs are a rapid, noninvasive measure that can be used to monitor cochlear outer hair cell function. Serial monitoring of OAEs is most clearly established for use in hearing conservation and ototoxicity monitoring programs in which they exhibit more frequent and earlier changes compared with pure-tone audiometry. They also show promise in recent human trials of otoprotectants. Questions remain, however, concerning the most appropriate OAE protocols to use and what constitutes a "significant" OAE response change. Measurement system capabilities are expanding and test efficacy will vary across locations and patient populations. Yet, standardizing minimal measurement criteria and reporting of results is needed including documentation of test-retest variability so that useful comparisons can be made across trials. It is also clear that protocols must be theoretically sound based on known patterns of damage, generate valid results in most individuals tested, be accurate, repeatable, and involve minimal time. Based on the potential value added, OAEs should be included in clinical trials when measurement conditions and time permit.

d-Methionine reduces tobramycin-induced ototoxicity without antimicrobial interference in animal models.

Fox DJ, Cooper MD, Speil CA, Roberts MH, Yanik SC, Meech RP, Hargrove TL, Verhulst SJ, Rybak LP, Campbell KC.

J Cyst Fibros. 2016 Jul;15(4):518-30.
doi: 10.1016/j.jcf.2015.06.005. Epub 2015 Jul 10.

BACKGROUND: Tobramycin is a critical cystic fibrosis treatment however it causes ototoxicity. This study tested d-methionine protection from tobramycin-induced ototoxicity and potential antimicrobial interference.
METHODS: Auditory brainstem responses (ABRs) and outer hair cell (OHC) quantifications measured protection in guinea pigs treated with tobramycin and a range of d-methionine doses. In vitro antimicrobial interference studies tested inhibition and post antibiotic effect assays. In vivo antimicrobial interference studies tested normal and neutropenic Escherichia coli murine survival and intraperitoneal lavage bacterial counts.
RESULTS: d-Methionine conferred significant ABR threshold shift reductions. OHC protection was less robust but significant at 20kHz in the 420mg/kg/day group. In vitro studies did not detect d-methionine-induced antimicrobial interference. In vivo studies did not detect d-methionine-induced interference in normal or neutropenic mice.
CONCLUSIONS: d-Methionine protects from tobramycin-induced ototoxicity without antimicrobial interference. The study results suggest d-met as a potential otoprotectant from clinical tobramycin use in cystic fibrosis patients.

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CLINICAL TRIALS

ClinicalTrials.gov was searched using the following search terms: "ototoxicity", "noise induced hearing loss," "hearing loss" AND "pharmaceutical", and "tinnitus" AND "pharmaceutical." "Include only open studies" was selected and the search results, retrieved September 2016, derived 9, 27, 12 and 5 results, respectively, for a total of 53 results. 3 duplicates were removed and 10 studies were further eliminated from inclusion based on subjective determination of relevance by the editors for a total of 40 studies included below. It should be noted that relevance was considered broadly as any studies of potential interest, including in secondary outcomes listed, to any one of the PIHL committee focus areas (see editor's introduction for the general listing of these). An exception to the PIHL focus areas used was the category of noise exposure, to include both measurement and preventative assessments, as this opens such a large category of studies, not all of which would necessarily categorize as a clinical trial nor be required to register in clinicaltrials.gov, and thus inclusion herein would produce an indeterminately incomplete set. In previous PIHL Newsletters, studies where primary or secondary outcomes assessed an intervention for hearing or tinnitus outcomes the studies were included, whereas studies which only captured hearing or tinnitus outcomes as adverse events were excluded, most predominantly occurring in ototoxicity studies. However, for this Ototoxicity-focused issue, we've included these trials below.

Title: Phase 3 Clinical Trial: D-methionine to Reduce Noise-Induced Hearing Loss (NIHL)
Conditions: Noise-Induced Hearing Loss
Interventions: Drug: D-methionine, oral liquid suspension | Other: Placebo Comparator
Sponsor/Collaborators: MetArmor | United States Department of Defense
Phases: Phase 3
Start Date: September 2013
Outcome Measures: Pure tone air conduction threshold | Tinnitus scales
URL: https://ClinicalTrials.gov/show/NCT01345474

Title: A Phase 2b Study of SPI-1005 to Reduce the Incidence, Severity, and Duration of Acute Noise Induced Hearing Loss
Conditions: Noise Induced Hearing Loss
Interventions: Drug: SPI-1005 200mg | Drug: SPI-1005 400mg | Drug: Placebo
Sponsor/Collaborators: Sound Pharmaceuticals, Incorporated
Phases: Phase 2
Start Date: September 2016
Outcome Measures: Reduction in the Incidence of a Significant Threshold Shift | Improvement in word recognition score
URL:https://ClinicalTrials.gov/show/NCT02779192

Title: Prevention of Noise-induced Damage by Use of Antioxidants
Conditions: Noise-induced Tinnitus | Noise-induced Hearing Loss
Interventions: Drug: Antioxidantia
Sponsor/Collaborators: University Hospital, Antwerp
Start Date: November 2012
Outcome Measures: Protection against noise-induced tinnitus due to antioxidants | Change of tinnitus duration
URL: https://ClinicalTrials.gov/show/NCT01727492

Title: Randomized Trial Comparison of Ototoxicity Monitoring Programs
Conditions: Cisplatin Ototoxicity | Hearing Loss
Interventions: Other: COMP-VA | Other: Standard of care | Other: Program evaluation
Sponsor/Collaborators: VA Office of Research and Development
Start Date: April 2015
Outcome Measures: Audiology Clinic use | Counseling tools | Hearing test and quality of life measure.
URL: https://ClinicalTrials.gov/show/NCT02099786

Title: Does Aspirin Have a Protective Role Against Chemotherapeutically Induced Ototoxicity?
Conditions: Hearing Loss | Ototoxicity
Interventions: Drug: aspirin | Drug: placebo
ponsor/Collaborators: University Health Network, Toronto
Start Date: February 2008
Outcome Measures: hearing loss | hearing loss and tinnitus questionnaires
URL: https://ClinicalTrials.gov/show/NCT00578760

Title: Preventing Nephrotoxicity and Ototoxicity From Osteosarcoma Therapy
Conditions: Osteosarcoma | Nephrotoxicity | Ototoxicity
Interventions: Drug: Pantoprazole | Drug: High-dose methotrexate infusion duration
Sponsor/Collaborators: Children's Hospital of Philadelphia | Gateway for Cancer Research
Phases: Phase 2
Start Date: April 2013
Outcome Measures: Change of urinary biomarker concentration from pre treatment and 24 hours after cisplatin or High-dose Methotrexate | Change of urinary biomarker concentration from pre treatment and 7 days after cisplatin or High-dose Methotrexate | Toxicity | Response to neoadjuvant therapy | Validating urinary biomarkers | Tissue microarray | Bone specific alkaline phosphatase (BSAP) | Nutritional status | Patient reported measure of symptoms | Ototoxicity
URL: https://ClinicalTrials.gov/show/NCT01848457

Title: Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, Stage II, or Stage III Childhood Liver Cancer
Conditions: Liver Cancer | Ototoxicity
Interventions: Drug: cisplatin | Drug: sodium thiosulfate | Genetic: gene rearrangement analysis | Genetic: microarray analysis | Genetic: proteomic profiling | Other: immunohistochemistry staining method | Other: laboratory biomarker analysis | Procedure: adjuvant therapy | Procedure: neoadjuvant therapy | Procedure: therapeutic conventional surgery
Sponsor/Collaborators: Children's Cancer and Leukaemia Group | National Cancer Institute (NCI)
Phases: Phase 3
Start Date: December 2007
Outcome Measures: Rate of Brock grade ≥ 1 hearing loss determined after end of trial treatment or at an age of at least 3.5 years | Response to preoperative chemotherapy | Complete resection | Complete remission | Event-free survival (EFS) | Overall survival (OS) | Toxicity as graded by CTCAE v 3.0 | Long-term renal clearance | Feasibility of central audiology review
URL: https://ClinicalTrials.gov/show/NCT00652132

Title: Efficacy of Trans-tympanic Injections of a Sodium Thiosulfate Gel to Prevent Cisplatin-induced Ototoxicity
Conditions: DDP | Head and Neck Cancer | Adverse Effect
Interventions: Drug: Trans-tympanic injection of a sodium thiosulfate gel
Sponsor/Collaborators: Centre Hospitalier Universitaire de Québec, CHU de Québec
Phases: Phase 2
Start Date: January 2015
Outcome Measures: Hearing loss at high frequencies | Cochlear damage | Hearing loss at lower frequencies | Adverse effects of trans-tympanic injections
URL: https://ClinicalTrials.gov/show/NCT02281006

Title: Transtympanic Ringer's Lactate for the Prevention of Cisplatin Ototoxicity
Conditions: Hearing Loss
Interventions: Drug: Ringer's Lactate (0.03% Ciprofloxacin)
Sponsor/Collaborators: McGill University Health Center
Phases: Phase 1 | Phase 2
Start Date: April 2008
Outcome Measures: Audiogram | Otoacoustic Emissions
URL: https://ClinicalTrials.gov/show/NCT01108601

Title: Intratympanic Steroid Treatment For The Prevention Of Inner Ear Toxicity Associated With Systemic Treatment With Cisplatin.
Conditions: Cisplatin | Ototoxicity | Intratympanic Steroids
Interventions: Drug: Intra-tympanic Cisplatinum

Sponsor/Collaborators: Ziv Hospital
Start Date: January 2011
Outcome Measures: Post-Treatment change in hearing | Tinnitus
URL: https://ClinicalTrials.gov/show/NCT01285674

Title: Multichannel Vestibular Implant Early Feasibility Study
Conditions: Other Disorders of Vestibular Function, Bilateral | Bilateral Vestibular Deficiency (BVD) | Gentamicin Ototoxicity | Labyrinth Diseases | Vestibular Diseases | Sensation Disorders
Interventions: Device: Labyrinth Devices MVI™ Multichannel Vestibular Implant
Sponsor/Collaborators: Johns Hopkins University | National Institute on Deafness and Other Communication Disorders (NIDCD) | Labyrinth Devices, LLC
Start Date: April 2016
Outcome Measures: Identified adverse events to assess the safety of the Labyrinth Devices Multichannel Vestibular Implant (MVI). | Change in 0.5/1/2/4 kilohertz (kHz) pure tone threshold average to assess the effects of MVI on cochlear function | Change in three-dimensional (3D) angular vestibulo-ocular reflex (VOR) gain [dimensionless] during ~150 deg/sec passive head impulse with modulated prosthetic input to assess the preliminary efficacy of the MVI | Consonant-vowel nucleus-consonant (CNC) speech recognition scores to assess the effects of MVI™ implantation and use on cochlear function | Arizona Biomedical (AzBio) speech recognition scores to assess the effects of MVI™ implantation and use on cochlear function | Vestibulo-ocular reflex (VOR) three-dimensional (3D) alignment to assess the preliminary efficacy of the MVI | Ocular Vestibular Evoked Myogenic Potentials (oVEMP) to assess the effects of MVI™ implantation and use on utricular function | Cervical Vestibular Evoked Myogenic Potentials (cVEMP) to assess the effects of MVI implantation and use on saccular function | Changes in scores on 36-Item Short Form Health Survey (SF-36) to assess the effects of MVI implantation and use on activities of daily living and quality of life. | Changes in scores on Tinnitus Reaction Questionnaire (TRQ) to assess the effects of MVI implantation and use on activities of daily living and quality of life. | Changes in scores on Dizziness Handicap Inventory (DHI) to assess the effects of MVI implantation and use on activities of daily living and quality of life. | Changes in scores on the Health Utilities Index 3 (HUI3) to assess the effects of MVI implantation and use on activities of daily living and quality of life. | Changes in scores on the Vestibular Activities of Daily Living (VADL) to assess the effects of MVI implantation and use on activities of daily living and quality of life. | Changes in scores on the bilateral vestibular deficiency BVD-case definition subset of questions to assess the effects of MVI implantation and use on activities of daily living and quality of life. | Head thrust dynamic visual acuity (htDVA) to assess the feasibility and preliminary efficacy of the MVI™ | Bruininks-Oseretsky test of motor proficiency- balance subtest 2 (BOT2) to assess the feasibility and preliminary efficacy of the MVI™ | Dynamic Gait Index (DGI) to assess the feasibility and preliminary efficacy of the MVI™ | Gait speed to assess the feasibility and preliminary efficacy of the MVI™

URL: https://ClinicalTrials.gov/show/NCT02725463

Title: Aminoglycoside Plasma Level Measurement in Neonates With Infection
Conditions: Nephrotoxicity | Ototoxicity
Sponsor/Collaborators: Indonesia University
Study Types: Observational
Start Date: November 2010
URL: https://ClinicalTrials.gov/show/NCT01624324

Title: Intensity-Modulated Radiation Therapy or 3-Dimensional Conformal Radiation Therapy in Decreasing Hearing Loss in Patients Who Have Undergone Surgery for Parotid Tumors
Conditions: Head and Neck Cancer | Ototoxicity | Radiation Toxicity
Interventions: Procedure: adjuvant therapy | Procedure: assessment of therapy complications | Procedure: quality-of-life assessment | Radiation: 3-dimensional conformal radiation therapy | Radiation: intensity-modulated radiation therapy
Sponsor/Collaborators: Institute of Cancer Research, United Kingdom | National Cancer Institute (NCI)
Phases: Phase 3
Start Date: August 2008
Outcome Measures: Proportion of patients developing sensory-neural hearing loss of at least 10 dB at bone conduction as assessed by audiograms at 4000 Hz one year after treatment | Auditory assessment at 6 and 12 months following radiotherapy (RT) and then annually thereafter for up to 5 years | Vestibular assessment at baseline, at 6 and 12 months following RT, and then annually thereafter for up to 5 years | Quality of life at 6 and 12 months following RT and then annually thereafter for 5 years | Local and regional tumor control | Time to tumor progression | Overall survival | Acute and late side effects of RT as assessed by NCI CTCAE v 3.0 and the LENT SOMA and late RT scoring systems
URL: https://ClinicalTrials.gov/show/NCT01216800

Title: Proton Beam Radiotherapy for Medulloblastoma and Pineoblastoma
Conditions: Brain Tumor | Medulloblastoma | Pineoblastoma
Interventions: Radiation: proton beam radiation
Sponsor/Collaborators: Massachusetts General Hospital | M.D. Anderson Cancer Center | National Cancer Institute (NCI)
Phases: Phase 2
Start Date: April 2010
Outcome Measures: Ototoxicity | Endocrine dysfunction | Neurocognitive Effects | Progression Free Survival | Treatment efficiency | Acute toxicity
URL: https://ClinicalTrials.gov/show/NCT01063114

Title: Melphalan, Carboplatin, Mannitol, and Sodium Thiosulfate in Treating Patients With Recurrent or Progressive CNS Embryonal or Germ Cell Tumors
Conditions: Adult Central Nervous System Germ Cell Tumor | Adult Ependymoblastoma | Adult Medulloblastoma | Adult Pineoblastoma | Adult Supratentorial Primitive Neuroectodermal Tumor | Childhood Atypical Teratoid/Rhabdoid Tumor | Childhood Central Nervous System Germ Cell Tumor | Childhood Ependymoblastoma | Medulloepithelioma | Ototoxicity | Recurrent Adult Brain Neoplasm | Recurrent Childhood Central Nervous System Embryonal Neoplasm | Recurrent Childhood Malignant Germ Cell Tumor | Recurrent Childhood Medulloblastoma | Recurrent Childhood Pineoblastoma | Recurrent Childhood Supratentorial Primitive Neuroectodermal Tumor
Interventions: Drug: Carboplatin | Drug: Mannitol | Drug: Melphalan | Other: Quality-of-Life Assessment | Other: Questionnaire Administration | Drug: Sodium Thiosulfate
Sponsor/Collaborators: OHSU Knight Cancer Institute | National Cancer Institute (NCI) | National Institute of Neurological Disorders and Stroke (NINDS)
Phases: Phase 1 | Phase 2
Start Date: September 2009
Outcome Measures: MTD based on the incidence of dose-limiting toxicity (DLT), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Phase I) | Response rate (Phase II) | Change in neurocognitive assessment scores (Phase II) | OS rate (Phase II) | Progression free survival (PFS) rate (Phase II) | Proportion of patients with ototoxicity, graded according to the NCI CTCAE v4.0 (Phase II)
URL: https://ClinicalTrials.gov/show/NCT00983398

Title: The Platinum Study Comparison Group
Conditions: Testicular Neoplasms
Interventions: Behavioral: Questionnaire
Sponsor/Collaborators: Lawrence Einhorn | Indiana University
Start Date: May 2015
Outcome Measures: Proportion of patients with ototoxicity | Proportion of patients with neurotoxicity | Proportion of patients with obesity | Proportion of patients with hypertension | Proportion of patients who use antidepressants/anxiolytics
URL: https://ClinicalTrials.gov/show/NCT02890030

Title: Proton Radiotherapy for Pediatric Brain Tumors Requiring Partial Brain Irradiation
Conditions: Brain Tumor | Low Grade Glioma | Astrocytoma | Ependymoma | Ganglioglioma
Interventions: Radiation: Proton radiotherapy
Sponsor/Collaborators: Massachusetts General Hospital | Dana-Farber Cancer Institute | National Cancer Institute (NCI)
Phases: Phase 2
Start Date: January 2011

Outcome Measures: Endocrine dysfunction | Neurocognitive sequelae | Disease control | Acute effects | Auditory function
URL: https://ClinicalTrials.gov/show/NCT01288235

Title: Safety and Effectiveness of Artemisinin-based Combination Therapies (ACTs) With Repeated Treatments for Uncomplicated Falciparum Malaria Over a Three-year Period
Conditions: Malaria
Interventions: Drug: Artemether-lumefantrine combination
Sponsor/Collaborators: Liverpool School of Tropical Medicine | Malawi-Liverpool-Wellcome Trust Clinical Research Programme | National Malaria Control Programme, Malawi | Research for Equity and Community Health Trust
Phases: Phase 4
Start Date: October 2010
Outcome Measures: Prevalence of ototoxicity at 18 months and 36 months of enrolment. | Incidence of clinical malaria during 18 months and 36 months of follow-up
URL: https://ClinicalTrials.gov/show/NCT01038063

Title: Treatment Outcome and Quality of Life in Patients With Pediatric Extra-Cranial Germ Cell Tumors Previously Treated on Clinical Trial CCLG-GC-1979-01 or CCLG-GC-1989-01
Conditions: Childhood Germ Cell Tumor | Extragonadal Germ Cell Tumor | Gastrointestinal Complications | Infertility | Long-term Effects Secondary to Cancer Therapy in Children | Neurotoxicity | Ovarian Cancer | Pulmonary Complications | Sexual Dysfunction | Urinary Complications
Interventions: Procedure: assessment of therapy complications | Procedure: quality-of-life assessment
Sponsor/Collaborators: Children's Cancer and Leukaemia Group | National Cancer Institute (NCI)
Start Date: June 2006
Outcome Measures: Ototoxicity as measured by audiogram and Health Utilities Index in patients previously treated with cisplatin or carboplatin | Nephrotoxicity as measured by serum magnesium, calcium, and creatinine and glomerular filtration rate in patients previously treated with cisplatin or carboplatin | Myelodysplasia and second malignancies in patients previously treated with etoposide | Pulmonary toxicity as measured by lung function test and respiratory symptom questionnaire in patients previously treated with bleomycin | Bladder and bowel dysfunction, sexual function, and fertility as measured by patient-completed questionnaires and lower limb and neurological dysfunction as measured by clinician-completed questionnaires in patients with pelvic or sacrococcygeal tumors | Quality of life (QOL) as measured by pediatric cancer quality-of-life inventory or Short Form 36 questionnaires
URL: https://ClinicalTrials.gov/show/NCT00436774

Title: Evaluation of the High Frequency Digit Triplet Test in Cystic Fibrosis

Conditions: Cystic Fibrosis | Sensorineural Hearing Loss
Interventions: Other: HFDT test | Other: Pure tone Audiogram
Sponsor/Collaborators: University of Nottingham | Nottingham University Hospitals NHS Trust | Heart of England NHS Trust | Birmingham Children's Hospital NHS Foundation Trust
Start Date: January 2015
Outcome Measures: Proportion of patients in whom the HFDT test accurately predicts the presence of absence of hearing loss. | The youngest age at which 80% of children are able to perform the HFDT test. | The prevalence of hearing loss in a CF population. | The prevalence of genetic mutations that are associated with hearing loss in a CF population.
URL: https://ClinicalTrials.gov/show/NCT02252601

Title: A Study to Evaluate the Efficacy and Safety of Trastuzumab in Combination With Capecitabine and Oxaliplatin as First-line Chemotherapy for Inoperable, Locally Advanced or Recurrent and/or Metastatic Gastric Cancer
Conditions: Gastric Cancer
Interventions: Drug: Trastuzumab+Capecitabine+Oxaliplatin
Sponsor/Collaborators: Peking University
Phases: Phase 2
Start Date: May 2011
Outcome Measures: Objective response rate | progression free survival | overall survival of participants | adverse events
URL: https://ClinicalTrials.gov/show/NCT01364493

Title: THE USE OF N-ACETYLCYSTEINE ATTENUATING CISPLATIN-INDUCED TOXICITIES BY OXIDATIVE STRESS
Conditions: Head and Neck Neoplasms
Interventions: Drug: N-acetylcysteine
Sponsor/Collaborators: University of Campinas, Brazil
Phases: Phase 4
Start Date: October 2014
Outcome Measures: Hematologic, Nephro, and Hepato Toxicity - Degree of toxicity by Common Toxicity Criteria for Adverse Effects (CTCAE - version 4.0) | Gastrointestinal Toxicity - Degree of toxicity by CTCAE (version 4.0) | audiometric testing | Nephrotoxicity | Quality of Life | Cellular and plasma oxidative stress biomarkers | Effectiveness of anticancer therapy
URL: https://ClinicalTrials.gov/show/NCT02241876

Title: IV Colistin for Pulmonary Exacerbations: Improving Safety and Efficacy
Conditions: Cystic Fibrosis
Interventions: Drug: Colistin | Drug: Tobramycin
Phases: Phase 4
Start Date: August 2016

Outcome Measures: absolute change in forced expiratory volume at one second (FEV1) % predicted between study arms with acute pulmonary exacerbation (APE) treatment | rate of occurrence of the development of acute kidney injury (AKI) during APE treatment | time to achievement of steady state with pharmacokinetic (PK)-adjusted colistin therapy | longitudinal differences in exacerbation rates and antimicrobial resistance between tobramycin and colistin use as seen in readmission rate and sputum culture results | differences in occurrences of neurotoxicity and ototoxicity related side effects between study arms as reported by treating physician(s) | measurement of pharmacokinetics of colistin's active metabolites in a broad CF population through peak, trough, and midpoint blood draws | comparison of plasma pharmacokinetics of colistin's active metabolites with levels achieved in the sputum, in order to calculate epithelial lining fluid concentrations, through mass spectrometry | novel biomarkers of nephrotoxic AKI, prior to serum creatinine increases, based on urine protein:creatinine ratios | novel biomarkers of nephrotoxic AKI, prior to serum creatinine increases, based on the urine biomarker Nephrocheck® point-of-care assay
URL: https://ClinicalTrials.gov/show/NCT02918409

Title: Phase 2 Study of Alisertib Therapy for Rhabdoid Tumors
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Malignant Rhabdoid Tumor | Atypical Teratoid Rhabdoid Tumor
Interventions: Drug: alisertib | Drug: methotrexate | Drug: cisplatin | Drug: carboplatin | Drug: cyclophosphamide | Drug: etoposide | Drug: topotecan | Drug: vincristine | Procedure: Surgical resection | Radiation: Radiation therapy
Sponsor/Collaborators: St. Jude Children's Research Hospital | Millennium Pharmaceuticals, Inc.
Phases: Phase 2
Start Date: May 2014
Outcome Measures: Sustained response rate of pediatric participants with recurrent or refractory AT/RT treated with alisertib (stratum A1) | Sustained response rate of pediatric participants with recurrent or refractory MRT treated with alisertib (stratum A2) | 3-year progression free survival rate (stratum B1) | 1-year progression free survival rate (stratum B2) | 3-year progression free survival rate (stratum C1) | 1-year progression free survival rate (stratum C2) | Single dose and steady state pharmacokinetics and pharmacodynamics of alisertib | Duration of objective response by stratum A1 and A2 | 1-year progression-free survival (PFS) by stratum A1 and A2 | 5-year Progression-free survival (PFS) rate in patients with newly diagnosed AT/RT (strata B1, B2, B3, C1, C2) | 5-year Overall survival (OS) rate in patients with newly diagnosed AT/RT (strata B1, B2, B3, C1, C2) | Proportion of local and distant failure in strata B1, B2, B3, C1 and C2
URL: https://ClinicalTrials.gov/show/NCT02114229

Title: Sulodexide Efficacy in Chronic Idiopathic Subjective Tinnitus (SECIST)

Responsible Party: Dr. Joseph Maarrawi, St Joseph University, Beirut, Lebanon
Conditions: Tinnitus, Subjective
Interventions: Drug: Sulodexide; Drug: Placebo
Phases: 2
Start Date: August 2015
Description Provided: Patients with chronic idiopathic subjective tinnitus, since at least 1 year, re recruited from our Ear, Nose and Throat (ENT) clinic. After verification of inclusion and exclusion criteria, patients consenting to enter the study are assigned randomly to one of the following groups: 1- Sulodexide 25 mg for 40 days 2- Placebo for 40 days. Clinical evaluation of the patient is performed; tinnitus is assessed according to Tinnitus Handicap Inventory score, Mini Tinnitus Questionnaire score, and their combination score. Adverse effects are also noted. Patients are followed at 40 days post-treatment and outcome measures are assessed.
URL: https://ClinicalTrials.gov/show/NCT02737670

Title: HeadStart4: Newly Diagnosed Children (<10 y/o) With Medulloblastoma and Other CNS Embryonal Tumors
Responsible Party: Jonathan Finlay, Nationwide Children's Hospital
Conditions: Medulloblastoma; Central Nervous System Embryonal Tumors
Interventions: Drug: Induction; Drug: Single Cycle Intensive Chemotherapy; Drug: Tandem 3 Cycle Intensive Chemotherapy
Phases: 4
Start Date: September 2015
Description Provided: Due to the inferior response and event-free survival data of Regimens D and D2 on "Head Start III" for all children with supratentorial embryonal tumors, in comparison with the published data from "Head Start II" with Regimen A2 for metastatic patients, all such patients will receive the "Head Start II" Induction Regimen A2, on "Head Start 4", for either three or five cycles, depending upon whether or not they achieve complete remission by the end of Induction cycle #3. They will then undergo randomization to either single cycle or three tandem cycles of Consolidation marrow-ablative chemotherapy with AuHPCR.
Because of the unsatisfactory event-free survival for young children with non-desmoplastic/extensive nodular medulloblastoma (predominantly non-Shh and non-Wnt medulloblastoma subgroups) on Regimens D and D2 of "Head Start III", all these patients will receive the "Head Start II" Induction Regimen A2 on ""Head Start 4"", for either three or five cycles, depending upon whether or not they achieve complete remission by the end of Induction cycle #3. They will then undergo randomization to either single cycle or three tandem cycles of Consolidation marrow-ablative chemotherapy with AuHPCR.
Because of the excellent event-free and overall survival for young children with good risk medullo-blastoma (Shh or Wnt subgroups) treated with up-front "Head Start" chemotherapy strategies, such patients will undergo risk-tailored reduction of duration of Induction therapy from five cycles to three cycles of the "Head Start II" Induction

Regimen A2 on "Head Start 4" for patients achieving a complete response to 3 cycles, followed, provided they are also without evidence of residual tumor following recovery from Induction cycle #3. They will NOT then undergo randomization, but will follow with a single cycle of Consolidation marrow-ablative chemotherapy as in "Head Start" studies.
URL: https://ClinicalTrials.gov/show/NCT02875314

Title: NAC to Prevent Cisplatin-induced Hearing Loss
Responsible Party: Etan Orgel, Children's Hospital Los Angeles
Conditions: Neuroectodermal Tumors, Primitive; Liver Neoplasms; Neoplasms, Germ Cell and Embryonal; Osteosarcoma; Other Childhood Cancers Using Cisplatin-based Regimens
Interventions: Drug: N-Acetylcysteine
Phases: 1
Start Date: March 2016
Description Provided: The study is a dose-finding study of N-acetylcysteine (NAC) to protect hearing in children receiving cisplatin for the treatment of their cancer. NAC also has potential to protect the kidneys from cisplatin toxicity.
The study uses a 3+3 dose-escalation scheme to determine the dose of NAC necessary to achieve serum levels consistent with hearing protection in pre-clinical animal models. Three dose levels are predefined. Once the maximum tolerated dose is determined, an expansion cohort will then be enrolled to further evaluate tolerability as well as intra-patient and inter-patient variability in achieved serum levels. An option to enroll in a separate arm for study assessments only is available for those who do not wish to receive NAC. Hearing loss in the cohort will be assessed in the entire cohort in comparison to historical and non-treated children to evaluate for trends toward efficacy.
URL: https://ClinicalTrials.gov/show/NCT02094625

Title: Lidoderm Patch (Lidocaine 5%) for Tinnitus Treatment
Responsible Party: HaEmek Medical Center, Israel
Conditions: Tinnitus
Interventions: Device: Lidoderm patch (Lidocaine 5% patch); Other: Tegaderm patch. (neutral patch, containing no drug): Procedure: blood test- serum lidocain levels; Other: Hearing tests
Phases: 4
Start Date: April 2016
Description Provided: The purpose of the study is to investigate whether lidoderm patch (lidocain 5% patch) cream decreases tinnitus by comparing pretrial questionnaires to post trial questionnaires. First the investigators are going to invite tinnitus patients for the first visit. The participants will get full explanation about the trial.
URL: https://ClinicalTrials.gov/show/NCT02750969

Title: Treating Tinnitus Using the Neuromonics Tinnitus Treatment Program: A Randomized, Double-blind Study
Responsible Party: William A. Ahroon, Ph.D., United States Army Aeromedical Research Laboratory
Conditions: Tinnitus
Interventions: Device: Neuromonics Tinnitus Treatment Program; Device: Placebo Device
Phases: 0
Start Date: April 2016
Description Provided: The objective of the study is to determine the effectiveness of individualized sound stimuli used in a FDA classified tinnitus masker device, the Neuromonics, Inc. Oasis™. Research Question: Is there a difference in clinical outcomes for tinnitus patients treated with the NTTP compared with the same treatment using a placebo-control device? The placebo-control device is otherwise identical to the NTTP device except that the sound stimuli are not matched to the patients' audiograms and tinnitus profile and are not specifically designed to promote relaxation. Assignment of tinnitus patients to the treatment and placebo groups is performed off site and the experimenters have no information on group assignment.
Hypothesis: In the Active Duty, Reserve, and National Guard military and recently separated veteran populations with complaints of tinnitus, the NTTP group will have significantly improved tinnitus clinical outcomes in comparison to placebo-control group at 6 months. Clinical outcomes are described in Section B5.4 and Table 1 below.
Null Hypothesis: In the Active Duty, Reserve, and National Guard military and recently separated veteran populations with complaints of tinnitus, the NTTP group will have tinnitus clinical outcomes statistically indistinguishable from the placebo-control group at 6 months.
URL: https://ClinicalTrials.gov/show/NCT02829073

Title: Evaluating Possible Improvement in Speech and Hearing Tests After 28 Days of Dosing of the Study Drug AUT00063 Compared to Placebo (QuicKfire)
Responsible Party: Autifony Therapeutics Limited
Conditions: Hearing Loss; Hearing Impairment
Interventions: Drug: AUT00063; Drug: Placebo
Phases: 2 and 3
Start Date: May 2016
Description Provided: Reduced activity at certain sites in the brain called "voltage-gated potassium channels", has been linked to hearing problems. The study drug, AUT00063, has been developed to help improve the recognition of speech by aiming to improve the action of the voltage-gated potassium channels in the hearing pathways in the brain and so help to treat the hearing problem.
The main purpose of this study is to find out whether AUT00063 can improve the understanding of speech after 28 days of treatment compared with a placebo

(dummy drug which does not contain the study drug) in patients who have received a cochlear implant (CI) for post-lingual deafness.
Efficacy will be investigated through a number of assessments including speech recognition testing, parameters of central auditory processing measured using tests that involve direct stimulation via the CI, and questionnaires.
Safety assessments will also be conducted throughout the study including physical examinations, ECGs and blood sampling.
It is planned that up to 20 people who have received a cochlear implant within the last 9 to 36 months will take part in the study. The people will be recruited from around 4 hospital sites in the UK.
URL: https://ClinicalTrials.gov/show/NCT02832128

Title: Efficacy and Safety of AM-111 as Acute Sudden Sensorineural Hearing Loss Treatment (ASSENT)
Responsible Party: Auris Medical, Inc.
Conditions: Hearing Loss, Idiopathic Sudden Sensorineural
Interventions: Drug: AM-111 0.4 mg/ml; Drug: AM-111 0.8 mg/ml; Other: Placebo
Phases: 3
Start Date: June 2016
Description Provided: This is a Phase III, randomized, double-blind, placebo-controlled, parallel group, multi-center, efficacy and safety trial of AM-111 in the treatment of subjects suffering from severe to profound idiopathic sudden sensorineural hearing loss. The active pharmaceutical ingredient of AM-111 is a JNK inhibitor (D-JNKI-1), a synthetic peptide consisting of 31 D-amino acids, which acts as a c-Jun N-terminal kinase (JNK) ligand. The study consists of one treatment visit and a follow-up period until day 91. Study participants will receive, after topical anesthesia of the tympanic membrane, AM-111 0.4 mg/mL or 0.8 mg/mL or placebo, administered into the affected ear. Following the administration, subjects will rest in a supine or reclined position for 30 minutes. Study participants will have the option for a course of oral corticosteroids.
URL: https://ClinicalTrials.gov/show/NCT02809118

Title: Benefits of the HiResolution Bionic Ear System in Adults With Asymmetric Hearing Loss
Responsible Party: Advanced Bionics
Conditions: Hearing Loss; Ear Diseases; Hearing Disorders; Otorhinolaryngologic Diseases; Asymmetrical Hearing Loss; Single-Sided Deafness
Interventions: Device: HiResolution Bionic Cochlear Implant
Phases: 0
Start Date: July 2016
Description Provided: Primary Outcome Measures: Change in Speech Perception (Implanted Ear only) [Time Frame: Baseline and Twelve months]
[Designated as safety issue: Yes]; CNC word scores compared to preimplant word scores - Change in Unaided Hearing Thresholds (Contralateral, Non-Implanted Ear, only)

[Time Frame: Baseline and Twelve months] [Designated as safety issue: Yes]; Unaided audiometric thresholds compared to preimplant; Change in Speech Perception (Bilateral Listening Condition) [Time Frame: Baseline and Twelve months] [Designated as safety issue: Yes]; AzBio sentence scores in noise twelve months post implantation compared to preimplant bilateral sentence scores; Change in Lateralization Ability Testing (Bilateral Listening Condition) [Time Frame: Baseline and Twelve months] [Designated as safety issue: Yes]; Lateralization ability compared to preimplantation.
URL: https://ClinicalTrials.gov/show/NCT02811549

Title: Rilonacept for Treatment of Autoimmune Neurosensory Hearing Loss
Responsible Party: Stanley Cohen, Metroplex Clinical Research
Conditions: Autoimmune Neurosensory Hearing Loss (ANSHL)
Interventions: Drug: Rilonacept
Phases: 0
Start Date: July 2016
Description Provided: Ten (10) patients in total will be enrolled in this study at Metroplex Clinical Research Center in Dallas, TX. Patients may be identified and referred by local area audiologist. The ANSHL study population will be defined by inclusion and exclusion criteria designed to limit enrollment to individuals with idiopathic, progressive, bilateral sensorineural hearing loss, to ensure appropriate candidates for treatment with study medications, and to identify those with a high likelihood of complying with the study protocol.
URL: https://ClinicalTrials.gov/show/NCT02828033

Title: SPI-1005 for Prevention and Treatment of Aminoglycoside Induced Ototoxicity
Responsible Party: Sound Pharmaceuticals, Incorporated
Conditions: Ototoxicity
Interventions: Drug: Placebo; Drug: SPI-1005 Ebselen 200mg Capsule x1; Drug: SPI-1005 Ebselen 200mg Capsule x2; Drug: SPI-1005 Ebselen 200mg Capsule x3
Phases: 1 and 2
Start Date: August 2016
Description Provided: Randomized, double-blind, placebo-controlled, dose-escalating, safety, PK, and PD study of oral SPI-1005 in CF patients with active pulmonary exacerbation about to receive a 14-day course of IV tobramycin (10 mg/kg/d). All patients will undergo baseline testing and have their severity of lung function, sensorineural hearing loss, tinnitus and vertigo determined before the start of SPI-1005 treatment. SPI-1005 treatment will start within first two days of IV tobramycin treatment and be administered concomitantly. At the end of the 14-day course of SPI-1005 and 28 days following the cessation of SPI-1005, patients will have their hearing loss, tinnitus and vertigo reassessed. Assessments may also include additional audiometric and pulmonary testing, and additional follow-up testing.
URL: https://ClinicalTrials.gov/show/NCT02819856

Title: SPI-1005 for Prevention and Treatment of Chemotherapy Induced Hearing Loss
Responsible Party: Sound Pharmaceuticals, Incorporated
Conditions: Lung Cancer; Head and Neck Cancer; Hearing Loss; Ototoxicity; Tinnitus; Neuropathy
Interventions: Drug: SPI-1005 Low Dose; Drug: SPI-1005 Middle Dose; Drug: SPI-1005 High Dose; Drug: Placebo
Phases: 2
Start Date: August 2016
Description Provided: Chemotherapy treatment with the platinum containing chemotherapies (e.g. cisplatin, carboplatin) are well noted and studied for their ability to cause ototoxicity which includes hearing loss, tinnitus, vertigo, or dizziness. It is the objective of this study to determine the safety and efficacy of SPI-1005 at three dose levels when delivered orally twice daily for 3 days, surrounding each cycle of platinum chemotherapy for head and neck or non-small cell lung cancer patients to prevent and treat chemotherapy induced hearing loss and tinnitus.
SPI-1005, a proprietary oral formulation of ebselen is a small molecule mimic and inducer of the enzyme Glutathione Peroxidase. GPx reduces reactive oxygen species (ROS) by reacting with glutathione. SPI-1005 has been shown to reduce cisplatin induced hearing threshold shift in animal studies.
URL: https://ClinicalTrials.gov/show/NCT01451853

Title: A Phase 2b Study of SPI-1005 to Reduce the Incidence, Severity, and Duration of Acute Noise Induced Hearing Loss (NIHL)
Responsible Party: Sound Pharmaceuticals, Incorporated
Conditions: Noise Induced Hearing Loss
Interventions: Drug: SPI-1005 200mg; Drug: SPI-1005 400mg; Drug: Placebo
Phases: 2
Start Date: September 2016
Description Provided: Randomized, double-blind, placebo-controlled, safety and efficacy study of oral SPI-1005 in adults with Noise Induced Hearing Loss (NIHL). All recruited subjects will have their severity of NIHL determined before the start of SPI-1005 treatment using otoscopy, tympanometry and audiometry. Subjects with >15 and </= 40 decibel (dB) NIHL will be enrolled and randomized to either placebo or SPI-1005. Patients will be dosed with either placebo or SPI-1005 for 7 days, beginning 1 day before an acute NIHL. Patients will have audiometry and Words In Noise Testing (WINT) before and immediately after a calibrated sound challenge (CSC). The CSC involves listening to 4 hours of pre-recorded music (100 dBA SPL) through insert earphones. The CSC induces a slight acute NIHL. Follow-up audiometry and WINT will be performed at 1 and 7 days post-CSC. A total of four clinic visits will be required over 10-14 days.
URL: https://ClinicalTrials.gov/show/NCT02779192

Title: Gas Supply, Demand and Middle Ear Gas Balance: Specific Aim 3

Responsible Party: William J. Doyle, University of Pittsburgh
Conditions: Middle-ear Function
Interventions: Other: varied middle-ear pressure; Drug: varied middle-ear gas composition; Other: varied ear-canal pressure
Phases: 0
Start Date: September 2016
Description Provided: 3 hypothesized stimulus-effector pairings in 10 otherwise healthy adult subjects with no history of significant ME disease and normal audiologic testing. A custom ear plug will be made for use in Visits 3-7. The protocol includes 1 screening visit and 3 experiments requiring 7 experimental sessions of approximately 3-4 hours duration each done at a minimum interval of 3 days. Briefly, in Experiment 1 (Visit 2), ear canal pressure will be varied to change the position of the TM while simultaneously monitoring mTVP tonus by electromyography (EMG). Then, a unilateral ventilation tube (VT) inserted into the TM to allow access to the ME cavity. For Experiment 2, (Visits 3-7), the ME will be washed with physiologic, hypocarbic, hypercarbic, hypooxic and hyperoxic gas compositions (reference ME normal) while monitoring the ET periluminal tissue pressures measured as the ET resistance to gas flow. For Experiment 3 (Visit 8), total ME pressure will be varied while monitoring mTVP tonus by EMG. At the completion of Experiment 3, the VT will be removed and, then, the subjects will be followed weekly (Visits 9+) until documented healing of the TM at which time a standard audiologic assessment will be done. If the hypotheses are supported, selected activation of the feedback mechanisms would improve ET function and could be exploited as one component of a treatment protocol to improve ME pressure-regulation.
URL: https://ClinicalTrials.gov/show/NCT01925495

Title: Evaluation of the Benefit of Antiviral Treatment With Valganciclovir on Congenital CMV Infection-related Deafness on Hearing and Balance (GANCIMVEAR)
Responsible Party: Assistance Publique - Hôpitaux de Paris
Conditions: Congenital Cytomegalovirus (CMV)
Interventions: Drug: Valganciclovir
Phases: 2 and 3
Start Date: October 2016
Description Provided: Congenital cytomegalovirus (CMV) infection is the leading cause of non-genetic neurosensory deafness and affects 0.5 to 1% of births. Twenty to thirty per cent of children will develop deafness, some of whom will progress gradually to profound bilateral deafness. No curative treatment is currently offered for this deterioration in hearing and management involves the use of a hearing aid or cochlear implant. Many studies describe the utility of antiviral treatment on the course of the deafness. These mostly involve neonates with multi-system symptomatic forms of the infection who have been given 6 weeks of ganciclovir possibly switched to valganciclovir, which has shown benefit in stabilizing auditory loss, or even improvement.
URL: https://ClinicalTrials.gov/show/NCT02606266

Title: Treatment of Wolfram Syndrome Type 2 With the Chelator Deferiprone and Incretin Based Therapy

Responsible Party: David Zangen, Hadassah Medical Organization
Conditions: Diabetes Mellitus; Iron Metabolism Disorders; Gastroduodenal Ulcer; Optic Atrophy; Sensorineural Hearing Loss; Platelet Dysfunction
Interventions: Drug: Deferiprone; Drug: Acetylcysteine; Drug: Sitagliptin and Metformin
Phases: 2 and 3
Start Date: December 2016
Description Provided: In WFS2 mutation the protein nutrient-deprivation autophagy factor-1(NAF-1) is affected.
Given the known result of NAF-1 protein dysfunction in animal and cultured cell line models namely a toxic accumulation of iron in the mitochondria,leading to mitochondrial destruction and oxidative stress we aim to obtain fibroblast samples from the patients and (use laboratory fibroblasts from healthy subjects as controls) These cell cultures will initially be studied for intracellular iron accumulation and then re-evaluated following treatment by Deferiprone and/or Glucagon-like peptide 1 (GLP-1) ex-vivo in the laboratory .
If repeated (n>=3) histological evidence confirms the beneficial effect of Deferiprone and/or GLP-1(incertin based therapy) in the patient's cultured fibroblasts by reversing the toxic iron accumulation in the patient's mitochondria to a normal level, he/she will be offered "in vivo" therapy using the oral chelating agent - with or without dipeptidylpeptidase-4 inhibitor (DPP-4) inhibitors or GLP-1 receptor agonists. Adding GLP-1 based therapy will depend on the diabetic status of the patient.
Prior and following 60 and 150 days of Chelator and/or GLP-1 therapy they will go through the following clinical and laboratory evaluations which will establish the baseline and post therapeutic parameters (outcome) to be compared:
detailed medical history and physical examination complete blood count (CBC) and iron levels platelet aggregation studies Fundoscopy and visual evoked potentials (VEP) Hearing evaluation Oral glucose Tolerance Test optional Intra venous glucose tolerance test (IVGTT) /glucagon/arginine test HBA1C Daily profile of blood glucose Optional CGMS (continuous glucose monitoring system) Gastroscopy and gastric biopsy if the patient suffers from abdominal pain, hematemesis, melena or iron deficiency anemia or if peptic ulcer disease is clinically suspected.
Based on the routine use of the iron chelator, FDA approved, Deferiprone for Thalassemia (with detailed official guidelines of the Israel association for Pediatric Hematology) and for a similar subcellular iron accumulating disease - e.g. Friedreich Ataxia, we will initially use a dose of 20 mg per kilogram body weight (BW) daily divided in two equal doses. N-Acetylcystein an over the counter drug which also is an anti-oxidant will be given orally in the dose of 200mg twice daily to have a synergistic effect with Deferiprone.
In addition if they suffer from diabetes they will receive Januet (Sitagliptin/metformin).
URL: https://ClinicalTrials.gov/show/NCT02882477

Title: Prevention of Noise-induced Hearing Loss
Responsible Party: Judith Lieu, Washington University School of Medicine
Conditions: Noise-induced Hearing Loss
Interventions: Drug: Zonisamide; Drug: Methylprednisolone
Phases: 1 and 2
Start Date: June 2017
Description Provided: Specific Aim 1: Examine zonisamide as a possible prophylactic medication to prevent noise-induced hearing loss, using an escalating dose protocol. Healthy volunteers would be given 100 or 200 mg of zonisamide as one-time doses or as a daily medication for two week (to establish a steady-state). They would be exposed to digitally-modified pop or rock music for 4 hours and undergo serial testing of hearing and monitoring for side effects after their sound exposure for 3-4 hours. They would be monitored at one day and one week post-exposure for hearing and other side effects. Hypothesis: Zonisamide is able to protect against noise-induced hearing loss in humans. Specific Aim 2: Examine methylprednisolone as a possible prophylactic medication to prevent noise-induced hearing loss, using an escalating dose protocol. Healthy volunteers would be given 32 or 64 mg of methylprednisolone as one-time doses. They would undergo the same music exposure and post-sound exposure monitoring as described above. Hypothesis: Methylprednisolone is able to protect against noise-induced hearing loss in humans.
URL: https://ClinicalTrials.gov/show/NCT02040207

FUNDING OPPORTUNITIES

Refer to the HCE website (http://hearing.health.mil/Research/FundingInformation.aspx) for up-to-date hearing-related research funding opportunities.

EPILOGUE

Thank you for reading our Newsletter!

Copies of all previous PIHL Newsletters can be found online in the PIHL WG section of the DoD HCE website: http://hearing.health.mil/Research/PIHL-Working-Group.

The DoD HCE PIHL WG Ototoxicity Committee is working toward releasing two special issues in well-respected peer-reviewed journals on ototoxicity. The first special issue will focus on ototoxicity monitoring, as described above in the article by Boudin-George, King and Konrad-Martin. The second special issue will focus on the underlying biomedical (e.g., cellular) mechanisms of ototoxicity. They are expected to be published in 2017. The Ototoxicity Monitoring Program Committee is in the process of creating a clinician's tool-kit, also described in the article by Boudin-George, King and Konrad-Martin, which will include a) a breakdown of existing guidelines, b) modifiable handouts and presentations as well as other resources, and c) a framework for the creation of clinical standard operating procedures.

http://hearing.health.mil/EducationAdvocacy/Newsletters.aspx

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