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Viewpoint

# What's New in Ototoxicity Management?

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ABSTRACT

**Purpose:** Ototoxic medications and chemical agents in the workplace can put individuals' hearing and vestibular health at risk for permanent injury. Proactive ototoxicity management (OtoM) strategies aim to minimize exposure, avoid onset of symptoms, provide ongoing monitoring, and manage auditory and vestibular changes as the clinical needs of the patient evolve. During a 2021 American Speech-Language-Hearing Association Special Interest Groups Open House, members of the International Ototoxicity Management Group discussed how best to integrate OtoM into routine clinical practice, what tools to use, and what special considerations need to be understood to best support patients and their families. Here, we have summarized their viewpoints to encourage widespread adoption of improved OtoM services for at-risk individuals.

**Conclusions:** The field of audiology needs to move to a place where we better understand the full extent of ototoxicity and can agree on expanding minimum guidelines that can be implemented more universally to mitigate, detect, and manage the damage from ototoxic exposures. Only recently has our field seen a therapeutic drug that can protect against ototoxicity; however, the population served is restricted only to children receiving treatment for nonmetastatic carcinoma. This is hopefully just the beginning of future therapeutic interventions to come, but, in the meantime, ototoxicity resulting from other medications in different patient populations and chemical agents persists.

Correspondence to Laura Dreisbach: ldreisba@sdsu.edu. ***Disclosure:*** *Angela Garinis currently consults for Horizon Therapeutics, Dawn Konrad-Martin is the co-inventor on two patents involving an ototoxicity monitoring method and portable test system, Gayla L. Poling is a contributing author of the American Academy of Audiology (2009) Position Statement on Ototoxicity and received an honorarium from American Speech-Language-Hearing Association (ASHA) to her institution for ASHA 2021 Continuing Education Online Course on ototoxicity management, Kelly M. Reavis is the co-inventor on a patent involving an ototoxicity monitoring method, and Victoria A. Sanchez has sponsored clinical research contracts (to institution) to support research activity from Otonomy Inc., Frequency Therapeutics, Pipeline Therapeutics, Aerin Medical, Oticon Medical, Helen of Troy Ltd., consulting fees from Autifony Therapeutics, Boehringer Ingelheim. The views expressed are those of the authors and of the International Ototoxicity Management Group (IOMG) and do not necessarily reflect the official position of or are endorsed by any particular organization, including the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, the Department of Veterans Affairs, or the U.S. government. Additionally, mention of any company or product does not constitute endorsement by any organization. All authors are members of the IOMG. This article is intended to align with the IOMG mission and views regarding effective ototoxicity management (https://www.ncrar.research.va.gov/ClinicianResources/IOMG.asp).*

Major health care gaps exist worldwide in the audiological management of individuals, following exposure to medical, occupational, or environmental ototoxicants. Ototoxicants are specific pharmaceuticals, solvents, asphyxiants, nitriles, metals, or compounds that pose a significant risk to the auditory and/or vestibular system(s) (Centers for Disease Control and Prevention, 2018). Individuals exposed to these agents can experience ototoxicity-related adverse events, including permanent hearing loss, tinnitus, or balance disorders (Biswas et al., 2022; Blankenship et al., 2021; Dillard et al., 2022, 2021; Van Hecke et al., 2017). Efforts to provide individuals at risk greater control over their hearing and balance health are needed to preserve their social participation and quality of life (QoL). Due to the lack of vestibulotoxicity research related to the mechanism and standards for detection, knowledge of the functional impact that these agents have on balance remains limited (Myers et al., 1993; Schaefer et al., 1985).

However, ototoxicity-related auditory deficits, following exposure to certain aminoglycoside antibiotics and platinum-based chemotherapies, are better characterized and are common adverse events from treatment in many regions of the world (Dillard et al., 2021, 2022). Currently, the World Health Organization (WHO) recommends that people receiving ototoxic medications and those exposed to environmental hazards, such as ototoxicants, have their hearing appropriately managed (WHO, 2021).

Yet, the widespread adoption of ototoxicity management (OtoM) programs, particularly in adults, is severely lacking in the clinical community (Konrad-Martin et al., 2018). Children are more closely monitored when there is a known period of risk to their hearing from exposure to a clinically necessary ototoxic medication (reviewed by Meijer et al., 2021). Pediatric studies have shown that hearing loss may detrimentally impact the development of critical language and speech acquisition, education, and social development (Olusanya & Newton, 2007; Yoshinago-Itano, 2000). In older populations, it is important to recognize that even mild hearing losses can have a substantial impact on an individual and the greater community, particularly among older adults who may also be experiencing cognitive decline (Lin et al., 2013). Unaddressed hearing loss can drastically impair listening and communication with the people who matter most and is therefore associated with social isolation, loneliness, and mental health deficits (Jung & Bhattacharyya, 2012; Kramer et al., 2002; Monzani et al., 2008; Shukla et al., 2020). This casts light on the substantial need for hearing health care in the aging population.

Implementation and standardization of an OtoM program require expert consensus and support from the professional community. The International Ototoxicity Management Group (IOMG) is a global consortium of hearing health advocates from clinics, universities, task forces, health foundations, professional societies, government agencies, and patients. Currently, there are no standardized approaches to OtoM. Efforts are underway, in part through IOMG, to generate recommendations for prospective OtoM across the life span and in a variety of different clinical settings. The aim is to develop feasible, contextually relevant clinical objectives and guidelines, recommendations for their implementation, and toolkits by focusing on systems, pathways, and coordination of care.

Additionally, IOMG is working to develop educational tools that will be useful for patients, and their care team, through their decision-making process. Harmonizing expert opinions with the voices of those most at risk for developing ototoxicity will be key to successful implementation of effective OtoM (Garinis et al., 2018; King & Brewer, 2018; Konrad-Martin et al., 2023). On October 19, 2021, the American Speech-Language-Hearing Association's (ASHA) Special Interest Groups (SIGs) 6 (Hearing and Balance Sciences: Research and Clinical Applications), 7 (Auditory Rehabilitation), 8 (Public Health Audiology), and 9 (Pediatric Hearing and Hearing Disorders) hosted a special virtual Open House Event entitled "What's New in Ototoxicity Management for Audiologists and SLPs?" This event welcomed IOMG members to an expert panel discussion of the risks, outcomes, and clinical management of hearing loss due to ototoxic exposure(s) across the life span. As hearing deficits are more commonly characterized in research and more often managed clinically, the focus of discussion was on hearing loss rather than vestibular and tinnitus-related issues. The objective of this viewpoint is to convey the thoughts, opinions, and experiences of IOMG clinicians and researchers shared during this event as they related to ASHA SIG-generated questions pertaining to the mitigation and development of programs for the detection and management of hearing loss due to ototoxic exposures.

It can be advantageous to view hearing loss resulting from exposure to ototoxicants through a public health lens rather than focusing on the individual. The goal of a public health framework is to protect and improve the health of a population. One way to bring audiology and public health together is through a prevention framework: primary, secondary, and tertiary prevention (Reavis et al., 2016). Primary prevention aims to prevent disease or injury before it befalls an individual and includes activities such as health promotion and education, with the goal of changing attitudes and behaviors to prevent disease (Abdalla & Omar, 2011; Alberti, 1996). For example, educating physicians and providers, including SLPs, about ototoxicity, its risk factors, and the integral role of the audiologist in OtoM is a critical component in the

primary prevention of ototoxic drug-induced hearing loss and balance problems. Partnering care team members may be better poised to flag patients at risk for ototoxicity and positioned to make timely referrals for OtoM. Another pillar of primary prevention is antibiotic stewardship, with the goal of improving responsible aminoglycoside antibiotic practices, which can protect patients from hearing loss caused by unnecessary antibiotic use (Chiotos et al., 2019; Dillard et al., 2022). In the workplace, primary prevention includes strategies such as elimination of the health hazard, substitution with a less toxic agent, engineering and administrative controls, and personal protective equipment. However, primary prevention has its limitations, and people will still be prescribed medications or experience workplace exposures that can lead to ototoxicity-related adverse events. Secondary prevention includes disease and injury surveillance, or more precisely, monitoring for symptoms. In the context of managing ototoxicity, the goal is to reduce the impact of these adverse events that may occur following an ototoxic exposure through early detection and timely access to treatment (Watkin et al., 2007). For secondary prevention strategies to be successful, they need to be goal directed, have a clear understanding of what defines a clinically meaningful change for the population under surveillance, and be accessible to individuals at risk (Konrad-Martin et al., 2018). Finally, tertiary prevention includes the diagnosis and treatment for ototoxic-induced hearing loss to prevent associated disability. Audiological rehabilitation is a tertiary preventive measure.

## Mitigating Ototoxicity From Medical Exposures

Clinically used ototoxic medications, such as platinum-based anticancer drugs (e.g., cisplatin) and aminoglycoside antibiotics, are often unavoidable. These life-saving clinical drugs, used most often to treat certain cancers, heart disease, and serious infections, are a critical part of standard-of-care therapies but are considered ototoxic due to their negative effects on the auditory and vestibular systems (Kahlmeter & Dahlager, 1984). When platinum-based drug therapies or other ototoxic therapies are indicated, patients should be counseled on all elements of their treatment, including the risk of ototoxicity. If no other treatment option is available, patients should be referred to an audiologist for ototoxicity monitoring before, during, and after therapy as part of a formal OtoM program (American Academy of Audiology [AAA], 2009; ASHA, 1994; Strebel et al., 2022). If a change in hearing is identified early, alterations in therapy may be considered to prevent further hearing loss, or appropriate aural rehabilitation can be implemented to reduce the impact of ototoxicity. Unfortunately, this referral for hearing health care is often overlooked, or an appropriate OtoM program is not available to readily serve the patient.

## Mitigating Ototoxicity From Occupational Exposures

The best approach to mitigate the risk of ototoxicity in the workplace is to be proactive, taking the necessary steps to provide primary prevention strategies (education on risk and risk reduction) and secondary prevention strategies (monitoring hearing, before, during, and after exposure and providing timely reporting and referrals). Information obtained over the course of the monitoring period will help those individuals at risk and their health team determine how best to proceed with exposures to reduce further ototoxic damage and/or consider rehabilitation options to manage their functional impact. For example, knowing what ototoxicants exist in the workplace is critical and can often be learned by reviewing resources (American Conference of Governmental Industrial Hygienists, 2023; Centers for Disease Control and Prevention, 2018) to avoid auditory damage. If ototoxicants are identified, steps should be taken to control exposure by implementing substitutes when possible and through the use of personal protective equipment (e.g., gloves, gowns, masks).

Interaction of ototoxicants with exposures to hazardous levels of noise warrant added attention. Daily exposures to both noise and chemicals (e.g., solvents, metals, carbon monoxide) are common in modern industrial work environments. Much of the research conducted in the 1980s revealed that workers exposed to nonhazardous noise levels and chemicals had higher rates of hearing problems compared to workers exposed to chemicals alone (Campo et al., 2009; Morata et al., 1994). Of the numerous chemicals found in the workplace, only a few have been investigated for potential ototoxicity (Occupational Safety and Health Administration, 2018). Unfortunately, in cases of combined noise and chemical exposures, it is often true that there is greater hearing loss than there would have been for each exposure on its own (Morata et al., 2021). There are also scenarios of potentiation where a chemical agent, which by itself may not affect hearing, exacerbates a noise-induced hearing loss that is more prevalent and more serious. These can be challenging issues to address.

Researchers and clinicians have started using the media to communicate the risks to the public. Now, informed patients may come to the clinic and provide the information that they were exposed to a certain agent. Much of our understanding of the harm chemicals present is provided through the patient's report, in addition to

what is provided by occupational agencies. Hearing loss associated with chemical exposures is a complex pathological entity and may be due to a combination of ototoxicity and neurotoxicity. A mismatch between audiometric results and self-reported listening difficulties is a common finding among those who experience auditory symptoms associated with chemical exposures (Campo et al., 2009; Dreisbach et al., 2022; Johnson & Morata, 2010). This scenario can be considered a sentinel alert for the need for an evaluation of central auditory function.

## Developing OtoM Programs

Widespread adoption of OtoM programs is hindered by inadequate professional support from regulatory agencies, lack of interdisciplinary coordination for referrals and timely intervention, inadequate institutional support, strains on personnel and clinical resources, a limited understanding of the prevalence and magnitude of ototoxic damage, and discrepancies in recommended ototoxicity monitoring guidelines (Ganesan et al., 2018; Konrad-Martin et al., 2018). Thus, the establishment of a successful OtoM program, first and foremost, requires "buy-in" from advocates such as policy makers, clinicians, referring physicians, patients, employers, and employees (Brandt et al., 2014; Skinner et al., 2022). It is not a small undertaking to provide the necessary resources and personnel to conduct multiple clinical visits for patients requiring baseline, monitoring, and follow-up care (Paken et al., 2020). Beyond the hearing and balance evaluations, OtoM includes a significant educational component to inform not only audiologists but also patients/employees and referring physicians/SLPs/employers of ototoxic risks, intervention and counseling options, and long-term symptom management. Institutes, clinics, and agencies must be fully committed to the engagement in multidisciplinary teams for an OtoM program to be effective.

Understanding the needs of the patients served, the roles and responsibilities of the audiologist and others in the multidisciplinary care team (including SLPs), and the systems of care within which the audiologist will need to be involved are crucial for optimizing the long-term auditory health for individuals at risk for ototoxicity. Having a "champion" for the cause may be necessary to develop an OtoM program if no framework currently exists. This individual will be tasked with making clinical connections with patients and staff, identifying resources, and finding opportunities to initiate an OtoM program that may not exist within their own setting. Embedding audiology into the different layers of care systems, and into the different care teams, helps to identify key contacts (i.e., nurse coordinator on the team, physician, physician lead). For example, audiologists can attend infectious disease and oncology grand rounds and participate on tumor boards to understand how to better coordinate care when plans include ototoxic exposures. The care team and the patient populations primarily served can vary by institution.

Understanding the process and the role of the audiologist in that process should be defined at the outset. Audiology services should never be viewed as supplemental to a care team, rather as part of an integral team-based approach for those individuals undergoing treatments requiring ototoxic medications or being exposed to ototoxicants in the workplace.

In cases where disease or illness is so complex that it is not reasonable to ask patients to make multiple visits to a clinic for monitoring, OtoM program goals should aim to reduce barriers to audiologic care by taking audiology services to the patients' bedside, so that any necessary intervention can be promptly provided (Dreisbach et al., 2017; Garinis et al., 2021). Several automated solutions have been explored in clinical and research applications for general hearing wellness that could be utilized in OtoM programs (Dawood et al., 2021; Frisby et al., 2022; Koleilat et al., 2020; Mahomed-Asmail et al., 2016). Currently, portable technology exists that includes manual and automated protocols for monitoring ototoxicity in boothless settings (Brungart et al., 2018; Dille et al., 2015; Fernandez et al., 2021; Jacobs et al., 2012; Koleilat et al., 2020). The initial concept of tablet-based audiometry has expanded to include multiple, other auditory-related tests, which provides the opportunity to expand and improve upon how we, as clinicians, can evaluate the hearing of populations at risk, be it due to ototoxicant or noise exposure. However, limitations of automated, boothless systems include cost considerations and the need for controlled, quiet test environments (Bright & Pallawela, 2016). Although these tools can be improved, there will still be a need for defining the framework and care pathways to fully leverage these tools. As with any hearing loss, once identified, there will be a need to manage the patient's hearing health.

Additionally, outreach and education are critical elements to establish an OtoM program. This is the case not only for the patient, worker, audiologist, and policy makers but also for other clinicians, physicians, or clinical support staff that might not be as familiar with ototoxicity yet could be able to make timely referrals if equipped with the relevant knowledge. Minimally, information on the incidence, prevalence, and risk factors for ototoxicity, and the special considerations across the life span, need to be discussed with all advocates. In the past 10–15 years, clinical research has more clearly shown the prevalence of platinum-induced hearing loss in children (up to 60% of

treated children will acquire a cisplatin-induced hearing loss) and the long-reaching impact on social and academic development (Dillard et al., 2022; Knight et al., 2005; Olusanya & Newton, 2007; WHO, 2021). This has led to increased recognition of the need for OtoM programs by pediatric cancer care teams. Collaborating with the team that provides treatment within your institution or community is important for developing and maintaining services for patients and their families (Konrad-Martin et al., 2018). Additionally, long-term follow-up care is essential, since there is evidence that hearing loss progression can occur after treatment (Bertolini et al., 2004; Knight et al., 2005; Waissbluth et al., 2018).

For many patients, opportunities may arise to be involved in a clinical trial, for instance, to test the potential ototoxicity of a new investigational drug. Too often, these types of clinical trials are designed with no input from an audiologist or anyone that has auditory or vestibular expertise. This presents an opportunity to again be a "champion" for audiology and share expertise as pharmaceuticals are being developed and evaluated. If approached with this opportunity, the audiologist can indicate that they would be able to collect hearing and balance outcome data for the clinical trial and also provide a full monitoring program and encourage compliance with published guidelines on ototoxicity grading scales (King & Brewer, 2018). This would not only educate the other health care providers on the study team but also serve to educate industry sponsors for future trials and drug development considerations, such as what measurements they should be including in a trial where ototoxicity is possible, and the appropriate timelines for monitoring/management. Furthermore, this could also be a synergistic way to provide opportunities for improvements in standard of care. Once the research relationship forms, the standard of care referrals and interprofessional consultations can lead to additional growth of an OtoM program. Physicians, nurses, and other key health care providers on the study team will see the value of audiology and may consider future referrals unrelated to a clinical research trial. Ototoxicity adverse events are typically permanent insults that will require ongoing management to support patient communication and/or balance needs.

## Detecting Ototoxicity

Detecting ototoxicity involves understanding the functional outcomes of associated hearing loss and identifying key outcomes from clinical test batteries that should be considered a crucial part of a monitoring plan (Ganesan et al., 2018; Lord, 2019). This can look different across the life span, especially when it comes to patients who are very young or advanced in age, and in various settings. OtoM programs should emphasize the need for evidence-based recommendations by which patients and care teams make decisions on monitoring schedules and assessment protocols based on medication/exposure, risk, treatment alternatives, resources, and patient/family priorities. Minimally, patients need a pretreatment auditory assessment to later identify significant changes in hearing or new perceivable concerns related to treatment. This baseline evaluation may be enhanced with the use of validated hearing-related QoL questionnaires (e.g., Meijer et al., 2021). In addition to self-reports, auditory function should be assessed both behaviorally and physiologically at baseline and at subsequent visits, as outlined by ASHA (1994). This means completing audiometry at extended-high frequencies (EHFs > 8000 Hz) as well as conventional frequencies to determine where behavioral responses are present. Speech perception measurements are recommended, not only in quiet to capture optimal performance but also in noise to obtain more ecologically valid hearing capabilities in everyday life.

An important physiologic measure for ototoxicity monitoring is distortion product otoacoustic emissions (DPOAEs), because they are a more direct measure of outer hair cell function and have been shown to be more sensitive to initial ototoxic damage compared to behavioral hearing thresholds (Dreisbach et al., 2017; Konrad-Martin et al., 2016; Ress et al., 1999). Commercially available clinical equipment allows for DPOAE measurements to be recorded reliably out to 6000 or 8000 Hz. This upper frequency limit is driven by the frequency response of the transducers used to produce the stimuli. Although it is possible to generate responses at frequencies greater than 8000 Hz (Dreisbach et al., 2006, 2017, 2018; Dreisbach & Siegel, 2001; Poling et al., 2012, 2014, 2019), current clinical equipment does not provide sufficient stimulus levels at higher frequencies allowing for reliable measures. However, recording DPOAEs is still highly recommended for conventional frequencies and looking to the literature to determine what stimulus parameters could be used and how to interpret results is suggested (Konrad-Martin et al., 2016; Poling et al., 2014, 2019; Reavis et al., 2015).

It is important to consider the potential burden on both the patient and clinical resources when developing an ototoxicity monitoring plan, as well as the patient/family needs. Portable technology may ease some of the physical strain for patients with limited mobility, but streamlined test batteries can also minimize the duration of monitoring visits for patients that are often exhausted from treatment. For example, knowing that ototoxicity affects basal cochlear function initially (Sha et al., 2001), once full baseline measures have been established, a targeted monitoring protocol like the sensitive range of ototoxicity can be helpful for both behavioral (e.g., ASHA, 1994; Fausti et al., 1994, 1999) and physiological (Dreisbach et al.,

2017) testing to reduce test time while still monitoring for ototoxicity during subsequent visits. Once a significant change has been observed, then a full audiogram and DPOAE evaluation will be necessary to assess the extent of change in hearing and outer hair cell function.

If and when a clinically meaningful change in hearing has been detected following an ototoxic exposure, the expected functional impact on the patient will need to be communicated to the individual as well as to the care team or employers. However, in situations where a drug-induced hearing loss is detected, a single definition of impact does not exist (King & Brewer, 2018; Paken et al., 2020). Various ototoxicity classification systems have been developed for specific populations, medications, and purposes (King & Brewer, 2018; Waissbluth et al., 2017). As an example, when monitoring hearing thresholds, the ASHA (1994) published guidelines state that a 20-dB change at any single frequency, a 10-dB change at two or more consecutive frequencies, or a loss of response at three or more consecutive frequencies constitute a "clinically significant" threshold shift. Although clinically significant changes in otoacoustic emission levels for monitoring have been explored (Konrad-Martin et al., 2016; Reavis et al., 2015), no widely accepted clinical guidelines exist. A meta-analysis consisting of 10 observational studies by Reavis et al. (2015) reported DPOAE level shift reference limits for adults ranging from 1.7 to 2.4 dB for 1000, 2000, 4000, and 6000 Hz over a time frame of less than 20 days. The authors encouraged clinicians to make as many DPOAE measurements as needed to assist with interpreting results. They emphasize, however, that clinicians should identify one "watch frequency," or a band of frequencies to monitor for a clinically significant DPOAE level change. They also note that the DPOAE level shift reference limits do increase over longer monitoring periods and at higher frequencies. For pediatric patients with cancer, ototoxicity monitoring may coincide with developmental changes in the auditory system, particularly during the first year of life. Interpreting DPOAE findings in this context requires that DPOAE test–retest differences be considered in relation to age-specific normal variability. A recent study evaluated serial DPOAE measures conducted in 38 healthy children with normal hearing who ranged in age from 1 month to 10 years at the initial (baseline) visit (Konrad-Martin et al., 2020). The study found a consistent pattern of age-related changes in DPOAE level across the children in the study. DPOAE level decreased over most of the conventional frequency range, by 3–4 dB, from 1 to 13 months of age followed by a more gradual decline of < 1 dB/year. Because an $f_2$ of 6000 Hz showed minimal maturation and measurement error, the authors suggested that it may be an optimal watch frequency to select for ototoxicity monitoring in pediatric patients. The authors emphasize the need to validate any normative data with locally developed normative data to ensure that similar test performance is achieved.

Taken together, audiologists should use everything that they have in their "toolbox" to assess ototoxicity-related changes. Currently, there is no status quo for ototoxicity monitoring. ASHA (1994) and AAA (2009) guidelines encourage clinicians to not only assess patients using the behavioral audiogram at both conventional and EHFs but also indicate that audiologic tests beyond the audiogram be used whenever possible. This includes immittance measures, speech audiometry, and otoacoustic emissions. For example, studies have shown that using DPOAEs to monitor ototoxic effects is beneficial as changes are often seen in DPOAE levels prior to changes noted on the audiogram (Dreisbach et al., 2017; Konrad-Martin et al., 2016; Ress et al., 1999). By increasing awareness of the need for ototoxicity monitoring, the field will start to have a better understanding of what the most sensitive tools are for early detection of hearing loss.

## Managing Ototoxicity

For the patient to be involved in OtoM programs, key information must first be provided for them to learn how to identify initial signs of ototoxicity in order to tell their clinical team immediately, so the team can make an informed decision about their treatment regimens or workplace exposures. All patients and families should receive an age-appropriate informational brochure about ototoxicity, as well as online resources, and be advised of local clinics to assist with managing hearing loss. It is important to stress that self-advocacy for the patient is important and this can be achieved by asking their clinical team about adverse events associated with new or current treatments/exposures. In addition, counseling related to strategies for the prevention of further hearing loss is critical (understanding risk scenarios and managing exposures to noise or music, hearing protection in noise, and asking care providers about adverse events related to treatments and potential alternatives). Audiologists should consider having sample hearing protectors to offer along with informational brochures (Byrne et al., 2012). Importantly, the audiologist and broader care team should gather information about impacts on QoL to provide further guidance on management. Once hearing difficulties have been detected, management can take various forms depending on the needs and age of the individual. The approach can be adjusted to balance the need for intervention (e.g., amplification vs. communication strategies) versus ongoing ototoxicity monitoring. Although we may have practice guidelines (e.g., AAA, 2009; ASHA, 1994), it is important

to keep in mind that what is published are merely frameworks that can, and often will, require some adjustments for individual patients, their care teams, and the clinic. For example, a recent article was published that is specific to OtoM program recommendations in persons with cystic fibrosis (Garinis et al., 2021). This article provides realistic considerations for clinics to develop and implement a hearing health care model for their patients without a strong burden on the clinic itself, the patient, and audiology. Recommendations may differ across the life span, since adults may be able to complete a more comprehensive diagnostic protocol compared to pediatrics. For example, the Children's Oncology Group (2018) has long-term follow-up recommendations that specify a schedule for monitoring children exposed to cranial radiation only and those treated with both cranial radiation and platinum agents. Once hearing loss is identified, typical recommendations for follow-up and intervention are similar to what would be recommended for any patient who has hearing loss and are based on the patient's age and the stability of the hearing loss.

## Future Directions/Call to Action

There are hundreds of known ototoxins that pose a threat to hearing health (e.g., Lee et al., 2005; Rizk et al., 2020). As new medications seek approval, the Food and Drug Administration (FDA; https://www.fda.gov) will consult with scientific experts, patients and patient advocates, industry, academics, and community members throughout the drug development and review process to ensure that they have the appropriate perspectives when making regulatory decisions that may impact an individual's health. Following FDA approval and labeling, postmarketing surveillance is achieved through "MedWatch," which is the FDA's medical product safety reporting program for health professionals, patients, and consumers. MedWatch offers adverse events reporting tools that allow medical professionals and the public to report medication errors and medical product injuries. Regarding the labeling of ototoxicity of environmental and occupational exposures, it varies by country and each will have different authoritative agencies that evaluate, document, and disseminate toxicity information through their channels. Often the information is focused on a specific scenario of exposure (intentional, environmental, or occupational). In the United States, the most complete information on toxicity of common chemicals can be found in the Toxicological Profile series of the Agency for Toxic Substances and Disease Registry (n.d.). Refined monitoring protocols and increased overall OtoM will supply these interested parties with the necessary information to make future decisions and help diagnose, treat, and manage individuals currently undergoing treatment with or exposed to already identified ototoxicants.

However, hearing loss is not the only adverse event of ototoxic exposures that clinicians need to manage. Tinnitus (Dille et al., 2010; Frisina et al., 2016), balance/vestibular impairments (Kros & Steyger, 2019; Van Hecke et al., 2017), and neurotoxicity (Park et al., 2013; Sastry & Kellie, 2005; Staff et al., 2017) are all potential threats, and minimal research exists for these ototoxicity-related impacts. Additionally, the field is currently lacking large-scale outcome data from randomized clinical trials utilizing validated surveys and both physiologic and behavioral assessments that would identify the full range of ototoxic adverse events. Given the range of ototoxicity-related symptoms, audiologists should gather information on exposure histories and the functional outcomes these can have on their patients. The use of questionnaires can fulfill this need (Griest-Hines et al., 2021; Henry et al., 2021). In addition, sensitive tools and determination of "clinically significant" changes in function for the detection of ototoxicity continue to be explored. For example, when baseline results are available, EHF DPOAE responses are sensitive to insults from platinum derivatives, and often changes in the DPOAE responses precede those at the same frequencies measured behaviorally with audiometry (Dreisbach et al., 2017; Poling et al., 2019). However, caution should be exercised, as mentioned previously, when testing frequencies greater than 8000 Hz for both audiometry and DPOAEs as specialized transducers are required. EHF transducers for audiometry are readily available but this is not the case for DPOAE testing currently. Achieving reliable and repeatable DPOAE responses at EHFs is possible with equipment that is currently not commercially available for clinical use. Further research into the reliability of EHF DPOAE responses within patients and over time is needed to appropriately determine the feasibility of using this objective, quick measure of outer hair cell function as an ototoxicity screening tool. Once the value added of DPOAEs can be confirmed, advancements and availability in clinical and tablet equipment will likely follow.

Screening, assessment, and management of ototoxicity should be grounded in science, and these findings used to inform care. Research investigating OtoM strategies and the impacts on functional outcomes are lacking. To optimize the clinical impact of OtoM, the field will therefore need substantial investment in pragmatic (effectiveness) trials to determine how to best provide OtoM programs in various settings. Such information is important for planning and implementing interventions to minimize the damage and otherwise reduce the impact of ototoxicity. The establishment of a central data repository to which health care providers can contribute to would be invaluable for enabling the systematic collection of data relating ototoxic

exposures to development and exacerbation of functional and QoL metrics. These data are needed to better estimate the magnitude of the problem, identify modifiable risk factors, and evaluate the utility of preventive and rehabilitative management strategies going forward. Given the range of ototoxicity-related adverse events and symptom burden, one size will not fit all when it comes to OtoM programs.

## Conclusions

This panel was convened to draw attention to issues related to the mitigation, detection, and management of ototoxicity resulting from medical, occupational, and/or environmental exposures. Vestibulotoxicity and tinnitus remain poorly understood; however, ototoxicity-related hearing loss is a significant, permanent condition impacting an individual's overall QoL. Existing research and the first-hand experiences expressed during the panel highlight the need for ongoing OtoM across the life span. Although our field now has a therapeutic drug that can protect against ototoxicity in some children treated for nonmetastatic carcinoma, ototoxicity resulting from other agents in other patient populations still exists. Currently, clinical studies aimed at mitigating the effects of ototoxic medications are ongoing (Lee et al., 2023); however, the need remains to advance to a place where we can better understand the full extent of ototoxicity and can agree on minimum guidelines that can be implemented to benefit our patients. Moreover, the role of individualized management is crucial to consider as well as the larger scoping component of toxicity. Many audiologists see patients in the clinic that present with similar looking audiograms, yet the effects of the hearing loss may have very devastating effects for one person and not so for another. Thus, although the goal is the widespread adoption of OtoM programs, at the individual level, the programs themselves must be adaptable to accommodate the special considerations of both patients and clinics.

## Author Contributions

**Gayla L. Poling:** Conceptualization (Lead), Project administration (Lead), Supervision (Lead), Writing – review & editing (Equal). **Katharine A. Fernandez:** Conceptualization (Lead), Project administration (Lead), Supervision (Lead), Writing – original draft (Lead). **Laura Dreisbach:** Conceptualization (Lead), Project administration (Lead), Supervision, Writing – original draft (Lead). **Angela Garinis:** Writing – review & editing (Equal). **Kristin Knight:** Writing – review & editing (Equal). **Dawn Konrad-Martin:** Writing – review & editing (Equal). **Thais Morata:** Writing – review & editing (Equal). **Kelly M. Reavis:** Writing – review & editing (Equal). **Victoria A. Sanchez:** Writing – review & editing (Equal).

## Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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## References

**Abdalla, F. M., & Omar, A. M.** (2011). The role of the health system in the prevention of hearing loss among children in sub-Saharan Africa. *Sudanese Journal of Paediatrics, 11*(1), 8–19.

**Agency for Toxic Substances and Disease Registry (ATSDR, CDC).** (n.d.). *Toxicological profiles.* https://www.atsdr.cdc.gov/toxprofiledocs/index.html

**Alberti, P. W.** (1996). The prevention of hearing loss worldwide. *Scandinavian Audiology. Supplementum, 25*(42), 14–19.

**American Academy of Audiology.** (2009). American Academy of Audiology's position statement and practice guidelines on ototoxicity monitoring. https://www.audiology.org/practice-guideline/position-statement-and-practice-guidelines-on-ototoxicity-monitoring/

**American Conference of Governmental Industrial Hygienists.** (2023). TLV/BEI guidelines. https://acgih.org/science/tlv-bei-guidelines/

**American Speech-Language-Hearing Association.** (1994). Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. *ASHA, 36*(Suppl. 12), 11–19.

**Bertolini, P., Lassalle, M., Mercier, G., Raquin, M. A., Izzi, G., Corradini, N., & Hartmann, O.** (2004). Platinum compound-related ototoxicity in children: Long-term follow-up reveals continuous worsening of hearing loss. *Journal of Pediatric Hematology/Oncology, 26*(10), 649–655. https://doi.org/10.1097/01.mph.0000141348.62532.73

**Biswas, R., Genitsaridi, E., Trpchevska, N., Lugo, A., Schlee, W., Cederroth, C. R., Gallus, S., & Hall, D. A.** (2022). Low evidence for tinnitus risk factors: A systematic review and meta-analysis. *Journal of the Association for Research in Otolaryngology, 24*(1), 81–94. https://doi.org/10.1007/s10162-022-00874-y

**Blankenship, C. M., Hunter, L. L., Feeney, M. P., Cox, M., Bittinger, L., Garinis, A. C., Li, L., McPhail, G., & Clancy, J. P.** (2021). Functional impacts of aminoglycoside treatment on speech perception and extended high-frequency hearing loss in a pediatric cystic fibrosis cohort. *American Journal of Audiology, 30*(3S), 834–853. https://doi.org/10.1044/2020_AJA-20-00059

**Brandt, B., Lutfiyya, M. N., Kean, J. A., & Chioreso, C.** (2014). A scoping review of interprofessional collaborative practice and education using the lens of the Triple Aim. *Journal of Interprofessional Care, 28*(5), 393–399. https://doi.org/10.3109/13561820.2014.906391

**Bright, T., & Pallawela, D.** (2016). Validated smartphone-based apps for ear and hearing assessments: A review. *JMIR Rehabilitation and Assistive Technologies, 3*(2), Article e13. https://doi.org/10.2196/rehab.6074

**Brungart, D., Schurman, J., Konrad-Martin, D., Watts, K., Buckey, J., Clavier, O., Jacobs, R. G., Gordon S., & Dille, M. F.** (2018). Using tablet-based technology to deliver time-efficient ototoxicity monitoring. *International Journal of Audiology, 57*(Suppl. 4), S78–S86. https://doi.org/10.1080/14992027.2017.1370138

**Byrne, D. C., Themann, C. L., Meinke, D. K., Morata, T. C., & Stephenson, M. R.** (2012). Promoting hearing loss prevention in audiology practice. *SIG 8 Perspectives on Public Health Issues Related to Hearing and Balance, 13*(1), 3–19. https://doi.org/10.1044/hcoa13.1.3

**Campo, P., Maguin, K., Gabriel, S., Möller, A., Nies, E., Gómez, M. D. S., & Toppila, E.** (2009). *Combined exposure to noise and ototoxic substances.* EU-OSHA—European Agency for Safety and Health at Work. https://osha.europa.eu/en/publications/combined-exposure-noise-and-ototoxic-substances

**Centers for Disease Control and Prevention.** (2018). *Preventing hearing loss caused by chemical (ototoxicity) and noise exposure.* Publication No. 2018–124.

**Children's Oncology Group.** (2018). *Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers.* http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf

**Chiotos, K., Tamma, P. D., & Gerber, J. S.** (2019). Antibiotic stewardship in the intensive care unit: Challenges and opportunities. *Infection Control and Hospital Epidemiology, 40*(6), 693–698. https://doi.org/10.1017/ice.2019.74

**Dawood, N., Asmail, F. M., Louw, C., & Swanepoel, D. W.** (2021). Mhealth hearing screening for children by non-specialist health workers in communities. *International Journal of Audiology, 60*(Suppl. 1), S23–S29. https://doi.org/10.1080/14992027.2020.1829719

**Dillard, L. K., Lopez-Perez, L., Martinez, R. X., Fullerton, A. M., Chadha, S., & McMahon, C. M.** (2022). Global burden of ototoxic hearing loss associated with platinum-based cancer treatment: A systematic review and meta-analysis. *Cancer Epidemiology, 79,* Article 102203. https://doi.org/10.1016/j.canep.2022.102203.

**Dillard, L. K., Martinez, R. X., Perez, L. L., Fullerton, A. M., Chadha, S., & McMahon, C. M.** (2021). Prevalence of aminoglycoside-induced hearing loss in drug-resistant tuberculosis patients: A systematic review. *Journal of Infection, 83*(1), 27–36. https://doi.org/10.1016/j.jinf.2021.05.010

**Dille, M. F., Konrad-Martin, D., Gallun, F., Helt, W. J., Gordon, J. S., Reavis, K. M., Bratt, G. W., & Fausti, S. A.** (2010). Tinnitus onset rates from chemotherapeutic agents and ototoxic antibiotics: Results of a large prospective study. *Journal of the American Academy of Audiology, 21*(6), 409–417. https://doi.org/10.3766/jaaa.21.6.6

**Dille, M. F., McMillan, G., Helt, W. J., Konrad-Martin, D., & Jacobs, P.** (2015). A store-and-forward tele-audiology solution to promote efficient screenings for ototoxicity during cisplatin cancer treatment. *Journal of the American Academy of Audiology, 26*(9), 750–760. https://doi.org/10.3766/jaaa.15028

**Dreisbach, L., Ho, M., Reid, E., & Siegel, J.** (2017). Effects of oxaliplatin, carboplatin, and cisplatin across treatment on high-frequency objective and subjective auditory measures in adults. *Perspectives of the ASHA Special Interest Groups, 2*(6), 17–36. https://doi.org/10.1044/persp2.SIG6.17

**Dreisbach, L., Murphy, S., Arevalo, R., Schlocker, C., Miller, T., & Guthrie, O. W.** (2022). Is jet fuel exposure associated with central auditory nervous system difficulties: An exploratory study in military personnel. *The Journal of the Acoustical Society of America, 151*(3), 2027–2038. https://doi.org/10.1121/10.0009845

**Dreisbach, L., Zettner, E., Chang Liu, M., Meuel Fernhoff, C., MacPhee, I., & Boothroyd, A.** (2018). High-frequency distortion-product otoacoustic emission repeatability in a patient population. *Ear and Hearing, 39*(1), 85–100. https://doi.org/10.1097/AUD.0000000000000465

**Dreisbach, L. E., Long, K. M., & Lees, S. E.** (2006). Repeatability of high-frequency distortion-product otoacoustic emissions in normal-hearing adults. *Ear and Hearing, 27*(5), 466–479. https://doi.org/10.1097/01.aud.0000233892.37803.1a

**Dreisbach, L. E., & Siegel, J. H.** (2001). Distortion-product otoacoustic emissions measured at high frequencies in humans. *The Journal of the Acoustical Society of America, 110*(5), 2456–2469. https://doi.org/10.1121/1.1406497

**Fausti, S. A., Henry, J. A., Helt, W. J., Phillips, D. S., Frey, R. H., Noffsinger, P. D., Larson, V. D., & Fowler, C. G.** (1999). An individualized, sensitive frequency range for early detection of ototoxicity. *Ear and Hearing, 20*(6), 497–505. https://doi.org/10.1097/00003446-199912000-00005

**Fausti, S. A., Larson, V. D., Noffsinger, D., Wilson, R. H., Phillips, D. S., & Fowler, C. G.** (1994). High-frequency audiometric monitoring strategies for early detection of ototoxicity. *Ear and Hearing, 15*(3), 232–239. https://doi.org/10.1097/00003446-199406000-00004

**Fernandez, K. A., Allen, P., Campbell, M., Page, B., Townes, T., Li, C.-M., Cheng, H., Garrett, J., Mulquin, M., Clements, A., Mulford, D., Ortiz, C., Brewer, C., Dubno, J. R., Newlands, S., Schmitt, N. C., & Cunningham, L. L.** (2021). Atorvastatin is associated with reduced cisplatin-induced hearing loss. *The Journal of Clinical Investigation, 131*(1). https://doi.org/10.1172/JCI142616

**Frisby, C., Elkelboom, R., Mahomed-Asmail, F., Kuper, H., & Swanepoel, D. W.** (2022). m-Health applications for hearing loss: A scoping review. *Telemedicine Journal and E-Health, 28*(8), 1090–1099. https://doi.org/10.1089/tmj.2021.0460

**Frisina, R. D., Wheeler, H. E., Fossa, S. D., Kerns, S. L., Fung, C., Sesso, H. D., Monahan, P. O., Feldman, D. R., Hamilton, R., Vaughn, D. J., Beard, C. J., Budnick, A., Johnson, E. M., Ardeshir-Rouhani-Fard, S., Einhor, L. H., Lipshultz, S. E., Dolan, M. E., & Travis, L. B.** (2016). Comprehensive audiometric analysis of hearing impairment and tinnitus after cisplatin-based chemotherapy in survivors of adult-onset cancer. *Journal of Clinical Oncology, 34*(23), 2712–2720. https://doi.org/10.1200/JCO.2016.66.8822

**Ganesan, P., Schmiedge, J., Manchaiah, V., Swapna, S., Dhandayutham, S., & Kothandaraman, K. P.** (2018). Ototoxicity: A challenge in diagnosis and treatment. *Journal of Audiology and Otology, 22*(2), 59–68. https://doi.org/10.7874/jao.2017.00360

**Garinis, A. C., Keefe, D. H., Hunter, L. L., Fitzpatrick, D. F., Putterman, D. B., McMillan, G. P., Gold, J. A., & Feeney, M. P.** (2018). Chirp-evoked otoacoustic emissions and middle ear absorbance for monitoring ototoxicity in cystic fibrosis patients. *Ear and Hearing, 39*(1), 69–84. https://doi.org/10.1097/AUD.0000000000000464

**Garinis, A. C., Poling, G. L., Rubenstein, R. C., Konrad-Martin, D., Hullar, T. E., Baguley, D. M., Burrows, H. L., Chisholm, J. A., Custer, A., Dresibach Hawe, L., Hunter, L. L., Marras, T. K., Ortiz, C. E., Petersen, L., Steyger, P. S., Winthrop, K., Zettner, E. M., Clark, K., Hungerford, M., . . . Brewer, C. C.** (2021). Clinical considerations for routine auditory and vestibular monitoring in patients with cystic fibrosis. *American Journal of Audiology, 30*(3S), 800–809. https://doi.org/10.1044/2021_AJA-21-00031

**Griest-Hines, S. E., Bramhall, N. F., Reavis, K. M., Theodoroff, S. M., & Henry, J. A.** (2021). Development and initial validation of the lifetime exposure to noise and solvents questionnaire in U.S. Service members and Veterans. *American Journal of Audiology, 30*(3S), 810–824. https://doi.org/10.1044/2021_AJA-20-00145

**Henry, J. A., Griest, S., Reavis, K. M., Grush, L., Theodoroff, S. M., Young, S., Thielman, E. J., & Carlson, K. F.** (2021). Noise Outcomes in Servicemembers Epidemiology (NOISE) study: Design, methods, and baseline results. *Ear and Hearing, 42*(4), 870–885. https://doi.org/10.1097/aud.0000000000000974

**Jacobs, P. G., Silaski, G., Wilmington, D., Gordon, S., Helt, W., McMillan, G., Fausti, S. A., & Dille, M.** (2012). Development and evaluation of a portable audiometer for high-frequency screening of hearing loss from ototoxicity in homes/clinics. *IEEE Transactions on Biomedical Engineering, 59*(11), 3097–3103. https://doi.org/10.1109/TBME.2012.2204881

**Johnson, A.-C., & Morata, T. C.** (2010). Occupational exposure to chemicals and hearing impairment. *Arbete och Hälsa, 44*(4), Article 177. https://gupea.ub.gu.se/handle/2077/23240

**Jung, D., & Bhattacharyya, N.** (2012). Association of hearing loss with decreased employment and income among adults in the United States. *Annals of Otology, Rhinology & Laryngology, 121*(12), 771–775. https://doi.org/10.1177/000348941212101201

**Kahlmeter, G., & Dahlager, J. I.** (1984). Aminoglycoside toxicity - a review of clinical studies published between 1975 and 1982. *The Journal of Antimicrobial Chemotherapy, 13*(Suppl. A), 9–22. https://doi.org/10.1093/jac/13.suppl_A.9

**King, K. A., & Brewer, C. C.** (2018). Clinical trials, ototoxicity grading scales and the audiologist's role in therapeutic decision making. *International Journal of Audiology, 57*(Suppl. 4), S89–S98. https://doi.org/10.1080/14992027.2017.1417644

**Knight, K. R. G., Kraemer, D. F., & Neuwelt, E. A.** (2005). Ototoxicity in children receiving platinum chemotherapy: Underestimating a commonly occurring toxicity that may influence academic and social development. *Journal of Clinical Oncology, 23*(34), 8588–8596. https://doi.org/10.1200/JCO.2004.00.5355

**Koleilat, A., Argue, D. P., Schimmenti, L. A., Ekker, S. C., & Poling, G. L.** (2020). The GoAudio quantitative mobile audiology test enhances access to clinical hearing assessments. *American Journal of Audiology, 29*(4), 887–897. https://doi.org/10.1044/2020_AJA-20-00060

**Konrad-Martin, D., Knight, K., McMillan, G. P., Dreisbach, L. E., Nelson, E., & Dille, M.** (2020). Long-term variability of distortion-product otoacoustic emissions in infants and children and its relation to pediatric ototoxicity monitoring. *Ear and Hearing, 41*(2), 239–253. https://doi.org/10.1097/AUD.0000000000000536

**Konrad-Martin, D., Polaski, R., DeBacker, J. R., Theodoroff, S. M., Garinis, A., Lacey, C., Johansson, K., Mannino, R., Milnes, T., Hungerford, M., & Clark, K. D.** (2023). Audiologists' perceived value of ototoxicity management and barriers to implementation for at-risk cancer patients in VA: The OtoMIC survey. *Journal of Cancer Survivorship: Research and Practice, 17*(1), 69–81. https://doi.org/10.1007/s11764-022-01316-7

**Konrad-Martin, D., Poling, G. L., Dreisbach, L. E., Reavis, K. M., McMillan, G. P., Lapsley Miller, J. A., & Marshall, L.** (2016). Serial monitoring of otoacoustic emissions in clinical trials. *Otology and Neurotology, 37*(8), e286–e294. https://doi.org/10.1097/MAO.0000000000001134

**Konrad-Martin, D., Poling, G. L., Garinis, A. C., Ortiz, C. E., Hopper, J., O'Connell Bennett, K., & Dille, M. F.** (2018). Applying U.S. national guidelines for ototoxicity monitoring in adult patients: Perspectives on patient populations, service gaps, barriers and solutions. *International Journal of Audiology, 57*(Suppl. 4), S3–S18. https://doi.org/10.1080/14992027.2017.1398421

**Kramer, S. E., Kapteyn, T. S., Kuik, D. J., & Deeg, D. H.** (2002). The association of hearing impairment and chronic diseases with psychosocial health status in older age. *Journal of Aging and Health, 14*(1), 122–137. https://doi.org/10.1177/089826430201400107

**Kros, C. J., & Steyger, P. S.** (2019). Aminoglycoside- and cisplatin-induced ototoxicity: Mechanisms and otoprotective strategies. *Cold Spring Harbor Perspectives in Medicine, 9*(11). https://doi.org/10.1101/cshperspect.a033548

**Lee, C. A., Mistry, D., Uppal, S., & Coatesworth, A. P.** (2005). Otologic side effects of drugs. *The Journal of Laryngology and Otology, 119*(4), 267–271. https://doi.org/10.1258/0022215054020485

**Lee, J., Fernandez, K., & Cunningham, L. L.** (2023). Hear and now: Ongoing clinical trials to prevent drug-induced hearing loss. *Annual Review of Pharmacology and Toxicology*. Advance online publication. https://doi.org/10.1146/annurev-pharmtox-033123-114106

**Lin, F. R., Yaffe, K., Xia, J., Xue, Q. L., Harris, T. B., Purchase-Helzner, E., Satterfield, S., Ayonayon, H. N., Ferrucci, L., Simonsick, E. M., & Health ABC Study Group.** (2013). Hearing loss and cognitive decline in older adults. *JAMA Internal Medicine, 173*(4), 293–299. https://doi.org/10.1001/jamainternmed.2013.1868

**Lord, S. G.** (2019). Monitoring protocols for cochlear toxicity. *Seminars in Hearing, 40*(2), 122–143. https://doi.org/10.1055/s-0039-1684042

**Mahomed-Asmail, F., Swanepoel, D. W., & Elkelboom, R. H.** (2016). Diagnostic hearing assessment in schools: Validity and time efficiency of automated audiometry. *Journal of the American Academy of Audiology, 27*(1), 42–48. https://doi.org/10.3766/jaaa.15041

**Meijer, A. J. M., van den Heuvel-Eibrink, M. M., Brooks, B., am Zehnhoff-Dinnesen, A. G., Knight, K., Freyer, D. R., Chang, K. W., Hero, B., Papadakis, V., Frazier, A. L., Blattmann, C., Windsor, R., Morland, B., Bouffet, E., Ruthowski, S., Tytgat,**

**G. A. M., Geller, J. I., Hunter, L. L., Sung, L., . . . Society of Paediatric Oncology Supportive Care Committee.** (2021). Recommendations for age-appropriate testing, timing, and frequency of audiologic monitoring during childhood cancer treatment: An International Society of Paediatric Oncology Supportive Care Consensus Report. *JAMA Oncology, 7*(10), 1550–1558. https://doi.org/10.1001/jamaoncol.2021.2697

**Monzani, D., Galeazzi, G. M., Genovese, E., Marrara, A., & Martini, A.** (2008). Psychological profile and social behaviour of working adults with mild or moderate hearing loss. *Acta Otorhinolaryngologica Italica, 28*(2), 61–66.

**Morata, T. C., Dunn, D. E., & Sieber, W. K.** (1994). Occupational exposure to noise and ototoxic organic solvents. *Archives of Environmental Health, 49*(5), 359–365. https://doi.org/10.1080/00039896.1994.9954988

**Morata, T. C., Hungerford, M., & Konrad-Martin, D.** (2021). Potential risks to hearing functions of service members from exposure to jet fuels. *American Journal of Audiology, 30*(3S), 922–927. https://doi.org/10.1044/2021_AJA-20-00226

**Myers, S. F., Blakley, B. W., & Schwan, S.** (1993). Is *cis*-platinum vestibulotoxic? *Otolaryngology—Head and Neck Surgery, 108*(4), 322–328. https://doi.org/10.1177/019459989310800403

**Olusanya, B. O., & Newton, V. E.** (2007). Global burden of childhood hearing impairment and disease control priorities for developing countries. *The Lancet, 369*(9569), 1314–1317. https://doi.org/10.1016/S0140-6736(07)60602-3

**Occupational Safety and Health Administration.** (2018). *Toxic and hazardous substances, hazard communication subpart Z 29 CFR 1910.1200*. https://www.osha.gov/sites/default/files/2018-12/fy07_sh-16625-07_hazcomhandout.pdf

**Paken, J., Govender, C. D., Mershen, P., & Sewram, V.** (2020). Perspectives and practices of ototoxicity monitoring. *South African Journal of Communication Disorders, 67*(1), e1–e10. https://doi.org/10.4102/sajcd.v67i1.685

**Park, S. B., Goldstein, D., Krishnan, A. V., Lin, C. S.-Y., Friedlander, M. L., Cassidy, J., Koltzenburg, M., & Kiernan, M. C.** (2013). Chemotherapy-induced peripheral neurotoxicity: A critical analysis. *CA: A Cancer Journal for Clinicians, 63*(6), 419–437. https://doi.org/10.3322/caac.21204

**Poling, G., Lee, J., Siegel, J., & Dhar, S.** (2012). Clinical utilisation of high-frequency DPOAEs. *ENT & Audiology News, 21*(4), 91–92.

**Poling, G. L., Siegel, J. H., Lee, J., Lee, J., & Dhar, S.** (2014). Characteristics of the $2f_1$-$f_2$ distortion product otoacoustic emission in a normal hearing population. *The Journal of the Acoustical Society of America, 135*(1), 287–299. https://doi.org/10.1121/1.4845415

**Poling, G. L., Vlosich, B., & Dreisbach, L. E.** (2019). Emerging distortion product otoacoustic emission techniques to identify preclinical warning signs of basal cochlear dysfunction due to ototoxicity. *Applied Sciences, 9*(15), Article 3132. https://doi.org/10.3390/app9153132

**Reavis, K. M., McMillan, G. P., Dille, M. F., & Konrad-Martin, D.** (2015). Meta-analysis of distortion product otoacoustic emission retest variability for serial monitoring of cochlear function in adults. *Ear and Hearing, 36*(5), e251–e260. https://doi.org/10.1097/AUD.0000000000000176

**Reavis, K. M., Tremblay, K. L., & Saunders, G.** (2016). How can public health approaches and perspectives advance hearing health care? *Ear and Hearing, 37*(4), 376–380. https://doi.org/10.1097/AUD.0000000000000321

**Ress, B. D., Sridhar, K. S., Balkany, T. J., Waxman, G. M., Stagner, B. B., & Lonsbury-Martin, B. L.** (1999). Third Place—Resident Clinical Science Award 1998: Effects of cis-platinum chemotherapy on otoacoustic emissions: The development of an objective screening protocol. *Otolaryngology—Head and Neck Surgery, 121*(6), 693–701. https://doi.org/10.1053/hn.1999.v121.a101567

**Rizk, H. G., Lee, J. A., Liu, Y. F., Endriukaitis, L., Isaac, J. L., & Bullington, W. M.** (2020). Drug-induced ototoxicity: A comprehensive review and reference guide. *Pharmacotherapy, 40*(12), 1265–1275. https://doi.org/10.1002/phar.2478

**Sastry, J., & Kellie, S. J.** (2005). Severe neurotoxicity, ototoxicity and nephrotoxicity following high-dose cisplatin and amifostine. *Pediatric Hematology and Oncology, 22*(5), 441–445. https://doi.org/10.1080/08880010590964381

**Schaefer, S. D., Post, J. D., Close, L. G., & Wright, C. G.** (1985). Ototoxicity of low- and moderate-dose cisplatin. *Cancer, 56*(8), 1934–1939. https://doi.org/10.1002/1097-0142(19851015)56:8<1934::AID-CNCR2820560807>3.0.CO;2-F

**Sha, S. H., Taylor, R., Forge, A., & Schacht, J.** (2001). Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. *Hearing Research, 155*(1–2), 1–8. https://doi.org/10.1016/S0378-5955(01)00224-6

**Shukla, A., Harper, M., Pedersen, E., Goman, A., Suen, J. J., Price, C., Applebaum, J., Hoyer, M., Lin, F. R., & Reed, N. S.** (2020). Hearing loss, loneliness, and social isolation: A systematic review. *Otolaryngology—Head and Neck Surgery, 162*(5), 622–633. https://doi.org/10.1177/0194599820910377

**Skinner, K., Maxwell, B., Baskerville, A., & Milanović, J.** (2022). Audiology, an important contributor to interprofessional holistic care: An interprofessional collaborative case example. *American Journal of Audiology, 31*(1), 204–210. https://doi.org/10.1044/2021_AJA-21-00118

**Staff, N. P., Grisold, A., Grisold, W., & Windebank, A. J.** (2017). Chemotherapy-induced peripheral neuropathy: A current review. *Annals of Neurology, 81*(6), 772–781. https://doi.org/10.1002/ana.24951

**Strebel, S., Mader, L., Sláma, T., Waespe, N., Weiss, A., Parfitt, R., am Zehnhoff-Dinnesen, A., Kompis, M., von der Weid, N. X., Ansar, M., & Kuehni, C. E.** (2022). Severity of hearing loss after platinum chemotherapy in childhood cancer survivors. *Pediatric Blood & Cancer, 69*(9). https://doi.org/10.1002/pbc.29755

**Van Hecke, R., Van Rompaey, V., Wuyts, F. L., Leyssens, L., & Maes, L.** (2017). Systemic aminoglycosides-induced vestibulotoxicity in humans. *Ear and Hearing, 38*(6), 653–662. https://doi.org/10.1097/AUD.0000000000000458

**Waissbluth, S., Chuang, A., Del Valle, Á., & Cordova, M.** (2018). Long term platinum-induced ototoxicity in pediatric patients. *International Journal of Pediatric Otorhinolaryngology, 107*, 75–79. https://doi.org/10.1016/j.ijporl.2018.01.028

**Waissbluth, S., Peleva, E., & Daniel, S. J.** (2017). Platinum-induced ototoxicity: A review of prevailing ototoxicity criteria. *European Archives of Oto-Rhino-Laryngology, 274*(3), 1187–1196. https://doi.org/10.1007/s00405-016-4117-z

**Watkin, P., McCann, D., Law, C., Mullee, M., Petrou, S., Stevenson, J., Worsforld, S., Yuen, H. M., & Kennedy, C.** (2007). Language ability in children with permanent hearing impairment: The influence of early management and family participation. *Pediatrics, 120*(3), e694–e701. https://doi.org/10.1542/peds.2006-2116

**World Health Organization.** (2021). *World report on hearing*. https://www.who.int/publications/i/item/9789240020481

**Yoshinago-Itano, C.** (2000). Successful outcomes for deaf and hard-of-hearing children. *Seminars in Hearing, 21*(4), 309–326. https://doi.org/10.1055/s-2000-13462