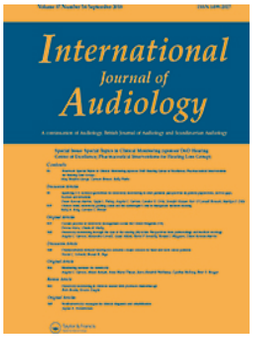

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Discussion Article

Applying U.S. national guidelines for ototoxicity monitoring in adult patients: perspectives on patient populations, service gaps, barriers and solutions

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Abstract

Objectives: To promote establishment of effective ototoxicity monitoring programs (OMPs), this report reviews the U.S. national audiology guidelines in relation to ''real world'' OMP application. Background is provided on the mechanisms, risks and clinical presentation of hearing loss associated with major classes of ototoxic medications. *Design*: This is a non-systematic review using PubMed, national and international agency websites, personal communications between ototoxicity experts, and results of unpublished research. Examples are provided of OMPs in various healthcare settings within the U.S. civilian sector, Department of Defense (DoD), and Department of Veterans Affairs (VA). *Study Sample*: The five OMPs compared in this report represent a convenience sample of the programs with which the authors are affiliated. Their opinions were elicited via two semi-structured teleconferences on barriers and facilitators of OMP, followed by a self-administered questionnaire on OMP characteristics and practices, with responses synthesized herein. Preliminary results are provided from an ongoing VA clinical trial at one of these OMP sites. Participants were 40 VA patients who received cisplatin chemotherapy in 2014–2017. The study arms contrast access to care for OMP delivered on the treatment unit versus usual care as provided in the audiology clinic. *Results*: Protocols of the OMPs examined varied, reflecting their diverse settings. Service delivery concerns included baseline tests missed or completed after the initial treatment, and monitoring tests done infrequently or only after cessation of treatment. Perceived barriers involved logistics related to accessing and testing patients, such as a lack of processes to help patients enter programs, patients' time and scheduling constraints, and inconvenient audiology clinic locations. Use of abbreviated or screening methods facilitated monitoring. *Conclusions*: The most effective OMPs integrated audiological management into care pathways of the clinical specialties that prescribe ototoxic medications. More OMP guidance is needed to inform evaluation schedules, outcome reporting, and determination of actionable ototoxic changes. Guidance is also lacking on the use of hearing conservation approaches suitable for the mass testing needed to support large-scale OMP efforts. Guideline adherence might improve with formal endorsement from organizations governing the medical specialty stakeholders in OMP such as oncologists, pulmonologists, infectious disease specialists, ototolaryngologists and pharmacists.

Key Words: Otoxicity, ototoxicity monitoring, hearing loss, conditions/pathology/disorders, hearing conservation/hearing loss prevention, medical audiology/pharmacology, tele-audiology/tele-health

Introduction

Platinum-based cancer chemotherapeutics and certain aminoglycoside antibacterial therapies can cause inner ear damage called *ototoxicity*, a leading cause of acquired hearing loss worldwide (Paken et al. 2016). Ototoxic agents tend to differentially affect the cochlear (i.e. hearing) and/or vestibular (i.e. balance) systems and, depending on the drug, can impair renal, hepatic, neural and blood marrow activity. According to the American Speech-Language-

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Abbreviations

AAA	American Academy of Audiology
ABR	Auditory Brainstem Response
AIDS	Aquired Immune Deficiency Syndrome
ASHA	American Speech-Language-Hearing Association
COG	Children's Oncology Group
CTCAE	Common Terminology Criteria for Adverse Events
CF	Cystic Fibrosis
CFIR	Consolidated Framework for Implementation Research
DoD	Department of Defence
FM	Frequency modulation personal amplification system
GLOBOCAN	the GLOBOCAN project, a joint project from the International Agency for Research on Cancer and World Health Organisation to provide global cancer statistics
HCE	Hearing Center of Excellence
MET	mechano-electrical transduction channels
MRSA	methicillin-resistant Staphylococcus aureus
NCRAR	VA National Center for Rehabilitative Auditory Research
NSAIDs	non-steroidal anti-inflammatory drugs
NTM	Non-tuberculosis Microbacteria
OMP	Ototoxicity monitoring programme
U.S.	United States
SRO	Sensitivity Range for Ototoxicity
VA	Veterans Affairs

Hearing Association (ASHA) guidelines, prospective hearing assessments can motivate treatment changes to reduce the progression of ototoxic damage, and rehabilitation to mitigate some of its functional impacts (ASHA 1994). Yet, monitoring during drug treatment is an inconsistent practice for adult oncology and infectious disease patients at risk for ototoxicity. Further, there is substantial variation in monitoring methods and outcome reporting among clinics that provide ototoxicity monitoring (Vasquez and Mattucci 2003; Konrad-Martin et al. 2010; Prescott 2014; Theunissen et al. 2015; Egelund, Fennelly, and Peloquin 2015; Garinis et al. 2017a). This is striking when one considers that the U.S. national audiology guidelines promoting ototoxicity monitoring programmes (OMPs) have been in place for over two decades with more recent guidelines confirming and expanding details of the approach for adult and paediatric populations (ASHA 1994; Children's Oncology Group [COG] 2008; American Academy of Audiology [AAA] 2009). The present report reviews the mechanisms, risks and clinical presentation of hearing loss associated with major ototoxic drug classes. The U.S. national audiology guidelines for monitoring adult patients receiving ototoxic drug treatments are then reviewed and examined within the context of ''real world'' OMP application among five healthcare settings spanning the U.S. civilian sector, Department of Defence (DoD) and Department of Veterans Affairs (VA). Perspectives provided on OMP service gaps, barriers and solutions are the views of the authors who are audiologists or audiology clinician–researchers. The overall goal is to increase understanding of the factors that influence effective OMP provision in order to foster development of new programmes, achieve improved parity across programmes and motivate future refinement of the U.S. national guidelines pertaining to ototoxicity monitoring in adult patients.

The case for prospective ototoxicity monitoring

Early detection and proactive management of hearing loss are the primary rationale for OMPs, recognising that hearing change is frequently overlooked by the impacted individual and, as a result, under-treated by health professionals, particularly for patients coping with a life-threatening disease (Durrant, Palmer, and Lunner 2005). In fact, the vast majority of hearing impaired people do not seek help for their hearing loss (National Academies of Sciences, Engineering, and Medicine 2016). Unfortunately, untreated hearing loss degrades interpersonal relationships and social–emotional well-being (Mulrow et al. 1990; Kochkin and Rogin 2000; Wiley et al. 2000), impedes the understanding of health and treatment-related information (Dalton et al. 2003; Amalraj et al. 2009) and is associated with increased hospital readmissions (Genther et al. 2015). Attending to hearing loss is therefore especially important in times of critical illness.

Prospective ototoxicity monitoring and related education and counselling can help patients appreciate the impacts on daily living of pre-existing hearing loss and worsened hearing. Such an awareness increases the likelihood that a patient will seek aural rehabilitation and use prescribed intervention (Knudsen et al. 2010; Saunders et al. 2013; Laplante-Levesque et al. 2015). Rehabilitative interventions generally involve the prescription of hearing aids; however, progressive treatment-related hearing changes can pose a challenge and some patients may elect to pursue hearing aids only after treatment is behind them. This highlights the need for appropriate referrals to avoid a loss to follow-up. It also increases the importance of the many other forms of aural rehabilitation. These can include instruction on coping and communication strategies, training to optimise use of auditory and visual speech cues and use of assistive listening devices (frequency modulated (FM) systems, television and phone amplification). Rehabilitation of hearing loss, particularly when comorbid with another illness, requires a high level of patient-centered care made possible by combining a full range of solutions (National Academies of Sciences, Engineering, and Medicine, 2016).

Beyond ototoxicity monitoring for the purpose of rehabilitation are considerations for informing drug treatment decisions. When ototoxicity is identified prospectively, the drug regimen can be altered to prevent further damage from occurring if it is medically reasonable to do so. Ototoxicity is more likely to be dose-limiting when tumour response to the drug has been good, ototoxicity presents as one of several toxic events impacting a patient's overall health, the patient reports hearing changes are impacting daily living and/or the loss becomes severe (Beilefeld and Henderson 2011; Garinis et al. 2017a). Established OMPs essentially facilitate the transition from a reactive to a proactive hearing health promotion culture, creating an opportunity for signs of ototoxicity to be identified before they become debilitating as well as for timely rehabilitation of unavoidable and/or pre-existing hearing loss.

Clinical presentation of ototoxicity

Major classes of common ototoxic drugs

Many pharmacological agents have the potential to cause ototoxicity, including platinum coordination complexes, aminoglycoside

antibiotics, loop diuretics and non-steroidal anti-inflammatory drugs (NSAIDs). A lack of direct auditory and vestibular system monitoring, interactions and potentially synergistic effects with concurrent radiotherapy and other ototoxic exposures cloud exact assessment of the risk of ototoxicity. Understanding the effects of ototoxic treatments on auditory and vestibular function may be also hampered by limitations in clinical measurements for subtle, preclinical inner ear changes (Van der Walt 2002).

Cisplatin is generally considered the most ototoxic compound in common clinical use, and the second generation platin drug, carboplatin, can also produce potent cochleotoxic effects at high cumulative doses (Obermair et al. 1998; Hartmann and Lipp 2003; Beilefeld and Henderson 2011). Ototoxic hearing loss as a side effect of oxaliplatin, a third derivative, appears to be less common with only a few individual case studies reported in the literature (Malhotra et al. 2010; Vietor and George, 2012; Oh et al. 2013; Hijri et al. 2014; Dreisbach et al. 2017). Additionally, vestibular system damage from platinum-based drugs may cause severe balance problems characterised by disequilibrium, dizziness and/or oscillopsia (difficulty fixing an image in the plane of view while moving) (Cass 1991; COG 2008; AAA 2009; Handelsman 2017).

Other highly cochleotoxic therapies involve certain aminoglycoside antibiotics, such as amikacin, tobramycin or streptomycin, which are frequently distributed in the U.S. for severe bacterial infections due to their effectiveness and broad-spectrum specificity toward various organisms. Aminoglycosides may also selectively target inner ear structures critical for vestibular function, resulting in balance disturbances in the absence of hearing loss. In some clinical cases, the aminoglycoside gentamicin is injected intratympanically in the ears of patients with Meniere's disease to ablate vestibular hair cells for therapeutic effect (Minor 1999). The incidence of vestibulotoxicity across different clinical populations is highly variable, due to similar drug and patient factors listed above for ototoxic hearing loss (Schwade 2000).

Largely reversible effects of ototoxicity have been associated with loop diuretics (such as furosemide), azines, NSAIDS and the glycopeptide antibiotic, vancomycin (Black, Gianna-Poulin, and Pesznecker 2001; also see review by Lonsbury-Martin and Martin 2007). More research is needed to understand the concomitant effects of these drugs with only minimal ototoxic potential when given alone, which can act synergistically when given with another ototoxin (AAA 2009). In the meantime, heightened clinical awareness of this potential is critical as many patients receive drugs for multiple comorbid conditions.

Pathophysiology and mechanisms of action

Aminoglycosides are thought to cross the blood-labyrinth barrier into cochlear tissues and fluids (Tran Ba Huy, Bernard, and Schacht 1986; Li and Steyger 2011), and enter hair cells through the mechano-electrical transduction (MET) channels (Marcotti, van Netten, and Kros 2005; Alharazneh et al. 2011). The MET channel is mechanically-gated by tip links between adjacent stereocilia (Kazmierczak et al. 2007), and is stretch-activated by stereociliary motion due to fluid pressure waves introduced into the cochlea by the motion of the stapes. Other mechanisms by which aminoglycosides may enter the hair cells include endocytosis (Hashino and Shero 1995), and infiltration through other aminoglycoside-permeant cation channels expressed by hair cells (Karasawa et al. 2008; Stepanyan et al. 2011). Serum concentrations of the drug are monitored to ensure patients are not being overdosed; however, these are only weakly related to known toxicities. Generally, nephrotoxicity raises the greatest clinical concern and thus kidney function is systematically monitored.

In comparison to aminoglycosides, the mechanism of cisplatin-induced ototoxicity has been more challenging to understand, partly due to the unique structure of the molecule. Preclinical studies have shown that cisplatin, on average has a distinctive molecular mass and potentially larger diameter than aminoglycosides, which suggests trafficking through MET channels is not the primary method of entering cochlear hair cells. Multiple trafficking routes, such as non-MET channels, might be responsible for cisplatin ototoxicity (Hilder and Hill 2009; Thomas et al. 2013; Karasawa and Steyger 2015). Cisplatin's unique molecular structure also accounts for a slow clearance rate of the drug in the cochlea (van Ruijven et al. 2005).

There are two main hypothesised mechanisms of ototoxic damage. One is that aminoglycosides and platin-based drugs can damage the synapse between the cochlear hair cell and neural afferents that may lead to degeneration of spiral ganglion neurons. The other possibility is the creation of reactive oxygen species that can damage inner ear cells and tissues. There is some support for the former hypothesis in animal models that have shown attenuation of this effect using antioxidants (Borse et al. 2017; Li et al. 2016). The latter hypothesis is comparatively well established in the literature.

Within the cochlea, aminoglycosides and platinum-based drugs cause hair cell and neuronal damage (Laurell et al. 2000; Lee et al. 2003; Riedemann et al. 2008; Arora et al. 2009; Hellberg et al. 2009; Mukherjea and Rybak 2011). The pattern of hair cell destruction begins with the outer hair cells, progressing in a lateral to medial direction starting at the cochlear base (high frequency coded), moving toward the apex (low frequency coded) with continued treatment (Schweitzer 1993). The sensorineural hearing loss that arises generally begins in the high frequencies, increases in severity and spreads to lower frequencies with increasing cumulative dose (Fee 1980; Wright and Schaefer 1982; Blakley and Myers 1993; Schuknecht and Gacek 1993; Fausti et al. 1999; Knight et al. 2007; Hellberg et al. 2009). Compared with cisplatin, carboplatin is thought to produce a greater mix of outer and inner hair cell loss and oxaliplatin is thought to be more toxic to the auditory nerve than the cochlear hair cells with reduced pharmacokinetic uptake in the cochlea (Ding, Allman, and Salvi 2012; Lobarinas, Salvi, and Ding 2013).

Treatment with cranial irradiation in addition to cisplatin appears to add to the progressive degeneration of the cochlea (Jereczek-Fossa et al. 2003; Kolinsky et al. 2010; Bass and Bhagat 2014). Exposure to noise increases the ototoxic effects of both cisplatin and aminoglycosides (Gratton et al. 1990; ASHA 1994; AAA 2009; Li et al. 2015). There also appear to be powerful potentiating effects of systemic inflammatory processes, which are still under investigation (Cross et al. 2015; Koo et al. 2015). Finally, it is important to know that the ototoxic effects of both cisplatin and aminoglycosides can progress even after treatment has ended (Tono et al. 2001; Bertolini et al. 2004; Kolinsky et al. 2010; Huth, Ricci, and Cheng 2011). Several foundational reviews on the topics covered in this section can be found in Chapters 10–13 in the 2007 book entitled, ''Pharmacology and Ototoxicity for Audiologists'', edited by Kathleen Campbell, and in AAA (2009).

Ototoxicity incidence among cancer patients

Worldwide, an estimated 19.3 million new cancer cases will be identified each year by 2025, an increase from 14.1 million in 2012

according to GLOBOCAN (Ferlay et al. 2013). Many of the most commonly occurring cancers are related to physical inactivity, poor nutrition, alcohol and tobacco use, infectious disease and/or sun exposure and as populations age, cancer prevalence increases. Regardless of economic development, 42% of all cancers among men are lung, prostate and colorectal cancer while, among women, 43% of cancers are breast, colorectal or lung cancers, and of these, lung, breast and colorectal account for the most commonly occurring cancers overall (Torre et al. 2015). According to the American Cancer Society, an estimated 1.6 million people in the U.S. will be newly diagnosed this year and most will live following their diagnosis and treatment (American Cancer Society [ACS] 2016). The 5-year relative survival rate for all cancers (2005–2011) in the U.S. is now 69%, up from 49% in the 1970s (American Cancer Society [ACS] 2016). Platinum-based drugs are the antineoplastic chemotherapeutic agents of choice for the treatment of many adult cancers (e.g. head and neck, lung, germ cell, colorectal and bladder). For example, cisplatin's effectiveness as an antitumor agent is well established from tumour response rates as high as 90% for head and neck tumours (Weaver et al. 1982) to long-term survival rates at 70–80% for testicular cancer (Priest and Vogelzang 1991).

Hearing loss from cisplatin and carboplatin is typically permanent and bilateral, but not necessarily symmetric or immediate, and can occur with or without tinnitus. It is difficult to predict how ototoxicity will manifest for any particular patient due to the wide range of patient characteristics and treatment regimens that are necessarily involved, and the large variety of ototoxicity metrics used in the literature. For example, Bokemeyer et al. (1998) found persistent ototoxic symptom prevalence of tinnitus (59%), hearing loss (18%) or both (23%) among fairly young patients (mean age 31 years; range 21–53 years) with cisplatin used to treat testicular cancer. Frisina et al. (2016) reported on a retrospective medical record review of ototoxicity in a cohort of 488 young men (median age 31 years; range 15–49 years) with germ cell cancer. The majority (66%) were diagnosed in the early stages of disease (I and II) and all were given cisplatin (median cumulative dose: 400 mg/m^2). None received concurrent treatments of radiation or the chemotherapy agent vincristine. Pre-treatment audiograms were not available. Post-treatment audiograms obtained on this cohort 1–30 years (median 4.5 years) following treatment were compared to published normative patterns in quartiles of hearing thresholds among males by age at 4, 6 and 8 kHz (Engdahl et al. 2005), the conventionally tested frequencies most likely to show ototoxicity. Only 20% of this cohort were found to have retained normal hearing post-treatment ($\leq$20 dB HL). As expected, post-exposure hearing loss was strongly correlated with increasing age ($R = 0.79$). Subjectively, up to 30% reported decreased hearing and 40% reported tinnitus. After adjusting for age, a cumulative dose of >300 mg/m^2 was found to be associated with higher quartile hearing loss in the 4–8 kHz range compared to those with doses $\leq$300 mg/m^2. Additionally, for every 100 mg/m^2 of cumulative dose, a 3.2 dB increase in hearing loss (4–12 kHz) was observed after age adjustment.

Among patients with head and neck cancers, Theunissen et al. (2015) systematically reviewed 2507 publications using the keywords of ''radiotherapy'', ''ototoxicity'' and ''head and neck squamous cell cancer''. Hearing was measured prospectively in most studies using a variety of approaches. Results showed hearing loss occurs with radiation alone, but the incidence of hearing loss was higher among those with chemoradiation in whom the risk was associated with cochlear radiation dose, cumulative cisplatin dose, follow-up time, age and baseline hearing results. They found that those patients with poorer hearing at baseline ended up with worse hearing after treatment but that the amount of hearing change was greatest for those with better hearing. Similarly, older age was associated with increased incidence of hearing loss; however, younger patients had larger hearing changes (Zuur et al. 2007, 2009). The ototoxicity criteria used was also an influencing factor. By definition the ASHA-significant hearing loss criteria (ASHA 1994) are more sensitive than ototoxic adverse events identified using the Common Terminology Criteria for Adverse Events (CTCAE) grading scale designed for cancer clinical trials, particularly when ultra-high frequencies are included. Ototoxicity incidence varied from 0% to 43% with radiation treatment alone and from 17% to 88% for chemoradiation among the 21 included studies. The highest incidence was found for a study by Zuur et al. (2007) of chemoradiation effects using bolus dosing (three courses at 100 mg/m^2) and ultra-high frequency audiometry (>8 kHz) graded by CTCAE v3.0 (Common Terminology for Criteria for Adverse Events [CTCAE] 2006).

Ototoxicity incidence among patients with severe infections

While many infectious diseases are controlled or eradicated in some parts of the world, in areas where they persist, they cause serious injury and death to millions. Approximately half of all deaths caused by infectious disease can be attributed to just three diseases: tuberculosis, malaria and aquired immune deficicency syndrome (AIDS) (www.infoplease.com/ipa/A0903696.html). In the US, broad spectrum aminoglycoside antibiotics are sometimes used to treat tuberculosis, endocarditis and sepsis. Additionally, drugs with potential for ototoxicity are used routinely in patients with cystic fibrosis (CF). Among this group, ototoxic drugs are administered by injection, intravenously and sometimes as less-ototoxic inhaled regimens for mycobacterial infections including those associated with bronchiectasis with chronic obstructive pulmonary diseases, chronic bronchitis, tuberculosis and emphysema (Drobnic et al. 2005; Orriols et al. 1999). Aminoglycosides are also routinely used to manage severe pulmonary infections caused by pseudomonas aureus or methicillin-resistant *Staphylococcus aureus* (MRSA) secondary to CF or compromised immune system function. In the developing world, tuberculosis mycobacterium is a significant problem and, increasingly, is an emerging problem in the developed world.

Although the treatment efficacy of these drugs is good, there is a risk of permanent hearing loss and balance disorder in as many as 20% of patients receiving aminoglycosides for extended periods of time (Forge and Schacht 2000). However, the incidence of hearing loss varies dramatically across studies and age groups. The variability among studies of patients with CF is likely due to differences in the actual amount of drug given, and similar to studies investigating cisplatin, depends on patient factors like hearing status, patient age, treatment duration, plasma drug levels, renal status, diabetes, sex, mitochondrial mutations, infection/inflammatory status and concomitant illnesses that might place an individual patient at higher risk of ototoxicity-induced hearing loss (Garinis et al. 2017b).

There is considerable variability among studies in the reported prevalence of hearing loss from aminoglycoside treatment in adult patients with CF, ranging from 0% to 56%, compared to prevalence of only 11–18% in age-matched groups of adults without a history of CF or aminoglycoside exposure (Al-Malky et al. 2015; Garinis et al. 2017b). Notably, patients with CF tend to be young with a life

expectancy of 37 years of age (Cystic Fibrosis Foundation [CFF] 2017). Therefore the incidence of sensorineural hearing loss in these patients is substantial compared to non-CF patients of the same age. Importantly, the co-administration of other drugs may also induce or increase the risk of ototoxicity including azithromycin (a macrolide), vancomycin (a glycopeptide) and furosemide (a loop diuretic), as described above. It is difficult to estimate the severity of ototoxic hearing changes in patients with CF because treatments often begin in childhood, confounding baseline hearing data in research participants studied as adults. A recent study by Garinis et al. (2017b) describes the audiometric profiles for 81 adult patients with CF with a wide cumulative range of lifetime antibiotic dosing. Consistent with the literature, hearing profiles vary widely for each dosing range examined, suggesting a genetic component to ototoxicity susceptibility (Conrad et al. 2008). The results also showed that long-term, regular exposure to intravenous aminoglycoside treatments and higher overall dosing are associated with increased risk of hearing loss. Interestingly, the variability within each dosing group shows that some patients, regardless of dosing had no hearing loss. Genetic variants that confer protection from ototoxicity may play a role in these cases (Tang et al. 2002; Garinis et al. 2017b).

U.S. national audiology guidelines pertaining to ototoxicity monitoring

In the US, there are two main governing bodies for audiologists, the American Speech-Language-Hearing Association (ASHA) and the American Academy of Audiology (AAA), that standardise specific aspects of professional practice, provide clinical certification and professional oversight. These groups have provided the primary guidance documents that serve as the foundation for OMPs nationally. They are the: ASHA Guidelines for the Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy (ASHA 1994) and the AAA Position Statement and Clinical Practice Guidelines on Ototoxicity Monitoring (AAA 2009). If applied effectively, these documents allow for standardisation of basic aspects of OMP provision and serve as a basis from which to develop more specific clinical objectives and protocols.

These guidelines were drafted prior to recent reports of cochlear neural degradation as a potential contributor to impaired temporal processing and speech understanding ability (as reviewed in Kujawa and Liberman 2015). Measures of the temporal fidelity of the group auditory nerve fibre response (high level auditory brainstem response [ABR], frequency following response [FFR]) as well as more sensitive speech understanding measures are being investigated for use in older and noise impaired individuals, and may impact clinical definitions of ototoxicity and other aspects of OMP provision. These issues are beyond the scope of this report, as are issues related to ototoxic-induced tinnitus or balance disorders for which monitoring is not fully addressed in current guidelines.

General goals of the OMP

ASHA provides a set of broad goals for monitoring cochleotoxicity. These include:

- Use a standard definition of an ototoxic hearing shift;
- Conduct pre-treatment counselling regarding potential cochleotoxic effects;
- Include a baseline evaluation preferably before but at least early in treatment;
- Perform monitoring visits at sufficient intervals to document hearing loss progression or fluctuations; and
- Perform a post-treatment evaluation followed by longer term monitoring based on the post-treatment outcomes.

Specific recommendations for when and how to monitor

The ASHA (1994) appendix provides what is described as an ''ideal schedule for early detection'' of cochleotoxicity, recognising several potential pitfalls of the approach, namely, that it may not always be practical to perform the testing in a sound booth, to use definitive diagnostic measures each visit, or for all testing to be performed by an audiologist. With those caveats, the ideal schedule is this:

- Baseline tests are recommended to occur no later than 24 h after initial cisplatin treatment and monitoring is recommended to precede each cisplatin subsequent dose.
- Baseline tests after administration of any aminoglycoside should occur no later than 72 h and monitoring should occur every 2–3 days or at least weekly during treatment.
- Monitoring should also ensue if hearing changes are noticed by the patient or care team.
- After cessation of drug treatment, the test schedule should include an immediate post-treatment test and follow-up at 3 and 6 months post-treatment.
- Finally, if a hearing shift is detected at any time, the standard advises a validating retest and subsequent testing at least weekly until the hearing has stabilised.

The ASHA (1994) appendix provides these recommendations for dealing with the potential pitfalls of this approach:

- Patients should be tested at bedside (or chairside in the oncology treatment unit) if necessary, although an audiometric sound room (booth) is considered the ideal test environment.
- Those patients with limited responsiveness should be tested using a shortened screening protocol including only those measures that significantly contribute to the OMP's goal of detecting threshold changes (i.e. air conduction (AC) conventional audiogram or a limited range of frequencies near an individual patient's high frequency hearing limit called the sensitive range for ototoxicity [SRO] described below).
- If the recommended test schedules ''cannot be met or maintained, monitoring of pure tone sensitivity should be conducted as often as possible, and interim testing should be done if the patient experiences any symptoms of cochleotoxicity'' (ASHA 1994, appendix p. 16).

In summary, these specific recommendations for when and how to monitor depend on exposure drug class (albeit only broadly as platinum drugs versus aminoglycoside antibiotics), patient report and the ability of the patient to tolerate and accurately perform behavioural testing.

Baseline test components

There is consensus that baseline testing should be as comprehensive as possible so that patients can serve as their own control to identify changes on tests done at a later date (ASHA 1994; AAA 2009).

However, obtaining a comprehensive baseline test prior to drug treatment can be extremely difficult, as discussed in the section below on OMP service gaps. Recommended tests include bilateral pure tone AC threshold from 0.25 to 8 kHz (including the half-octaves 3 and 6 kHz). Retesting is advised to establish reliability within ±5 dB along with otoscopy and immittance. Bone-conduction testing is recommended to document any conductive component and identify the potential for hearing fluctuation due to ototoxicity. To enhance test sensitivity, high frequency (>8 kHz) AC testing, including the SRO is highly recommended for its early detection of initial hearing changes and, finally, recording of otoacoustic emissions (OAEs) is advocated for its potential use as an objective ototoxicity measure should the patient become too ill to provide a reliable hearing test. Speech reception thresholds and word recognition are also recommended as substantial changes in speech understanding would provide strong motivation for treatment change.

Monitor test components

When it comes to hearing monitoring during drug treatment, guidelines describe a comprehensive hearing evaluation (essentially the baseline test battery described above is repeated). Guidance indicates that, should evidence of ototoxic damage be found, AC thresholds at the conventionally tested frequencies (after ruling out any conductive component to the loss) and speech recognition data ideally would be used for treatment decisions (AAA 2009). Because data need to be communicated to the patient–provider team before the next treatment to inform treatment decisions (i.e. to be actionable), monitoring occurs with the added pressure of time. Thus, ASHA and AAA guidelines describe a high-frequency AC-based screening protocol designed to sensitise threshold measures and allow time for follow-up testing. This patient-specific SRO is shown to identify the vast majority of initial ototoxic changes in adults (Vaughan et al. 2002; Fausti et al. 2003), although it is important to remember that exceptions can occur. The SRO method operationally-defines the highest audible frequency as the frequency at which the patient can reliably detect a tone of 100 dB SPL or less. Thresholds from this highest audible frequency and the next six frequencies below (which have thresholds better than 100 dB SPL) are measured at one-sixth octave interval steps and constitute the SRO. At most treatment intervals, only AC thresholds at these frequencies are screened and unless they reveal a hearing shift (or the patient/provider team reports signs of ototoxicity), no additional testing is completed.

Both sets of guidelines describe non-responsive inpatients as needing testing using objective measures. OAE testing is recommended for its speed and sensitivity as a potential screening measure in all patients. Further, AAA (2009) advocates the use of distortion-product OAE (DPOAE) testing over other objective measures, such as transient evoked OAEs (TEOAEs) and ABR testing, because of its ability to assess higher frequencies (compared with clinical TEOAE systems) and the fact that OAEs are generated by the structures (outer hair cells) most likely to show early ototoxic damage.

Guidance for specific OAE screening protocols is lacking; however, approaches are discussed elsewhere (Konrad-Martin et al. 2012, 2016) where a two-pronged approach has been suggested. First, the clinical protocols available with most standard OAE measurement equipment should be used to obtain a gross assessment of cochlear function over a broad frequency range. This has the advantage of providing fairly consistent data across treatment centres. Second, a more detailed investigation of stimulus frequencies and/or levels should be obtained. This can help substantially with test interpretation for example by revealing fine structure and broader patterns of change. It can also sensitise measurements if lower levels are included and/or high frequencies are emphasised (where changes associated with drug treatment are most common). An example is to target the highest one octave range where DPOAEs are measureable at baseline for obtaining responses to a series of levels from about 65–35 dB SPL for L2 (Reavis et al. 2011) or to fine stimulus-frequency steps of 1/12th to 1/24th octave (Dille et al. 2010; McMillan, Konrad-Martin, and Dille 2012).

Behavioural SRO can be conducted using sound-attenuating headphones and OAE testing with deeply inserted canal probes to help address ambient noise problems, which tend to be greater at lower-frequencies (see Figure 3 in Brungart et al. 2017). Thus, these measures might be especially useful for testing outpatients in the oncology unit, or inpatients, sometimes isolated with infectious disease, who cannot easily leave the hospital floor to travel to the audiology clinic. Attributing changes in either of these screening measures to ototoxicity requires confirmation of normal middle ear status using a tympanometer. Identification of middle ear dysfunction and/or failure on an ototoxicity screening measure is used to triage patients for more in depth follow-up testing. Depending on the screening results, additional testing could determine the extent that newly acquired hearing loss has begun to impact hearing thresholds at speech frequencies, erode functional speech measures and sort out conductive from cochlear components using bone conduction. Generally, once screening reveals hearing shifts within the conventional frequency range, OMP goals shift from early detection to AC threshold surveillance of the standard audiometric frequencies due to their importance for decisions regarding rehabilitation and/or drug treatment changes.

Definition of an ototoxic threshold shift

The following set of audiometric criteria for ototoxic hearing threshold shifts were proposed in the ASHA (1994) guidelines and reinforced by AAA (2009): a 20 dB shift at any single frequency, a 10 dB shift at two adjacent test frequencies and a loss of response at three adjacent high test frequencies where earlier responses were obtained close to the audiometer output limits. Shifts meeting any of these criteria must be confirmed by repeat testing within 24 h. These criteria were designed to identify small shifts in hearing, to provide a window of opportunity for counselling and, potentially, treatment changes to occur before damage becomes debilitating. Acceptable false positive rates have been demonstrated for these criteria in numerous studies using control samples in whom auditory function is presumed stable. These studies have included assessment of false positives occurring for conventional audiometric thresholds (meaning the octave intervals through 8 kHz), ultra-high thresholds and SRO thresholds, and for frequencies tested in 1/2-, 1/3- and 1/6-octave steps (which could span the conventional and ultra-high range) (Frank and Dreisbach 1991; Frank 2001; Konrad-Martin et al. 2010). Most were conducted in young, healthy research participants, however, to obtain false positive rates representative of sick patients, the control sample in one of these studies was comprised of inpatients obtaining care primarily at VA medical centres (Konrad-Martin et al. 2010). For the interested reader, Figure 5 in Konrad-Martin et al. (2010) contrasts percentages of

patients with a threshold shift of varying magnitudes at one, two or three adjacent frequencies with results plotted separately for those receiving a control drug versus an ototoxic medication.

Considerations for standardising the measurement and reporting of ototoxic events

A recent meta-analysis undertaken to assess the severity of cisplatin ototoxicity in patients with head and neck cancer could not draw definitive conclusions, citing a lack of comparable monitoring test time points and consistent pre- and post-treatment audiologic outcome measures as a major clinical problem (Theunissen et al. 2014). Additionally, a recent survey found that only 26% of adult CF clinics in the U.S. include audiometry to monitor adverse effects of aminoglycosides (Prescott 2014). Guidelines for the treatment of multiple drug-resistant tuberculosis (MDR-TB) provide no definitions or monitoring strategies for otoxocity monitoring (Abbara et al. 2015), although some protocols have been suggested for patients with non-tuberculous mycobacterial (NTM) diseases (Egelund, Fennelly, and Peloquin 2015). Standardisation of the measurement and reporting of ototoxic events is an important interdisciplinary topic of discussion that needs to occur.

Based on their review of the literature, Theunissen et al. (2014) favoured reporting ototoxicity severity using a pure tone average (PTA) of 1–4 kHz to signify the potential impact on speech intelligibility. They supported also reporting a separate metric sensitive to early changes. Their suggestion of using a fixed set of high frequencies (e.g. PTA of 8, 10 and 12.5 kHz) could be problematic because patients with poor pre-treatment hearing will vary in their high frequency hearing limit. This has lead some researchers to advocate use of the patient-specific SRO (Fausti et al. 1999) which tailors the tested frequency range to the patients pre-treatment hearing. Additionally, although ASHA guidelines provide a sensitive metric of ototoxic hearing change, there remains a lack of consensus on how to define a clinically important – and thus medically actionable – ototoxic hearing change in various populations (Brewer and King 2017). Clearly, patient-centered clinical decision-making requires patient education and input. At a minimum, the magnitude of the shift from baseline (the dB change) combined with a patient's pre-treatment hearing level could be used to assess the potential impact of ototoxic-induced hearing loss on communication. Results from additional tests beyond the audiogram (e.g. speech understanding tests) can be helpful for substantiating the need for intervention (ASHA 1994; AAA 2009; Brewer and King 2017).

Do U.S. national guidelines offer sufficient guidance?

Examples of OMP Service Gaps, Barriers and Facilitators in a Variety of Healthcare Settings.

Understanding the many clinical settings in which the U.S. national ototoxicity monitoring guidelines were designed to be applied provides insight into their utility for OMP provision and is crucial in the development of an efficacious programme (ASHA 1994; AAA 2009; Damschroder et al. 2009). Table 1 provides general characteristics of five OMPs including the targeted patient populations, how patients are identified and scheduled for testing, and where the testing takes place. Program data provided in this report were elicited via two semi-structured teleconferences on barriers and facilitators of OMP, followed by a self-administered questionnaire on OMP characteristics and practices. Once synthesised and tabulated by the first author, each respondent edited the text and tables and provided additional clarifying information. The authors were self-selected from among participants in a Department of Defence (DoD) national working group on ototoxicity monitoring and/or were suggested by the Editors of this special issue.

As seen in Table 1, these programmes target several distinct populations for monitoring at a variety of healthcare settings within the U.S. civilian sector (Mayo Clinic in Rochester, MN; Oregon Health & Science University [OHSU CF Clinic] in Portland, OR; Yale University in New Haven, CT), and public sector (Department of Veterans Affairs [VA Portland] in Portland, OR; DoD Walter Reed National Military Medical Center [Walter Reed] in Bethesda, MD). Outpatient settings predominated for both cancer care and infectious disease treatment, although most programmes included inpatients among the targeted populations. The OMPs were in various stages ranging from a pre-implementation plan to house an OMP within a hospital's CF clinic (OHSU CF Clinic) to a well-established OMP (Walter Reed). Yale University's large-scale programme was in the implementation phase. Mayo Clinic had implemented an OMP for paediatric oncology patients and more recently expanded their programme to include adult medical oncology and infectious disease patients. VA Portland's established programme flexed over recent years based on staffing losses and research study support.

The top service delivery gaps for the OMP programmes examined included patients never entering into the programme or lost to follow-up, baseline tests missed or conducted after the initial treatment and monitoring tests conducted infrequently or only after chemotherapy had concluded. All sites reported similar barriers but programmes were impacted to varying degrees. The specific barriers are as follows:

- Inconsistent referrals
- Scheduling limitations
- Location and space limitations
- Staffing limitations

Walter Reed did not experience these issues as substantial barriers; the OHSU CF Clinic and Yale University viewed them as substantial issues hampering programme implementation; Mayo Clinic and VA Portland viewed them as barriers to sustaining the current level of OMP provision without research support, and to programme expansion to include a wider range of at risk patients.

Inconsistent referrals

Yale University was without a codified cross-specialty programme or systematised referral process to identify patients being placed on an ototoxic drug regimen. They report that patient self-referral and physician referral often occurred after treatment or not at all so that many patients were not entering into the OMP. Further, many patients were lost to follow up after a baseline was obtained. Frequent staffing shifts by oncology and other medical residents in training rendered in services with stakeholder physicians a necessary but insufficient remedy for the problem. Inconsistent patient referrals were considered the greatest problem to overcome in the plan to create an OMP for patients seen at the adult CF Clinic at OHSU. To address the barriers of inconsistent referrals and insufficient lead time prior to treatment, Mayo Clinic and VA Portland reported this was facilitated through participation in

Table 1. Characteristics of the clinical ototoxicity monitoring programmes (OMPs) examined.

	Oregon Health & Science University (OHSU) CF Clinic	*Yale University*	*Mayo Clinic Rochester, MN*	*Veteran's Affairs Portland Health Care System (VA Portland)*	*Walter Reed*
OMP Stage	*Planning*	*Implementation*	*Implementation*	*Established*	*Established*
Facility Type	*Civilian (Clinic Effort)*	*Civilian (Clinic Effort)*	*Civilian (Clinic & Research Effort)*	*Government (Clinic Effort)*	*Government (Clinic Effort)*
Primary Patient Population					
Outpatient	Yes	Yes	Yes	Yes	Yes
Inpatient	No	No	No	No	No
Treatments Targeted					
Cisplatin (including chemoradiation)	No	Yes	Yes	Yes	Yes
Carboplatin (including chemoradiation)	No	Yes	Yes	Yes	Yes
Radiation Alone	No	No	Yes (primarily H/N)	No	Yes (primarily H/N)
AMGs	Yes (IV and inhaled)	No	Yes (IV and inhaled)	Yes (IV)	Yes (IV and inhaled)
Mode of Access to Patients					
Audiologist staffs MTD, TB and/or oncology clinics	Never	Never	Usually	Never[a]	Never
Oncology Referral prior to first treatment	Rarely	Rarely	Usually	Usually for cisplatin[a]	Always
Oncology Referral during treatment	Rarely	Sometimes	Usually	Sometimes	Always
Patient Referral during treatment	Rarely	Rarely	Rarely	Rarely	Rarely
Scheduling					
Audiology clinic responsible	Yes	Yes	Shared with Oncology	Yes	Shared with Oncology
Locations Used for Monitor Tests					
Sound treated booth	Sometimes	Usually	Usually	Usually	Usually
Portable equipment	Usually	Sometimes	Rarely	Rarely	Sometimes

Information is provided regarding the stage of OMP, facility type, aspects of the patient population, how patients are accessed and scheduled and where they are tested. The OMPs ranged from planning and implementation stages, to well-established programmes. Three facilities were civilian health care settings, whereas two were government hospitals. All programmes provided monitoring for any patient by request; however, patients rarely self-referred. Additionally, most sites had only occasional referrals from their physician providers of ototoxic drugs (i.e. from oncology, infections disease or pulmonary medicine). Only one site, Walter Reed, reported consistently obtaining referrals from physician providers in a schedule that supported optimal monitoring. Most facilities targeted only certain patient populations through specific outreach activities [e.g. creating consult templates for use in the medical record, cross-specialty inservices, in some cases, staffing tumour boards, multidisciplinary clinics (MTD) and/or treatment units].

AMG, Aminoglycoside antibiotics; H/N, head and neck cancer; OMP, Ototoxicity Monitoring Program; IV, Intravenous; MTD, Multidisciplinary clinics; TB, Tumour Board Meetings.

[a]The number of referrals at this site increased substantially when MTD and TB clinics began to be staffed as part of an ongoing clinical trial at the VA Portland site (described in Table 4). This is not a task performed by the clinical audiologists at this site.

oncology multidisciplinary team clinics (the stage at which the cancer treatment is determined). This was not considered a long-term solution for programmes with limited staffing given the frequency of meetings and multitude of oncology clinics (e.g. head and neck, lung, bladder) at a given hospital. Mayo Clinic found that regular (monthly or quarterly) involvement in the multidisciplinary team clinics created enough collaboration to permit standing (weekly) participants of multidisciplinary team clinics to alert audiology of patients being considered for an ototoxic treatment. Referrals from pharmacy have also been considered to grow multidisciplinary collaborations, but short lead times were expected with this method meaning that it might not adequately address the scheduling conflicts that prevent timely baseline tests. At the VA Portland site, having consistent referrals was insufficient for getting many of these patients scheduled into the audiology clinic as described below. The Walter Reed audiology department consistently obtained referrals for patients prior to treatment with an ototoxic drug, in part, because the oncology and infectious disease stakeholders were active in most aspects of OMP care coordination.

Other logistical barriers to monitoring (scheduling, staffing, equipment, test location)

Limitations related to the patients' schedules and compliance for audiology visits were considered major barriers to usual care OMP provision at VA Portland, and across most other programmes discussed here. At Yale University, Mayo Clinic and VA Portland, audiology was not co-located with the associated oncology or infectious disease treatment locations. The long walk or patient transport required to reach audiology contributed to difficulties related to the ability of patients to manage their complex medical care coordination demands. OMP counselling and testing is typically interleaved with many other appointments on the day of treatment (e.g. oncology, radiation, speech–language pathology, nutrition, social work), any of which can run late. All programmes needed to use ''creative scheduling'' (often during lunch and before or after audiology clinics' official hours). In contrast to the other sites, Walter Reed had multiple dedicated baseline and monitoring appointments available each day for OMP as well as supervised student support. Other sites were well-equipped for inpatient and outpatient OMP, but reported that OMP is restricted by the number of schedulers, available booths and audiologists. For example, at the time of this writing, Yale had 12 oncology departments providing care in buildings where audiology was not located and five audiologists running full outpatient audiology clinics. Being able to provide OMP support for a 2000 bed hospital (200 bed cancer hospital) in addition to traditional outpatient services was not feasible for comprehensive monitoring. Further, several cancer clinics associated with Yale had opened satellite locations around the state without audiology support. The sheer number of at-risk patients serviced by this hospital system would require a technician-based screening approach similar to those used by hearing conservation and new-born hearing screening programmes, as would system-wide expansion of OMP for Mayo Clinic and the VA. Because data arising from OMPs require review and interpretation by an audiologist, tele-audiology may be the future for many large-scale OMPs once approaches can be refined and validated.

Table 2 provides information on each OMP's objectives including baseline and monitor test schedules, protocols and the criteria used to identify ototoxic hearing shifts. Sites agreed with ASHA (1994) and AAA (2009) guidelines that a comprehensive audiometric evaluation is optimal to obtain for the baseline test, *if the patient can tolerate a complete evaluation as well as if the patient's schedule permits*, and for any subsequent tests that are *designed to focus on rehabilitation*. Sites also unanimously agreed that multiple comprehensive monitor tests were not feasible for many patients, including those considered behaviourally responsive. To be acceptable for the patient, provide timely data for the oncology team and be feasible for audiology staffing, monitor tests could not be labour- or time-intensive. The sites that were able to regularly perform monitoring visits within a target population did so by routinely using abbreviated testing protocols and screening approaches to optimise actionable data and minimise patient fatigue and cost. Tests were dropped from monitor test protocols (including speech testing) that did not directly contribute to the OMP's goal of detecting threshold shifts and early ototoxic damage, and/or were considered taxing to a patient's attention and memory. Additional test components were included only when deemed to be clinically necessary (e.g. when hearing shifts were found or rehabilitation was a focus of the evaluation). Furthermore, sites testing patients who were receiving ototoxic antibiotics or radiation alone, adopted a less frequent monitoring evaluation schedule than that suggested by ASHA (1994) and AAA (2009).

One site (Walter Reed) was able to perform monitoring using behavioural SRO and OAE screening measures in the audiology clinic located adjacent to otolaryngology, pulmonary and infectious disease clinics and in close proximity to the centre's outpatient oncology clinics. VA Portland, Mayo Clinic and Yale University frequently used an abbreviated monitoring protocol (otoscopy, tympanometry, AC thresholds in conventional and ultra-high frequencies). At VA Portland, monitor tests were primarily conducted in a clinic sound booth. At Mayo Clinic, testing usually was done in the outpatient clinic in close proximity to otolaryngology, oncology and infectious disease; however, testing was also done on the treatment unit or inpatient setting if necessary for scheduling. The Yale University clinic sometimes used portable equipment and is investigating alternative testing options such as tele-audiology.

Service delivery across the OMPs examined was clearly influenced by the hospital systems and clinical settings in which they exist. The most consistently delivered OMP examined was at Walter Reed where medical treatment comes at no direct cost to the patient. This OMP was only marginally impacted by logistical barriers and implemented as a cross-specialty collaboration. Their audiology department staff was only involved in the treatment and evaluation side of OMP rather than identifying at risk patients or tracking their ototoxic treatments, which provided major time savings. The audiology clinic location greatly facilitated effective OMP provision. Additionally, the scale of this small hospital system rendered it more tractable compared with some of the other OMPs. At Mayo Clinic and VA Portland, a patient-driven approach was taken to permit adaptation of monitoring schedules to be more or less frequent based on the clinical needs of the patient. At Mayo Clinic, individuals receiving higher doses, those with better pre-exposure hearing and younger in age tend to have larger shifts during treatments and were monitored more frequently. At VA Portland, greater audiology resources were devoted to those patients receiving the most ototoxic drug, cisplatin; many had late-stage cancers and were older with significant pre-exposure hearing loss.

Researchers at VA Portland are conducting a randomised clinical trial to determine if a comprehensive OMP delivered

Table 2. Ototoxicity Monitoring Program (OMP) Objectives, Protocols and Hearing Change Criteria.

	Oregon Health & Science University (OHSU) CF Clinic	*Yale University*	*Mayo Clinic Rochester, MN*	*Veteran's Affairs Portland Health Care System (VA Portland)*	*Walter Reed*
OMP objectives	Patient and provider education on ototoxicity For inhaled AMGs: Consistent monitoring throughout treatment; No specific timeline for tests For IV-AMGs: Inpatient: baseline, Day 1, 7, 14 and 1-month post Outpatient: bi-annual hearing tests to monitor for hearing shifts. Counseling and Rehabilitation services	Patient and provider education on ototoxicity Consistent monitoring throughout treatment Counseling and Rehabilitation services	Patient and provider education on ototoxicity Baseline prior to or w/in 24 h of first treatment Monitor prior to each dose for platin drugs; prior to each cycle for AMGs or radiation alone Post-treatment follow up Counseling and Rehabilitation services	Patient and provider education on ototoxicity Patient-driven monitoring schedule during and after treatment Counseling and Rehabilitation services	Patient and provider education on ototoxicity Baseline prior to or w/in 24 h of first treatment Monitor prior to each dose for platin drugs; prior to each cycle for AMGs or radiation alone Post-treatment follow up Counseling and Rehabilitation services
OMP protocol					
Recommended baseline	Comprehensive eval Tinnitus and dizziness questions	Comprehensive eval Tinnitus and dizziness questions	Comprehensive eval + ultra-high frequencies + DPOAEs Tinnitus and dizziness questions	Comprehensive eval + ultra-high frequencies 9–12 kHz; Optional DPOAEs Tinnitus and dizziness questions	Comprehensive eval + SRO + DPOAEs Tinnitus and dizziness questions
Monitor	AC only 0.25–16 kHz + Tympanometry; DPOAEs If changes detected Comprehensive eval Tinnitus and dizziness questions	Comprehensive eval preferred, however, testing abbreviated if time or equipment, or patient tolerance for testing or constrains eval (e.g., no bone conduction, no available high-frequency audiometer) Tinnitus and dizziness questions	AC only 0.25–16 kHz + Tympanometry; DPOAEs If changes detected Comprehensive eval Tinnitus and dizziness questions	Comprehensive if patient schedule permits or if rehabilitation is a focus Otherwise, AC only 0.25–12 kHz + Tympanometry; Additional tests as needed If changes retest within 24–48 h Tinnitus and dizziness questions	AC only SRO frequencies; Tympanometry; DPOAEs If changes detected Comprehensive eval Tinnitus and dizziness questions
Post-treatment	Comprehensive eval Tinnitus and dizziness questions	Comprehensive eval Tinnitus and dizziness questions	Comprehensive eval Tinnitus and dizziness questions	Done only if patient and clinician decide further rehabilitative intervention is necessary; Testing typically is comprehensive eval	Comprehensive eval Tinnitus and dizziness questions
Hearing Change Criteria					
ASHA	Yes	Yes	Yes	Yes	Yes
CTCAE	No	No	Yes	No	Yes

Facilities had similar OMP objectives, aside from the planned OMP in the Oregon Health & Science University (OHSU) cystic fibrosis (CF) clinic which was solely focussed on monitoring for aminoglycoside (AMG)-induced ototoxicity. Each site recommended obtaining a comprehensive audiometric evaluation at baseline, but all five sites routinely abbreviated monitoring tests. Yale University and VA Portland often attempted comprehensive monitoring tests, but reported having to shorten testing to accommodate patients and adapt to equipment available (i.e. when patient time was limited, testing occurred on the treatment unit or at satellite clinics without sound booths or extensive equipment). All sites reported using American Speech-Language-Hearing (ASHA) 1994 criteria to identify ototoxic hearing shifts. Walter Reed and Mayo Clinic reported also providing oncologists with an indication of whether a hearing shift met Common Terminology Criteria for Adverse Events (CTCAE v4.03, 2010) criteria for an ototoxic adverse event.

AC: Air Conduction Thresholds; AMG: Aminoglycosides; ASHA: American Speech Language Hearing Association; BC: Bone Conduction Thresholds; CTCAE: Common Terminology Criteria for Adverse Events.

Table 3. Randomised clinical trial contrasting two ototoxicity monitoring approaches at the Portland VA.

	Ototoxicity Monitoring Randomised Clinical Trial at VA Portland	
	Usual Care Arm[a]	*Experimental (OtoID) Arm*
Primary Patient Population		
Outpatient	Yes	Yes
Inpatient	No	No
Treatments Targeted		
Cisplatin (including chemoradiation)	Yes	Yes
Mode of Access to Patients		
Audiologist staffs MTD, TB and/or oncology clinics	Never[b]	Usually
Oncology Referral prior to first treatment	Usually[c]	Always
Oncology Referral during treatment	Sometimes, tends to rely on patient compliance with testing	Rarely, patients are managed as part of the OMP
Patient self-referral during treatment	Never for patients in this trial	Never
Scheduling	Audiology clinic	Research team, in coordination with oncology nurses
Locations used for monitor tests		
Sound booth	Usually	Rarely (follow-up/verification tests only)
Portable equipment	Rarely	Usually
OMP protocol		
Monitor	Comprehensive if patient schedule permits or if rehabilitation is a focus Otherwise, AC only 0.25–12 kHz + Tympanometry; Additional tests as needed If changes retest within 24–48 h Tinnitus and dizziness questions	Patient Self-test includes AC in SRO frequencies only with results forwarded to audiologist for review; If ASHA shift is detected: Otoscopy, tympanometry, Clinician retests hearing to confirm change and may test the speech frequencies for functional hearing shifts and/or DPOAEs Hearing Handicap Inventory for adults (HHIA) or for the Elderly (HHIE), Tinnitus Functional Index (TFI), Functional Assessment of Cancer Therapy (FACT) QOL questionnaire
Post-treatment	Done only if patient and clinician decide further rehabilitative intervention is necessary; Testing typically is comprehensive eval	AC only 0.5–20 kHz + SRO, Tympanometry, DPOAEs, TFI, HHIA/E, TFI questionnaire, FACT Routed to clinic for additional testing to serve rehabilitive needs
Hearing Change Criteria	ASHA	ASHA + CTCAE

A description of the two arms of the trial are provided. Format of the table is the same as for Table 1. Patients receiving chemotherapy with cisplatin were eligible to take part in the clinical trial. Exclusions included being cognitively or physically unable to participate, having Meniere's disease or active/recent middle ear disorder. Willing participants not excluded were randomised to one of two arms: usual care as provided in the audiology clinic versus monitoring conducted by the research team primarily in the oncology unit using a portable high-frequency audiometer with store and forward capabilities (Oto-ID, experimental arm). For the usual care arm, ototoxicity monitoring services were accessed by patient self-referral and/or treatment provider referral. For the experimental arm, the study team tracked each patient's treatments using the electronic medical record and sent reminders to the oncology nurses prompting them to provide Oto-ID to patients on each day of treatment with the appropriate baseline comparison test loaded on the device. By comparing protocols for the two arms, it can be seen that testing was more comprehensive for the usual care arm. However, testing occurred far less frequently for the usual care arm (see Table 4 and accompanying text).

AMG, Aminoglycoside antibiotics; H/N, head and neck cancer; IV, Intravenous; MTD, Multidisciplinary clinics; Oto-ID, portable ultra-high frequency audiometer with store and forward telehealth capability; TB, Tumour Board Meetings.

[a]Usual Care Arm protocol is the VA Portland audiology clinic protocol, replotted from Table 2. Individuals who decline participation in the research study may still obtain usual care ototoxic monitoring in the audiology clinic.

[b]The number of referrals at this site increased substantially when MTD and TB clinics began to be staffed as part of an ongoing clinical trial at the VA Portland site (described in Tables 3 and 4).

[c]The research audiologists associated with the trial staff the MTD and TB clinics (i.e., this is not a task performed by the clinical audiologists) at this site.

Table 4. Clinical trial study arm comparison: number of hearing evaluations by patient and cisplatin dose.

	Study arm	
	Usual care (Arm n = 19)	*Oto-ID (Arm n = 21)*
Total (N)		
Doses of cisplatin administered	109	103
Baseline hearing tests obtained	9	21
Monitor hearing tests obtained	13	103
Average (range)		
Doses of cisplatin per patient	5.7 (2–20)	4.9 (1–8)
Monitor hearing tests per patient	0.7 (0–3)	4.9 (1–8)

A baseline hearing evaluation is defined as a hearing test that occurs prior to or within 24 h of the first dose of cisplatin. A monitor evaluation is defined as hearing test that is completed during treatment, after first dose and before last dose of cisplatin. Table shows the number of patients that received a baseline or monitor hearing evaluation by study arm in relation to the number of administered cisplatin doses by study arm for those individuals who had concluded cancer treatment. Less than 50% (9/19) of patients randomized to usual care obtained a baseline prior to treatment. Monitor tests occurred in 47% (9/19) of these patients. Most received just one monitor test during treatment (6 patients) and only 11% (2/19) patients completed a hearing monitor prior to each dose. All 21 patients randomized to the Oto-ID arm had a baseline and a monitor tests prior to each dose. This was facilitated by patient self-testing using the Oto-ID while receiving pre-treatment hydration on the oncology unit.

chair-side on the treatment unit can facilitate the monitoring recommendations set out by national guidelines. As shown in Table 3, the two arms of this trial compare usual care as provided in the audiology clinic versus monitoring conducted primarily using the Oto-ID, a portable high-frequency audiometer with store-and-forward telehealth capabilities (described in Dille et al. 2015; Brungart et al. 2017). Research participants randomised to the experimental (Oto-ID) arm, do not pay for OMP-related visits and this audiological management is inserted into the patient's oncology care flow with scheduling done in coordination with the oncology nurses. Much of the testing is done by the patient him/herself using a simple automated SRO screening test on each day of treatment, typically as the patient receives pre-treatment hydration through an IV. A day ahead of each treatment, the research team sends a secure email reminder to the oncology nurse with a code corresponding to the patient's stored baseline test. The day of treatment, the nurse selects the baseline test indicated in the email as the control against which the monitor test will be compared and signs out the Oto-ID unit. The Oto-ID software re-orients the patient to the testing procedure. The SRO hearing results are securely and automatically transmitted to the research audiologist via text message for comparison to the baseline test. Hearing is tested by the audiologist if changes are found. Alternatively, the audiologist can elect to perform a more complete audiometric evaluation in lieu of the patient SRO self-test if hearing shifts are impinging on those frequencies important for speech understanding, the treatment team notices a hearing change or a patient complains of a change in hearing or tinnitus. The latter generally begins with AC testing on the oncology unit using the Oto-ID. Additional tests are included as indicated by the AC threshold results.

Table 4 shows the number of baseline and monitor tests for patients enrolled in the clinical trial by research arm. Both study arms have the advantage of the research team staffing multidisciplinary clinics (usually for head and neck, lung and sometimes for bladder cancers) thus increasing the likelihood that an initial audiology consult is in place for patients treated with cisplatin. This facilitated OMP service delivery, however, even with the consult in place, less than 50% (9/19) of patients randomised to usual care obtained a baseline prior to treatment. Monitor tests also occurred far less frequently in this group. Only 47% (9/19) received one or more hearing tests during treatment. Few patients (2/19 or 11%) completed a hearing monitor test prior to each dose. In contrast, all 21 patients randomised to the Oto-ID arm had a true baseline and monitor tests prior to each cisplatin dose. Thus the ideal evaluation schedule based on ASHA (1994) guidelines fared well when implemented as a self-administered screening approach in the oncology unit. In general, scheduling for sound booth testing in the clinic was found to be limited by outpatient appointment availability and to strongly depend on the patient's ability and willingness to travel to the medical centre specifically for the audiology appointment. Of note, had all participants in both arms of the clinical trial received a baseline and monitor tests each dose, an estimated 247 visits to the audiology clinic would have been needed for these 43 patients. This further illustrates the importance of time and cost-efficient testing, such as the patient-administered screening approach examined in this study.

Conclusions

Service delivery varies across OMPs, partly as a reflection of system and programme-level priorities and resources. Within a programme, services do not always support even the most basic monitoring practices. Monitoring hearing occurs more often when instituted within a formalised, systematic OMP that can deliver services on the day of treatment, in or near the treatment unit. Facilitators of effective OMPs are flexible staffing, time-efficient protocols and depending on the setting, portable equipment and/or

telehealth. Existing ASHA (1994) and AAA (2009) recommendations provide good general guidance and some basis for programme standardisation, while remaining flexible enough to enable tailoring of OMP clinical goals. Specific evaluation schedules provided in these national guidelines may prove impractical to implement. More guidance is needed regarding the frequency of testing that yields the best cost–benefit balance. This warrants further investigation of the severity of ototoxicity as a function of patient and drug treatment factors, and the effectiveness of various OMP practices. A clear prerequisite for large-scale OMP efforts is the mass testing characteristic of similarly scaled hearing conservation and newborn hearing screening programmes. Guidance on these aspects of OMP will be necessary for applications beyond boutique programmes (e.g. on how to ensure the accuracy of tests conducted using remotely driven audiometers and/or portable equipment). Related to this, it is unclear how much additional testing beyond AC and tympanometry is needed to confirm changes identified on monitoring tests when the added pressure of time is substantial as the patient–provider team prepares for the next dose. An important related question is what should constitute an actionable hearing change from the perspectives of the patient and treatment team. Successful OMPs have the referral support of the nurses and physicians that provide ototoxic medications for life-preserving medical care, as well as their consensus on OMP goals and the implications of monitoring for treatment decisions. Finally, to achieve widespread OMP provision, formal endorsement may be needed from governing bodies of the medical stakeholders (e.g. medical oncology, pulmonology, infectious disease, otolaryngology, pharmacy). This could potentially compel physician partners to support OMP.[1]

Note

1. As an example, oncologic practice for clinical trials already requires standardized reporting of ototoxic ''adverse events'', such as the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v 4.03, 2010). Additionally, recent guidelines for extended-interval dosing of non-tuberculosis mycobacterial pulmonary infections consider ototoxicity from aminoglycosides as a common serious adverse drug reaction and recommend baseline and periodic audiology evaluation on all patients receiving either systemic or inhaled amikacin (Egelund et al. 2015).

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