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Prevention and management of ototoxicity

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Prevention and management of hearing loss in patients receiving ototoxic medications

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Abstract

Following the efforts of patient advocates, the World Health Organization published updated guidelines for management of multidrug-resistant tuberculosis in 2018 that advised against the routine use of ototoxic second-line injectable drugs (amikacin, capreomycin and kanamycin). Although hearing loss is no longer considered an unavoidable harm for patients with multidrug-resistant tuberculosis, ototoxic medications continue to be used for several infectious and oncological disorders around the world. These drugs contribute to more than a half a million cases of hearing loss worldwide annually. Currently, there are no international standards for preventing and managing hearing loss associated with ototoxic medications. We present recent data on the prevention and management of hearing loss related to these drugs and highlight the variability in care across settings. More importantly, we aim to provide an evidence-based framework for evaluating, screening and preventing ototoxicity. Finally, we identify avenues for future research so that patients no longer have to choose between hearing loss and a disease cure. There remain significant gaps in our understanding about optimal screening and treatment of ototoxic hearing loss. Here we aim to inspire future international guidelines to address gaps in ototoxicity care and establish research agendas for eliminating ototoxic medications.

Introduction

Before 2018, second-line injectable drugs were core components of multidrug-resistant tuberculosis regimens. Major international treatment guidelines recommended their use despite weak in vitro evidence and conflicting results from retrospective cohort studies. Importantly, a review of ototoxicity associated with second-line injectable drugs reported irreversible hearing loss in up to 50% of exposed patients. With the introduction of novel antibiotics such as bedaquiline and delamanid, and the repurposing of antimicrobials such as linezolid and
clofazimine, new options emerged for multidrug-resistant tuberculosis treatment. Ultimately, driven by years of advocacy by patients around the world, second-line injectable drugs fell out of favour.\textsuperscript{5,6}

In 2018, this movement culminated in updated multidrug-resistant tuberculosis treatment guidelines by the World Health Organization (WHO). The guidelines, updated in 2020, advised against the use of second-line injectable drugs, kanamycin and capreomycin, due to the increased risk of treatment failure, relapse and severe side-effects.\textsuperscript{7} Amikacin and streptomycin, newly classified as a second-line drugs, are now recommended only after exhausting other treatment options and when audiometry monitoring is available.\textsuperscript{7} Similar guidance was released by the American Thoracic Society, European Respiratory Society and Infectious Diseases Society of America in 2019.\textsuperscript{8} Overall, this movement reaffirmed patients’ right to hearing and demonstrated that advocacy and research can lead to effective treatment alternatives.

However, patients continue to receive ototoxic medications for certain infectious diseases, cancers and chronic health conditions (Table 1). Globally, platinum-based chemotherapies and aminoglycosides are associated with over 500,000 and 50,000 annual cases of hearing loss, respectively.\textsuperscript{4,15} Currently, there are no international guidelines or protocols for the screening and management of hearing loss during treatment.\textsuperscript{7} Examination of several countries’ guidance for detection of ototoxicity shows that there is no universal approach to screening or diagnosing hearing loss.

Standardized guidance and research are needed, especially in low-resource settings, to detect and treat hearing loss from ototoxicity. Here, we propose an approach to early detection and management of ototoxic hearing loss, provide evidence-based treatment options and identify avenues for future research.

**Ototoxic drugs**
Commonly used ototoxic drugs, and their incidence and mechanisms of ototoxicity are summarized in Table 1.

**Ototoxic antibiotics**
Aminoglycosides are an injectable antibiotic class with a reported irreversible ototoxicity of 3–50\%\textsuperscript{16} Ototoxic effects occur in a dose-dependent fashion via reactive oxygen species generated in the patient’s cochlear hair cells. Given the lower cost and fewer supply-chain barriers,
aminoglycosides continue to be regularly used in low- and middle-income countries, as illustrated by a case study in Peru (Box 1). Additionally, there are certain infectious diseases for which no effective alternative has been developed (such as *Pseudomonas aeruginosa* commonly isolated in cystic fibrosis patients, tularaemia and multidrug-resistant urinary tract infections).

To decrease the use of ototoxic antibiotics, future research is needed to find novel antibiotic alternatives. For multidrug-resistant tuberculosis, the move away from ototoxic medications has been aided by the introduction of bedaquiline and delamanid, which are oral antibiotics with fewer associated side-effects. Parallel efforts are needed for other infectious diseases. Increasing multilateral organization support and government subsidies to low- and middle-income countries are key to accelerating this change.

Vancomycin and macrolides are two other antibiotic classes that have been associated with reversible ototoxic hearing loss, although the reported incidence is much lower compared with aminoglycosides. Whether vancomycin is directly responsible for hearing loss is contested in the literature, given that many patients are concurrently receiving other ototoxic medications (such as aminoglycosides or diuretics). Animal studies have demonstrated that vancomycin alone does not cause ototoxicity but may potentiate hearing loss from aminoglycosides. Macrolides have been found to be associated with sensorineural hearing loss, although the evidence is limited to case reports and focuses most commonly on systemic erythromycin. A review found that as of 2003, only 50–100 cases of macrolide-associated ototoxicity had been published. Risk factors associated with purported ototoxicity from vancomycin and macrolides include old age, kidney dysfunction and co-administration with other ototoxic agents. Given the relatively low incidence of ototoxicity and weak evidence that they are causative in the first place, further investigation is needed before moving away from these antibiotics.

**Platinum-based chemotherapy**

Platinum-based chemotherapies, such as cisplatin, have long been associated with irreversible hearing loss. Their mechanism for ototoxicity directly affects the stria vascularis, spiral ganglion cells and hair cells of the cochlea (cisplatin is thought to preferentially effect the outer hair cells, whereas carboplatin damages the inner hair cells). Similar to aminoglycosides, hearing loss first occurs in the high frequencies of sound and progresses towards lower frequencies with prolonged medication exposure. Recent evidence suggests that cisplatin is retained in the cochlea
for months to years after finishing treatment, underlying the importance of post-treatment screening. The incidence of hearing loss associated with carboplatin are estimated to be approximately 13.8% (95% confidence interval, CI: 8.7–20.3%). For cisplatin, conventional regimens are associated with a 49.2% (95% CI: 42.6–55.8%) incidence of hearing loss, and combination therapy with cisplatin is associated with a 56.1% (95% CI: 45.1–66.4%) incidence of hearing loss. The guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events are commonly applied when investigating ototoxicity for platinum-based compounds. However, the guidelines do not include high frequency hearing loss and may lead to underestimation of the true incidence of hearing loss. Platinum compounds are the principal treatment for several paediatric malignancies, therefore their overall impact on speech and language development in the setting of hearing loss is important.

Other drugs
Loop diuretics, salicylates and nonsteroidal anti-inflammatory drugs are all associated with reversible hearing loss, and their associated incidence of hearing loss are much lower compared with aminoglycosides and platinum-based chemotherapies. Loop diuretics are thought to act on the sodium, potassium and chloride cotransporter in the cochlea and on potassium levels in the endolymph. The mechanism by which salicylates and nonsteroidal anti-inflammatory drugs affect hearing is incompletely understood, but may be related to vasoconstriction with decreased blood supply to the stria vascularis of the cochlea. Approximately 7 in 1000 individuals and 11 per 1000 individuals experience ototoxicity while on diuretics and salicylates, respectively. Of note, incidence of ototoxicity are associated with concomitant use of other ototoxic drugs. Given the widespread use of these drugs and relatively low incidence of associated ototoxicity, efforts should focus on minimizing the concurrent use of other ototoxic agents, avoiding supra-therapeutic dosing and immediately stopping their use if hearing loss is determined.

Monitoring
Irreversible ototoxic medications
Patients who receive ototoxic medications with irreversible effects (such as aminoglycosides or platinum-based chemotherapies) should be monitored closely with audiometry to assess hearing loss. Currently, there are no universal or even comparable standards or guidelines for monitoring for ototoxic hearing loss. Practical country guidance recommends screening at frequencies less than 10 000 Hz, with follow-up screening every 2–4 weeks, or as soon as a patient
experiences subjective hearing loss (Table 2). Given that the earliest stages of ototoxic hearing loss occur at high frequencies that patients may not be aware of, we believe that screening programmes should aim to provide standard screening over a set frequency range and at specific time intervals.

Our suggested screening protocol for early detection and management of ototoxic hearing loss in both high-income and low- and middle-income countries is based on expert guidance from the American Speech-Language-Hearing Association and American Academy of Audiology (Fig. 1). We have added the sensitive range for ototoxicity, pre-operative evaluation and treatment options. This guidance represents an improvement over many national guidelines because it includes high-frequency monitoring, standardizes the hearing loss threshold for ototoxicity and defines a robust monitoring schedule (Table 2).

Hearing screening for ototoxic hearing loss should monitor frequencies between 250–8000 Hz, which span the frequencies for speech. The American Speech-Language-Hearing Association recommends a baseline measurement, followed by weekly testing during therapy, and at 3 and 6 months after stopping treatment. The Association defined ototoxic hearing loss as any of the following: (i) ≥ 20 decibels (dB) change at a single frequency; (ii) ≥ 10 dB change at two or more consecutive frequencies; or (iii) loss of response at three consecutive frequencies. Monitoring frequency can be adjusted for populations who are especially susceptible to ototoxicity, including those with underlying kidney disease, malnutrition or immunodeficiencies.

If countries have the capacity to expand hearing screening beyond the standard frequencies for speech, monitoring of ultra-high frequency thresholds (> 8000 Hz) may improve early detection since high frequencies are the first affected in ototoxic hearing loss. Countries such as Portugal, South Africa and the United States of America already include ultra-high frequency screening into their ototoxicity screening protocols, although the upper limit of screened frequencies varies from 10 000 to 20 000 Hz (Table 2). However, there are many countries that do not routinely screen using the full spectrum of speech frequencies or ultra-high frequency thresholds due to resource constraints. To improve the efficiency of hearing screening, the American Academy of Audiology recently proposed serial monitoring at an individual’s sensitive range for ototoxicity, which is the highest frequency with a threshold at or below 100 dB sound pressure level followed by the next six lower adjacent frequencies in one-sixth
octave steps. Follow-up studies found that this method significantly outperformed conventional frequency testing in detecting emergent hearing loss, and also avoided the challenges inherent to screening with ultra-high frequencies. Implementing protocols that test for the sensitive range for ototoxicity may help achieve a higher standard of audiology care in low-resource settings where high frequency screenings were not previously possible.

Using the earliest sign of hearing threshold shift as an indication to consider stopping the ototoxic agent is essential to minimizing drug ototoxicity. This is common practice across many ototoxicity screening protocols in both high-income and low- and middle-income country settings (Table 2). When performing ultra-high frequency monitoring, the first threshold shift will likely occur above 8000 Hz. If detected at this stage, a clinician can weigh other possible treatments before ototoxic damage occurs at the lower frequencies essential for speech. In South Africa, for example, this approach has proven effective in preventing severe ototoxicity among multidrug-resistant tuberculosis patients receiving second-line injectable drugs, while maintaining relatively high treatment success. Although stopping treatment may reduce the degree of hearing loss compared with continuing the ototoxic agent, it does not guarantee that no further loss will occur. Unfortunately, ototoxic effects may progress for up to 6 months after stopping an injectable drug. Similar to what is found in many other national protocols (Table 2), the American Speech-Language-Hearing Association recommendation to screen at 3 and 6 months after terminating ototoxic drugs allows delayed hearing loss to be detected.

In practice, researchers, especially those from low- and middle-income countries, report difficulty in properly implementing screening protocols, and have identified gaps in audiological surveillance. This may be due to the limited resources available and the time-intensive process required to complete a comprehensive hearing screen. Some help has come in the form of the recent expansion of mobile technologies that can be used for ototoxic hearing loss screening, including SHOEBOX (Shoebox Ltd, Ottawa, Canada) and hearScreen (HearX Group Ltd, Delaware, USA). Many of these tools are compatible with smart devices such as smartphones or tablet computers and have the potential to be broadly implemented in low-resource settings. To conform with American Academy of Audiology guidelines, many of these tools can be programmed to perform pure tone audiometry within the normal range of speaking (250–8000 Hz) and to screen at frequencies above 8000 Hz to identify and monitor a patient’s sensitive range for ototoxicity. Additionally, though still in the early stages of development,
decision-support algorithms such as OtoCalc\textsuperscript{56} can be implemented to help clinicians interpret audiology results and make adjustments to ototoxic medications.

Therapeutic drug monitoring should also be integrated into clinical care to provide complementary information about plasma concentrations of ototoxic agents. This information can be used to titrate doses to achieve, and not exceed, the optimal plasma concentration. This technique could mitigate any dose-related aspects of ototoxic hearing loss and other associated side-effects such as balance function.\textsuperscript{57,58}

**Reversible ototoxic medications**

For patients receiving ototoxic medications with reversible side-effects (such as loop diuretics, macrolides, vancomycin, salicylates or nonsteroidal anti-inflammatory drugs), patients need not be subjected to routine hearing screening unless they experience subjective changes in hearing, tinnitus or balance function. If patients experience any of these changes, referral for audiometric testing is appropriate. There may be a role for baseline audiograms in patients with prolonged or indefinite exposure to these medications. Future research is needed to determine what duration of time qualifies as prolonged drug exposure.

**Treatment**

Hearing aids and hearing assistive technology serve as the first-line treatment for ototoxicity-induced hearing loss.\textsuperscript{49} These interventions merely amplify sound. Most devices are effective for sounds below 4000 Hz (speech ranges from 500–2000 Hz), but may not address the high-frequency hearing loss associated with the early stages of injectable-related ototoxicity.

Cochlear implants can improve hearing in certain patients with severe ototoxicity. Cochlear implants are indicated in individuals who have mild or severe hearing loss and poor word recognition.\textsuperscript{34} Use of the devices requires proper otology evaluation and device monitoring; efforts should be made to expand their application in low-resource settings. Cochlear implants have been shown to successfully restore hearing in patients with drug-associated ototoxicity.\textsuperscript{59,60} However, some reports of cochlear implants used for irreversible ototoxicity have identified poorer than expected performance. This outcome may be due to damage to structures beyond the hair cells, such as the first-order neurons within the spiral ganglion.\textsuperscript{61}
Future research

Efforts to improve the feasibility of hearing screening, especially in low-resource settings, have been explored. Suggested protocols, which have yet to be validated, recommend focusing on the sensitive range for ototoxicity only and decreasing the screening frequency to monthly tests, and one test after treatment ends.\textsuperscript{44,62} To overcome the complexity of robust screening protocols, future operational and quality improvement research is needed to compare and validate the performance characteristics of simplified protocols.

The impact of ultra-high frequency hearing loss (> 8000 Hz) is unclear given that most sounds of daily life occur below this frequency. Future research should investigate whether hearing loss observed at these higher frequencies indicates degeneration at the lower frequencies important for speech, and whether the medication responsible should be stopped after detection of such ultra-high-frequency hearing loss. Before clinical recommendations are established, other methods with a higher sensitivity to detect hearing loss – such as otoacoustic emissions and auditory brainstem testing – require further validation in subjects receiving ototoxic drugs.\textsuperscript{47,63} Additionally, prospective research that includes therapeutic drug monitoring is needed to balance efficacy and safety of ototoxic medications.\textsuperscript{57,58} Future studies should explore ways to incorporate and combine these other monitoring techniques into standardized protocols.

For irreversible ototoxic agents there should be a focus on finding alternative chemotherapies, as well as developing strategies to mitigate their consequences. Recent research efforts have investigated the use of otoprotectants such as thiosulfates, antioxidants or iron chelators (such as N-acetylcysteine, deferoxamine) to neutralize reactive oxygen species and prevent hearing loss from aminoglycosides and platinum-based chemotherapies. There continues to be mixed evidence on whether these agents are effective.\textsuperscript{64,65} Additionally, recent research has implicated a mechanotransducer channel as a mediator for drug entry into hair cells. Efforts to therapeutically block the mechanotransducer channel or alter the drug structure to minimize hair-cell entry are under development.\textsuperscript{66} Limited evidence from studies on animals suggests that intratympanic steroids may reduce ototoxicity.\textsuperscript{67} However, with no clinical studies at this time, there is insufficient evidence to support the routine use of these agents during the use of injectable drugs. Future research is needed to explore how hearing loss can be treated or mitigated when irreversible ototoxic agents cannot be stopped.
Hearing loss dramatically impacts quality of life across all age groups, and is associated with an increased burden of mental illness and dementia.\textsuperscript{68} The primary reason that patients continue to receive ototoxic medications is because there are no treatment alternatives or that access to these alternatives is limited. However, new and repurposed medications may present effective alternatives. Hearing screening would then become more robust, and information from therapeutic drug monitoring incorporated into dosing, so that patients should no longer face such a difficult choice. When these medications are deployed, resources must be made available to deal with to their long-term consequences.

At the population level, avoiding and treating hearing loss is an excellent investment. Overall, the cost of hearing loss to the health-care sector, for adults and children, is estimated to range from 67 billion to 107 billion United States dollars (US$).\textsuperscript{69} Adults who acquire permanent hearing impairment due to ototoxic medications are estimated to have up to US$ 300 000 in medical costs. For paediatric patients who acquire prelingual hearing loss, costs can exceed US$ 1 million. Loss of productivity due to hearing loss and other costs to society from social isolation, communication difficulties and stigma are thought to add even greater costs each year.\textsuperscript{70} While cochlear implants are often considered prohibitively costly in settings with high burdens of tuberculosis, their cost is only US$ 77 240 per person, far less than the costs of untreated hearing loss as reported above.\textsuperscript{71}

**Conclusions**

New treatment options and revised guidelines will protect millions of people from unnecessary exposure to drugs that cause irreversible hearing loss. In the case of tuberculosis, second-line injectable drugs should be used as a last resort and should be stopped if other medication options are available. When agents that result in irreversible hearing loss are the only option, evaluation and adoption of internationally recognized guidelines are needed, alongside additional research, to prevent, manage and treat this unfortunate adverse event.

**Competing interests:**

None declared.
References


Page 12 of 19


Box 1. Case study: transitioning away from second-line injectable drugs for multidrug-resistant tuberculosis in Peru

Peru is a global leader in its efforts to combat multidrug-resistant tuberculosis. In 1994, a sampling study showed 12 out of 22 (54.4%) tested tuberculosis cases in Peru had antibiotic resistance. Through community-based treatment, Peru effectively created universal access to treatment for multidrug-resistant tuberculosis. Most recently, the health ministry reported that 139 (7.3%) of 1908 newly diagnosed cases and 44 (16.2%) of 272 previously treated patients have multidrug-resistant tuberculosis.

Up until 2018, Peru included ototoxic second-line injectable drugs in their recommended regimen. With newly published guidelines from the World Health Organization and participation in novel multidrug-resistant tuberculosis randomized controlled trials (the EndTB and EndTB-Q trials), Peru has begun to incorporate new drugs such as bedaquiline and delamanid. Peru has also repurposed drugs such as linezolid and clofazimine in its shift away from second-line injectable drugs. Still, challenges remain in eliminating these drugs from standard regimens.

Second-line injectable drugs are cheaper to purchase than some newer and repurposed drugs, although monitoring and managing toxicity caused by second-line injectable drugs is costly. Physicians’ fear of generating resistance to novel drug agents also limits the shift away from second-line injectable drugs. Many low- and middle-income countries face similar challenges.
Table 1. **Ototoxicity by drug class**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Mechanism of ototoxicity</th>
<th>Type</th>
<th>Incidence of ototoxicity&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Outer hair cells</td>
<td>Irreversible</td>
<td>40.6% (95% CI: 32.8–66.6%) of 1386 patients treated&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| Platinum-based compounds        | Outer hair cells, stria vascularis, spiral ganglion | Irreversible | Cisplatin: 49.2% (95% CI: 42.6–55.8%) of 3224 patients treated<sup>10</sup>  
Carboplatin: 13.5% (95% CI: 8.7–20.3%) of 742 patients treated<sup>12</sup> |
| Loop diuretics                  | Sodium, potassium and chloride channel          | Reversible | 3.3% (29/878) of patients treated<sup>11</sup> |
| Macrolides                      | Stria vascularis                                | Reversible | 50–100 total cases up to year 2003<sup>12</sup> |
| Vancomycin                      | Unknown                                         | Reversible | 8% (7/92) of patients treated<sup>13</sup> |
| Salicylates, nonsteroidal anti-inflammatory drugs | Vasoconstriction in stria vascularis             | Reversible | 250 cases per 19,832 person-years<sup>14</sup> |

CI: confidence interval.

<sup>a</sup> Incidence of ototoxicity is based on reported proportions in retrospective cohort studies. The evidence was not strong as the reported incidence of ototoxicity were widely variable and higher incidence were associated with higher doses or prolonged exposure. The 95% CI are from available meta-analyses with pooled data.
Table 2. Variability in audiogram-based hearing loss protocols for ototoxic drugs by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Monitoring schedule</th>
<th>Sound frequencies monitored, Hz</th>
<th>Threshold shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil(^{38})</td>
<td>Baseline test, then weekly audiogram monitoring</td>
<td>500 to 4000</td>
<td>≥ 15 dB in at least two frequencies</td>
</tr>
<tr>
<td>India(^{37,38})</td>
<td>Baseline test, then test every 2 months, then test at 3 and 6 months post-treatment</td>
<td>250 to 8000</td>
<td>(i) 20 dB or greater decrease at any one test frequency; (ii) 10 dB or greater decrease at any two adjacent frequencies; or (iii) loss of response at three consecutive frequencies where responses were previously obtained</td>
</tr>
<tr>
<td>Portugal(^{39})</td>
<td>Baseline test &lt; 72 hours after first dose, then weekly evaluation, then test at 3 and 6 months post-treatment</td>
<td>250 to 20 000</td>
<td>(i) 20 dB or greater decrease at any one test frequency; (ii) 10 dB or greater decrease at any two adjacent frequencies; or (iii) loss of response at three consecutive frequencies where responses were previously obtained</td>
</tr>
<tr>
<td>South Africa(^{40–42})</td>
<td>Wide variability. Most commonly, baseline test then monthly audiogram monitoring, then one test post-treatment</td>
<td>250 to 10 000</td>
<td>(i) 20 dB or greater decrease at any one test frequency; (ii) 10 dB or greater decrease at any two adjacent frequencies; or (iii) loss of response at three consecutive frequencies where responses were previously obtained</td>
</tr>
<tr>
<td>United States (American Speech-Language-Hearing Association)(^{43})</td>
<td>Baseline test, weekly audiogram monitoring, then test at 3 and 6 months post-treatment</td>
<td>250 to 20 000</td>
<td>(i) 20 dB or greater decrease at any one test frequency; (ii) 10 dB or greater decrease at any two adjacent frequencies; or (iii) loss of response at three consecutive frequencies where responses were previously obtained</td>
</tr>
<tr>
<td>United States-based protocol with improved feasibility(^{44})</td>
<td>Baseline test, then test after each treatment, then test at 1 and 6 months post-treatment</td>
<td>Sensitive range for ototoxicity</td>
<td>(i) 20 dB or greater decrease at any one test frequency; (ii) 10 dB or greater decrease at any two adjacent frequencies; or (iii) loss of response at three consecutive frequencies where responses were previously obtained</td>
</tr>
</tbody>
</table>

dB: decibel.

Note: Protocols focus on audiometry reporting and are not specific to anti-tuberculosis ototoxic medications.
Fig. 1. An approach to early detection and management of ototoxic hearing loss

Pre-antibiotic evaluation
- Rule out human immunodeficiency virus infection, malnutrition, end-stage renal disease and antioxidant deficiency
- Note that there is insufficient evidence to support genetic screening

Hearing loss screening
- Use pure tone audiometry at baseline, weekly, and 3 and 6 months post-treatment at 250–20 000 Hz
- Identify and screen patient's sensitive range for ototoxicity
- If possible, consider supplementing with distortion product otoacoustic emissions and auditory brainstem response monitoring at high frequencies outside of speech (> 10 kHz)

Treat
- Stop ototoxic medication
- Prescribe hearing aid
- Consider cochlear implant for severe-to-profound sensorineural hearing loss with poor word recognition

Source: Based on expert guidance from the American Speech-Language-Hearing Association and American Academy of Audiology.43,45