



## Prevención y diagnóstico precoz de la sordera por ototóxicos

## Prevention and Early Diagnosis of Ototoxic Hearing Loss

**Author: CODEPEH**  
(Faustino Núñez, Carmen Jáudenes, José Miguel Sequí,  
Ana Vivanco, José Zubicaray)

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The following are members of the CODEPEH:

**Dr Faustino Núñez-Batalla, Head**  
of the ENT Department, Hospital Universitario Central de Asturias-Oviedo  
In representation of the Spanish Society of Otolaryngology

**Ms Carmen Jáudenes-Casabón,**  
Director of FIAPAS  
In representation of the Spanish Confederation of Families of Deaf People

**Dr José Miguel Sequí Canet, member,**  
Head of the Pediatrics Department, Hospital Universitario de Gandía-Valencia  
In representation of the Spanish Association of Pediatrics

**Dr Ana Vivanco-Allende, member,**  
Paediatric Clinical Management Area, Hospital Universitario Central de Asturias-Oviedo  
In representation of the Spanish Association of Pediatrics

**Dr José Zubicaray-Ugarteche, member,**  
Paediatric ENT Department, Navarre Hospital Complex-Pamplona  
In representation of the Spanish Society of Otolaryngology



SPANISH CONFEDERATION OF FAMILIES OF DEAF PEOPLE



SPANISH MINISTRY OF HEALTH, CONSUMER AFFAIRS  
AND SOCIAL WELFARE  
ROYAL PATRONAGE FOR DISABILITY

## RESUMEN

La ototoxicidad se define como el daño, reversible o irreversible, producido sobre el oído interno por diversas sustancias que se denominan ototóxicos y que causan una hipoacusia y/o una alteración del sistema vestibular.

La hipoacusia permanente afecta significativamente a la calidad de vida y es especialmente importante en el caso de niños. Es frecuente la falta o el retraso en su detección, dado que muchas veces progresa de forma poco llamativa hasta que afecta a la comunicación y al desarrollo global. Este impacto puede minimizarse siguiendo una estrategia de monitorización audiológica de la ototoxicidad, que permita su detección y tratamiento precoz. En el presente documento se recomienda implantar dicha monitorización en los niños que van a ser tratados con cisplatino o aminoglucósidos.

Este documento de revisión y recomendaciones de la CODEPEH se enfoca a la detección precoz, la profilaxis, la otoprotección, el seguimiento y el tratamiento de la ototoxicidad por aminoglucósidos y antineoplásicos derivados del platino en la población pediátrica.

**PALABRAS CLAVE:** Ototoxicidad, Monitorización de la Ototoxicidad, Cisplatino, Aminoglucósidos, Tratamiento, Prevención..

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## ABSTRACT

Ototoxicity is defined as the damage, reversible or irreversible, produced in the inner ear by various substances that are called ototoxic and that cause a hearing loss and/or an alteration of the vestibular system.

Permanent hearing loss significantly affects the quality of life and is especially important in the case of children. Lack of or delay in its detection is frequent, as it often progresses in an inconspicuous manner until it affects communication and overall development. This impact can be minimised by following a strategy of audiological monitoring of ototoxicity, which allows for its early detection and treatment. In this document it is recommended to implement such monitoring in children who are going to be treated with cisplatin or aminoglycosides.

This CODEPEH review and recommendation document focuses on the early detection, prophylaxis, otoprotection, monitoring and treatment of ototoxicity by aminoglycosides and platinum-based antineoplastics in the paediatric population.

**KEYWORDS:** Ototoxicity, Ototoxicity monitoring, Cisplatin, Aminoglycosides, Treatment, Prevention.

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## 1. INTRODUCTION

Ototoxic medicinal products cause functional impairment and/or cellular degeneration of the tissue in the inner ear. Cochlear toxicity is defined as damage to the auditory system resulting in neurosensory hearing loss and/or tinnitus. Vestibulotoxicity, which may be associated, is caused by the impact on the vestibular system, and symptoms include vertigo, dizziness, and loss of balance (Roland and Rutka, 2004). Symptoms may occur after or during treatment, and bilateral or asymmetric presentation is more common.

Permanent hearing loss due to ototoxicity significantly alters the patient's quality of life, and is particularly harmful for children before and during language acquisition because it affects their psychosocial development and education (Knight, 2005: 8588-8596). It is sometimes accompanied by tinnitus and vestibular disorders, which are associated with considerable stress, anxiety, depression, and loss of quality of life.

Hearing loss derived from ototoxic drugs initially affects the high frequencies of the hearing spectrum, so performing high frequency audiometries may provide evidence of ototoxic damage during a subclinical stage. At this stage, the patient has not yet noticed any hearing difficulties. Given that pre- and post-treatment audiometries, which are necessary to assess ototoxicity, are not extensively performed, the actual incidence of ototoxicity may be underestimated (Abujamra *et al.*, 2013: 474-478).

### ***There are currently 600 drugs with ototoxic potential***

The effects of ototoxicity are usually permanent. However, ototoxicity of loop diuretics, macrolide antibiotics and quinine usually disappears after treatment is completed. The ototoxicity of salicylates occurs in the event of overdosing and resolves once the medicinal product is no longer taken. However, platinum derivatives, especially cisplatin, and aminoglycoside antibiotics (AGs) irreversibly damage the inner ear (Truong *et al.*, 2007: 1631-1638; Lanvers-Kaminsky *et al.*, 2017: 491-500).

Medicinal products considered as ototoxic include AGs, glycopeptides and macrolides, platinum-based chemotherapy drugs, loop diuretics, quinine, and salicylates. There are currently 600 drugs with ototoxic potential (Cianfrone *et al.*, 2011: 601-636), although this CODEPEH recommendation document will study the ototoxic drugs most often used in paediatrics, such as AG antibiotics and platinum-based chemotherapy

drugs (Arslan *et al.*, 1999: 1-14). *Table 1* lists a selection of the most well-known ototoxic medicinal products.

Ototoxicity can occur at any age and, although usually well documented, the overall magnitude of the problem and its incidence are unknown for several reasons. Among others, due to the existence of a variety of criteria to define it, its variability as a result of a wide range of reactions to a drug in different ethnic groups, the use of different audiological protocols for its assessment, and the absence of referral to specialist services because it is a complication that does not threaten survival, and which may also be reversible (Ganesan *et al.*, 2018: 59-68).

### ***The addition of hearing risk factors increases the possibility of ototoxicity, which can occur at any age***

Cisplatin-related ototoxicity usually occurs among 23% to 50% of adults and 60% of children (Knight *et al.*, 2005: 8588-8596; Coradini *et al.*, 2007: 355-360), but with great variability between the percentages recorded (from 1.7% to 90.1%). However, some studies have observed changes in audiometric thresholds in up to 100% of patients treated with Cisplatin (Bisht and Bist, 2011: 255-259), while this is estimated to occur in 63% of those receiving AG and 6-7% of those treated with furosemide (Rybak, 1993: 829-844).

In addition, the severity of hearing loss due to ototoxicity appears to be cumulative and dose-dependent, also influenced by other factors such as age, sex, comorbidities such as cardiac failure, renal failure, hypertension, genetic susceptibility, geographic factors, type of drug, form in which it is administered, duration of treatment, bioavailability, and pre-existing hearing loss. The addition of hearing risk factors increases the possibility of ototoxicity.

A common problem is the late detection of ototoxic hearing loss, as ototoxicity can be variable and inconsistent. It often progresses indolently until the major communication and quality of life problems it causes become apparent. But this impact can be minimised by following an audiological ototoxicity monitoring programme that allows for early detection and early treatment of ototoxicity (Ganesan *et al.*, 2018: 59-68).

The fact that children with moderate to severe neurosensory ototoxic hearing loss show significant deterioration in their overall development, in learning to read and perform mathematical analysis at the age of 5 (Olivier *et al.*, 2019: 1566-1575), and the fact that these sequelae can be avoided with appropriate audiological

treatment makes audiological care very important as of the start of ototoxic treatment (Clemens *et al.*, 2019: E29-E41).

Often, similar hearing loss or even normal audiograms are associated with varying degrees of difficulty in communicating. Rehabilitation should be based more on difficulties in communicating rather than on audiometric outcomes (Ganesan *et al.*, 2018: 59-68).

If permanent ototoxic damage occurs despite all preventive measures, auditory rehabilitation should be considered using devices such as hearing aids, implants and technologies, or other hearing support products, combined with the speech therapy intervention necessary to attend to the development of oral language and communication.

### **Symptoms may occur after or during treatment, and bilateral or asymmetric presentation is more common**

The first aspect to be analysed is that, despite the recommendations, monitoring for ototoxicity in children is insufficient. 72% of patients considered at risk underwent audiological testing during follow-up and only 43% were followed up with complete audiological monitoring before and after treatment (Weiss *et al.*, 2018: e26877).

Given the large number of potentially ototoxic medicinal products, it is unrealistic to consider monitoring each one. However, early detection of ototoxicity, even before patients perceive it, may allow for early treatment (e.g., seeking therapeutic alternatives, dose modification, and application of protective substances) and minimise - or even prevent - the progression of ototoxicity. Thus, audiological monitoring should be standard care for patients to be treated with cisplatin or AG, as these medicinal products may cause permanent hearing loss (Brock *et al.*, 2012: 2408-2417).

This CODEPEH review and recommendations document focuses on early detection, prophylaxis, otoprotection, monitoring, and treatment of ototoxicity due to AG antibiotics and platinum-based antineoplastics in the paediatric population.

## **2. PATHOPHYSIOLOGY OF OTOTOXICITY**

There are several therapeutic classes involved in ototoxicity. The main ones are aminoglycoside antibiotics (AGs), macrolides, salicylates, loop diuretics, certain antimitotic drugs (platinum salts), and quinine and its derivatives (Dulon *et al.*, 2013: 1-13). Ototoxic drugs are one of the main causes of deafness that can be prevented (Yorgason *et al.*, 2006: 383-399).

Ototoxics reach the inner ear via the *stria vascularis* when carried in the blood, or can spread through the round window into cochlear tissue after topical or intratympanic administration (Juhn *et al.*, 1981: 135-141; Salt and Plontke, 2005:1299-1306), where they can damage internal ciliated cells, support cells, spiral ganglion cells, and the auditory nerve, although ciliated cell damage is the primary effect of ototoxicity.

Topical medication bridges the haemato-labyrinthine barrier (HLB) and directly access the inner ear. This causes topical administration to increase the concentration at the administration site and increase its absorption and toxicity (Juhn *et al.*, 1981: 135-141). The drug mixed with the fluids of the inner ear is eliminated through the absorption of epithelial cells of the *stria vascularis* and dark cells of the cochlea and vestibule and then into the bloodstream.

### **Aminoglycosides (AG)**

This is a group of drugs widely used in serious infections. Their action is bactericidal, with various action points such as plasma membrane alteration, drug absorption, and intracellular binding to ribosomal subunits and other cellular machinery (Davis, 1987: 341-350). AGs work by directly binding to 16S ribonucleic acid (RNA) ribosome in the 30S subunit of the bacterial ribosome, interrupting or terminating protein synthesis prematurely.

Although they could cause renal and cochlear toxicity, it appears that there is no relationship between renal dysfunction and the degree of hearing loss that occurs (Dulon *et al.*, 1988: 219-225; Hirvonen *et al.*, 2005: 643-655). There is a genetic basis for aminoglycoside-induced hearing loss due to mutations in human 12S rRNA (Jing *et al.*, 2015: 95-103). It should also be considered that clearance of aminoglycosides is slower in the inner ear than in serum and, therefore, there is a latency in the ototoxic effects of AGs, and a later onset of hearing loss may be observed that continues after treatment has been discontinued. It is therefore recommended to monitor their ototoxic effects in the patient for at least 6 months.

The toxicity of AGs varies in their preference for the cochlea or the vestibule. Gentamicin and streptomycin are

more vestibule-toxic and dihydrostreptomycin, amikacin and neomycin are mainly cochlea-toxic. The following must be mentioned in decreasing order of ototoxic power: neomycin, gentamicin, kanamycin, tobramycin, dihydrostreptomycin, amikacin and netilmicin (Kotecha and Richardson, 1994: 173-184).

Cochlear toxicity results in hearing loss that usually begins at high frequencies and is explained by the irreversible destruction of the ciliated cells in the organ of Corti, predominantly at the basal turn of the cochlea. In the vestibular system, type I ciliated cells are more sensitive to AG toxicity than type II ciliated cells (Hirvonen *et al.*, 2005: 643-655).

Although the exact mechanisms of ototoxicity are not fully understood, it is thought that it can be multi-factorial, inducing damage to sensory and non-sensory ciliated cells by altering homeostatic functions in the inner ear that directly modulate their function. Lesions may also occur in the neural pathway, from the periphery of the inner ear to the cerebral cortex, interrupting auditory and vestibular perception. AGs bind to numerous proteins within cells, potentially involving multiple mechanisms, through which these drugs can lead to the death of ciliated cells (Kros and Steyger, 2019: a033548).

Numerous studies have shown that AGs produce apoptosis by activating caspases. Animal and *in-vitro* studies have shown that by inhibiting these enzymes, ototoxic lesions from AGs can be prevented (Rizzi and Hirose, 2007: 352-357).

AGs can also cause ototoxicity if administered locally, although only if drops are used in patients with tympanic membrane perforation (Dulon *et al.*, 2013: 1-13). A topical ototoxicity study with gentamicin and neomycin in chronic suppurative otitis media demonstrated a high rate of cochlear and vestibular involvement. Therefore, their use in these processes is not recommended (Yorgason *et al.*, 2006: 383-399). The use of topical AGs would only be recommended in the event of failure of prior treatment with non-ototoxic drugs, although their application should be no longer than 10 days (Dulon *et al.*, 2013: 1-13).

***The effects of ototoxicity are usually permanent. Sometimes associated with tinnitus and vestibular disorders***

## Platins

Cisplatin ototoxicity increases with individual dose level, cumulative dose of cisplatin, concurrent cranial irradiation, noise exposure, co-administration of other ototoxic or nephrotoxic drugs, pre-existing hearing impairment, or renal impairment. Unlike aminoglycosides, children under the age of 4 are the most susceptible to cisplatin-induced hearing loss compared to older children.

Because many cancer patients tolerated their scheduled cisplatin therapy without any sign of hearing impairment and other patients experienced ototoxicity after their first dose of cisplatin, the search for an individual genetic marker that predicted patient risk was encouraged (Lanvers-Kaminsky and Ciarimboli, 2017: 1683-1695).

Cisplatin is transported through the cell membrane by CTR1 membrane transporters. Under physiological conditions, the substrate of CTR1 is monovalent copper (Cu<sup>+</sup>), which is essential for different enzymatic reactions (Holzer *et al.*, 2004: 817-823). Cisplatin is bound to the same extracellular methionine-rich receptors as Cu<sup>+</sup>, thus allowing entry into the cell. In addition, administration of intratympanic copper sulphate, a CTR1 inhibitor, has been shown to prevent cisplatin-induced hearing loss (More *et al.*, 2010: 9500-9509).

Ototoxicity occurs in the nucleus of the cell and is related to the drug triggering of an apoptotic cascade (Forge and Li, 2000: 97-115). Key modulators of apoptosis are a family of kinases known as mitogen-activated protein kinases (MAPKs). Products of the apoptotic pathway are translocated into mitochondria, resulting in the release of the cytochrome C, which triggers caspase-dependent apoptosis (Lee *et al.*, 2004: 69-74). Cisplatin causes increased levels of ROS (reactive oxygen species), which also activate the apoptotic pathway described above (Watanabe *et al.*, 2003: 219-225).

Damage to the ciliated cells of the cochlea is responsible for the hearing loss caused by this ototoxicity. The external ciliated cells of the basal turn of the cochlea are those initially affected, which is consistent with the clinical observation that acute auditory spectrum frequencies are the first to be altered. If exposure to cisplatin continues, damage progresses to the mean and apical loops and internal ciliated cells, causing the mean frequencies, including the conversational frequencies, to be altered.

### 3. AUDIOLOGICAL MONITORING AND TRACKING STRATEGIES

Monitoring techniques should be effective, sensitive and specific to enable: the comparison of audiological results during the course of ototoxic treatment, and the early detection of changes in auditory thresholds, providing decisions on changes in treatment aimed at preventing hearing impairment, and the indication of more appropriate auditory rehabilitation to minimise the negative effects of ototoxicity. They must also consider the principles of early detection and early treatment that govern all actions in paediatric audiology.

#### *The impact can be minimised by following an audiological ototoxicity monitoring programme that allows for early detection and early treatment*

The technique considered to be the reference standard for audiological monitoring during treatment with ototoxics is tonal audiometry, although the use of objective evidence is essential in patients who are very young or whose general condition is severely affected (Bass and Bhagat, 2014: 760-774).

The recommended audiological methods for assessing the hearing of children undergoing cancer treatment do not differ substantially from those used in other clinical situations. However, there are challenges that must be understood and managed in this context. Some of these difficulties are easily solved by modifying audiometric techniques, such as the introduction of creative activities that avoid boredom for a child who will be subjected to serial testing. If possible, the most detailed audiometry (baseline audiometry) should be obtained before starting treatment so that future serial audiometries can focus on the high frequencies of the spectrum, as they are critical for determining hearing loss. It is also important to note that chemotherapy drugs and cranial radiotherapy predispose children to chronic serous otitis media, so they should be frequently subjected to bone audiometry.

All these difficulties make it necessary in many cases to carry out additional objective tests such as otoacoustic emissions (OAEs), brainstem auditory evoked potentials (BAEPs), and steady-state evoked potentials (SSEPs) (Bass and Bhagat, 2014: 760-774).

Within acoustic otoemissions, distortion products (DPOAEs) can study high frequencies and provide useful

information on the cochlear status of children treated with chemotherapy. They experience a reduction in their amplitude before changes in the auditory thresholds can be recorded in conventional audiometry, thus detecting hearing loss at a very early stage.

*Burst*-evoked or steady-state potentials are highly recommended to ascertain the response in the range of 2 to 4 kHz, although individually it is deemed inadequate for monitoring ototoxicity, and a combined approach of behavioural audiometry with evoked potentials and/or DPOAE is always recommended for reliable assessment.

The most effective form of early detection of signs of ototoxicity is prospective monitoring of auditory sensitivity. Although ototoxic therapy can often not be altered (dose modification or drug change), monitoring offers an opportunity to address hearing loss early and avoid the associated sequelae.

A complete audiological monitoring protocol for ototoxicity in the paediatric population should include a pre-treatment baseline assessment followed by audiological testing during the course of treatment (platin) and audiological testing at the end of treatment.

- **Baseline assessment.** Medical history including information on prior exposure to ototoxic agents, noise, or other risk factors. Otoscopy. Tympanometry Pure tone audiometry (air and bone). DPOAE. BAEP and SSEP only in patients who cannot contribute to pure tone audiometry.
- **Assessment during treatment.** Otoscopy, tympanometry and pure tone audiometry are recommended. DPOAE will be obtained if possible. In the case of cisplatin therapy, this monitoring will be scheduled after each cycle, especially when 200 mg/m<sup>2</sup> is administered, or if a cumulative dose of 400 mg/m<sup>2</sup> is achieved.
- **End-of-treatment assessment.** Complete and baseline assessment is recommended. Patients receiving cisplatin will be assessed as soon as possible at the end of cycles with review visits at 3, 6, 9, and 12 months after completion of treatment and then annually for 10 years.

Likewise, patients who undergo additional cranial radiotherapy must be assessed before it and once it is complete, and is not considered necessary during treatment.

Once the results of the assessment are obtained, it is important to transform them into information that can be interpreted by the other professionals involved, so as to facilitate flexible communication. To this end, a system must be in place to classify the severity of hearing loss caused by a standardised and widely-accepted ototoxic effect.

## **The assessment of neonates treated with ototoxics within the screening programme will rule out the existence of hearing loss, and follow-up will detect late development, should it occur**

Recently, a panel recommended the use of a scale based on the work of Lewis *et al.*, (Lewis *et al.*, 2009: 387-391), known as the *International Society of Paediatric Oncology Boston Ototoxicity (SIOP) Grading Scale*. It is currently undergoing validation. It uses only 4 categories, with grades that correspond to the functional result, based on significant loss of speech spectrum audibility. The authors combined the qualities of the Boston, Brock, and Chang Children's Hospital Grading Scales, creating a scale based on the measurement of absolute audiological thresholds, which is sensitive to high frequency losses, mild losses, and can be easily implemented in the clinic (Brock *et al.*, 2012: 2408-2417).

Other clinical cancer trials support the international use of the SIOP-Boston Grading Scale for the classification of child ototoxicity. It is therefore advisable to use it to monitor ototoxicity in children, as it will allow for the reporting of consistent, standardised results between the different institutions, and represents an opportunity for the updating and validation of the classifications of cochlear toxicity (Crundwell *et al.*, 2016: 65-74). Recent advances in cancer treatment, otoprotection, and genetic factors related to ototoxicity further support this need (Bass and Bhagat, 2014: 760-774).

Although many previously developed scales foresee a baseline assessment, it is often impossible to perform. The SIOP-Boston ototoxicity grading scale does not require this baseline assessment, as the classification criteria are based on absolute auditory thresholds. In addition, it is sensitive to small changes in high frequencies, making its assessment relevant for recording the reduced audibility of important speech phonemes. Furthermore, this system must know very low frequency thresholds in order to successfully assign the degree of hearing impairment. The scale is shown in *Table 2*, and *Figure 1* illustrates the procedure for obtaining the necessary thresholds.

The expert panel that developed the SIOP-Boston Grading Scale recommended a minimal audiometric battery to help the clinician prioritise the order of frequencies to explore (Brock *et al.*, 2012: 2408-2417). This minimal battery is not intended to replace full diagnostic audiometry, but recognises the challenge of performing a thorough examination on a sick child. *Figure 2* summarises the potential outcomes for cisplatin-treated children.

Grades 0 to 4 can be assigned based on severity of hearing loss, and none require assessment of more than three frequencies (Fligor, 2019: 154-161).

This approach of monitoring for ototoxic hearing loss should also be applied in cases receiving any other ototoxic drugs, such as AGs.

In the case of neonates treated with ototoxics, assessment within the screening programme will rule out the existence of hearing loss, and the recommended follow-up in the future will detect late development hearing loss, should it occur (Núñez *et al.*, 2015: 163-186).

In other settings, such as a serious infectious disease in children outside the screening programme (sepsis, pyelonephritis, etc.), in which an AG must be used, the minimum battery of the SIOP-Boston System must be performed to detect or classify hearing loss with subsequent monitoring or, failing this, the use of additional objective techniques, such as BAEPs, OAEs, and high-frequency audiometry.

In specific cases, when the necessary collaboration for audiometry is not achieved, BAEPs may be used to document ototoxic hearing loss. Although not yet validated, there is a severity rating scale (Knight *et al.*, 2017: 440-445), which aims to differentiate mild cases from those with significant functional impact that require monitoring (*Table 3*) (King and Brewer, 2018: S89-S98).

DPOAEs have the potential to identify changes in cochlear function before deterioration in audiometric thresholds can be observed, and are therefore effective in detecting ototoxicity. However, as with evoked potentials, ototoxicity classification protocols have not yet validated their use to classify hearing loss, so assigning a degree of severity using these methods is currently a challenge for any protocol.

High-frequency audiometry is more sensitive than conventional audiometry in the early detection of ototoxicity because the drug damages the cochlea from the base to the apex. However, high-frequency audiometry results require a baseline to compare with serial test results. In addition, there is a pragmatic obstacle in not having this type of audiometry in all paediatric audiology units.

## 4. ADDITIONAL TESTS FOR EARLY DIAGNOSIS

### 4.1 Serological markers of hearing loss

Certain lines of current research are aimed at discovering blood markers of cochlear damage that would anticipate the existence of lesions secondary to the use of ototoxic drugs. These include the determination of proteins, such as prestin and microRNA.

#### Prestin

Prestin is a protein specific to the inner ear. It is found in the basolateral membrane of external ciliated cells, where it plays an important role in voltage-dependent electromotility and cochlear sensitivity. Experimentally-induced damage to prestin has been shown to lead to a reduction in the electromotility of these cells and a decrease of approximately 40-60 dB in cochlear sensitivity. After cell damage, structural proteins, such as prestin, are transmitted to the systemic circulation.

High doses of cisplatin and amikacin were associated with increases in the serum prestin level and the cochlear damage score. These results suggest that prestin is a promising early indicator of cochlear damage (Dogan *et al.*, 2018: 594-598).

There are up to eight proteins unique to the inner ear (otolin-1, otoconin 90/95, prestin, otoancorin, otogelin,  $\alpha$ -tectorin,  $\beta$ -tectorin, and cocolin). Others initially found in the inner ear were subsequently identified outside the ear (oncomodulin, otospiralin and otoraplin). All of these proteins could be used for future research on potential biomarkers for inner ear diseases. And each of them could even express a certain type of damage, as demonstrated by a study in which prestin increases in an attempt to compensate for the lack of external ciliated cells, and yet otolin-1 could be a circulatory biomarker for otoconia damage (Hana and Bawi, 2018: 60-64; Mulry and Parham, 2020: 145-152).

#### MicroRNA

MicroRNAs (miRNAs) are powerful modulators of gene expression and are involved in almost all primary biological processes, including proliferation, apoptosis, differentiation, and organogenesis. MiRNA profiles appear to be cell-specific. Identifying an increased miRNA profile in circulating blood can help determine the diagnosis, type of injury, and affected tissue.

Following ototoxic damage, miR-205 circulation from the cochlea migrates through blood vessels to organs and is eventually found in the blood. In conditions of ototoxic hearing loss, the detection

of miR-205 circulating in the blood may be used to determine its extent. In the future, injury to the inner ear caused by ototoxicity could be identified simply by performing a blood test.

***Certain lines of study are aimed at discovering blood markers of cochlear damage that would anticipate the existence of lesions secondary to the use of ototoxic drugs.***

Several studies have been published on other miRNAs in different ototoxicity models. For example, miR-183 is actively expressed in kanamycin-induced ototoxicity; however, it is expressed only around injured tissues and not in blood. The disease signalling pathway caused by AGs is associated with reactive oxygen radicals (ROS), and miR-183 may be involved in this process. More studies on different miRNAs are needed (Lee *et al.*, 2018: E2836).

### 4.2 Genetic risk factors

Among the well-known risk factors for hearing loss, there is one of particular relevance related to the use of AGs. A small proportion of the paediatric population with mutations in mitochondrial rRNA genes is particularly sensitive to treatment with these antibiotics (sometimes even after a single dose) and may have immediate or subsequent secondary hearing loss despite the use of correct doses and/or maintaining of adequate levels. This group could represent up to 10-20% of patients with AG-induced ototoxicity (El-Barbary *et al.*, 2015: 1294-1298).

The MT-RNR1 gene encoding the mitochondrial ribosomal subunit 12S is responsible for mutations in aminoglycoside-induced hearing loss. There are several mutations responsible for this effect. In general, the most common mitochondrial mutation is A1555G, followed by C1494T (Igumnova *et al.*, 2019: 199-206; Nguyen and Jeyakumar, 2019: 15-19), but incidence varies across ethnicities.

The prevalence of m.1555A→G mutation in children in Europe is 1 in 520, i.e. 0.19% (Bitner-Glindzicz *et al.*, 2009: 640-642).

In Spain, a study in Cantabria found a prevalence of the A1555G mutation among 25.8% of patients with a family history of hearing loss and in 75% of patients with cochlear ototoxicity and a family history of hearing loss (Gallo-Terán *et al.*, 2002: 563-571). A detailed

maternal family history that may reveal a history of hearing loss after administering AGs is essential to establish initial suspicion (Vital *et al.*, 2015: 156-165).

With regard to cisplatin, genome-wide association studies (GWAS) provide an opportunity for large-scale research into the role genetic variation plays in the development of ototoxicity.

Drögenmüller demonstrates the role of variant ACYP2rs1872328 in cisplatin ototoxicity in different types of cancer, and so it may be of use (Drögenmüller *et al.*, 2018: 1866-1871). The Clemens Study (Clemens *et al.*, 2020: 294-305) highlights the need to identify genetic biomarkers for the individualised treatment of patients receiving cisplatin, and confirms two potential genetic markers: rs1872328 in acylphosphatase 2 (ACYP2) and rs316019 in organic cation transporter 2 (SLC22A2), although there is not enough evidence to date. Future association studies, including the genome-wide studies, may help identify appropriate genetic markers (Trendowski *et al.*, 2019: 1147-1155).

Some studies have also concluded that the development of the ototoxic effect of platinum-containing drugs is influenced by the presence or absence of certain types of glutathione S-transferase (GST) enzymes, which are partly responsible for its metabolism. On analysing the polymorphisms GSTT1, GSTM1 and GSTP1, they conclude that the genotypes GSTM1null and GSTT1null proved to be independent markers of uni and bilateral acute ototoxicity, respectively. The *initial* identification of this high-risk group may serve as the basis for a better definition of individualised treatment and targeted use of new otoprotective drugs (Budai *et al.*, 2020: 963-971).

## 5. PREVENTIVE STRATEGIES AND TREATMENTS

### 5.1 Preventive Strategies

Minimising the ototoxicity of drugs without inhibiting their efficacy is now a very active field of research. So far, no ideal therapy has been found to treat ototoxicity, so prevention may be a more effective strategy than trying to find a treatment (Guo *et al.*, 2019: 17-36).

The main preventive measure is to strictly observe the indications of ototoxic drugs, avoiding their use when it is not absolutely necessary. Furthermore, it is advisable to implement protocols for the management of ototoxicity in the hospital environment, as their existence is currently minority (some extensive studies show that they are missing in 72% of hospitals in developed countries) (Maru and Malky, 2018: 576-588). A simple and useful otoprotective measure to prevent further injury by the drug would be to reduce its dose, as lower doses are

associated with a lower ototoxic effect, although this is not always possible.

### **Minimising the ototoxicity of drugs without inhibiting their efficacy is now a very active field of research**

An attempt may also be made to change the dosing schedule, which could lead to safer pharmacodynamics, with a reduced concentration and even a drug-free period during treatment, resulting in its reduced accumulation in the inner ear. Hence changes in AG dosing intervals by age (Laurell, 2019: 434-439). Routine measurement of plasma levels is recommended for dose adjustments. The impact of gentamicin on hearing has been shown in the paediatric population to be minimised by scheduling short-term treatments, monitoring drug levels, and adjusting doses (El-Barbary *et al.*, 2015: 1294-1298). Plasma cisplatin levels are not commonly used in clinical practice and, therefore, these recommendations would not be useful in this case.

One option would be the development and use of less toxic drug variants. For example, etimicin is a fourth-generation AG currently used in clinical practice in China due to its high efficacy, and has demonstrated minimal oto-nephrotoxicity resulting from its reduced accumulation in mitochondria of target cells (Yao *et al.*, 2020: 866-878). Other AGs with lower toxicity under study include apramycin and gentamicin C1 (Ishikawa *et al.*, 2019: 2410).

Furthermore, research is being performed on the modification of existing AGs to try to reduce the incidence of hearing loss. For example, certain chemical modifications of apramycin and geneticin, considered among the least and most toxic AGs respectively, reduce auditory cell damage (Zada *et al.*, 2020: 3077-3087).

In the case of platins, the ototoxicity scale of several compounds is known, which may lead to a change in treatment in situations of otological risk (e.g. carboplatinum).

### 5.2 Otoprotective drugs

As indicated above, the molecular mechanisms of ototoxic injury are complex and involve multiple processes including induction of oxidative stress, characterised by production of reactive oxygen species (ROS) and lipid peroxidation, inflammation through activation of pro-inflammatory factors, and induction

of p53-dependent signalling pathways (O'Reilly *et al.*, 2019: 416).

The introduction of otoprotective drugs is a very interesting therapeutic option, with some promising results, resulting from the possibility of using drugs with antioxidant potential or other mechanisms to prevent the ototoxicity of several compounds (Le Prell, 2019: 162-176). They act as a shield for the inner ear, and increase the antioxidant machinery of mitochondria.

## **The introduction of otoprotective drugs is a very interesting therapeutic option, with some promising results**

Although quality studies regarding otoprotection are lacking, there are some publications that show that drugs can be used to prevent or reduce ototoxicity. Among these, the most studied are:

- **N-acetyl cysteine (NAC)**, which has several mechanisms of action with positive results in AG treatments. Controversial results exist in patients treated with cisplatin and regarding NAC. On one hand, it has been reported that high frequency hearing loss (8 kHz and higher) can be prevented in several studies with intratympanic or oral treatment. On the other, different studies have not detected this preventive effect in response to cisplatin-induced hearing loss. Further data on the optimal dose of NAC and the form of administration are needed to protect against noise-related ototoxicity, cisplatin and aminoglycosides. A combined approach with inhibition of NFAT (nuclear factor of activated T cells) together with an antioxidant such as NAC or L-carnitine could also be useful for the treatment and/or prevention of hearing loss in various cases (Sekulic-Jablanovic *et al.*, 2019: e14921).
- **Sodium thiosulphate (STS)**, the protective effect of which on hearing loss caused by cisplatin has been demonstrated in several clinical trials in children. Similar to NAC, it is inactive and eliminates cisplatin toxicity, reducing antitumour action. Therefore, a delay in its administration is recommended (approximately 6 hours after cisplatin) to minimise interference with the antitumour action of this drug (Dos Santos *et al.*, 2020: 111079).
- **Amifostine** is another substance that acts in a similar way to thiosulphate. This compound is

currently used as a nephroprotector in cisplatin treatments, but there are no studies that have confirmed its efficacy in hearing protection and, therefore, it is not used in clinical practice (Romano *et al.*, 2020: 1266; Dos Santos *et al.*, 2020: 111079).

- **D-methionine** is an amino acid that plays an important role in the re-synthesis of glutathione in response to its depletion, and acts as an antioxidant. Based on promising results in reducing cisplatin-induced hearing loss in animal models, a human clinical trial was also conducted that demonstrated reductions in threshold change for high frequencies (Laurell, 2019: 434-439).

There are a variety of nutritional supplements and even cosmetic ingredients to reduce oxidative stress in the inner ear that have shown some otoprotective effect in experimental animals or in humans. Furthermore, several L-type and T-type calcium channel blockers have been shown to reduce both external ciliated cell loss and noise-induced hearing loss (Laurell, 2019: 434-439).

### **Anti-inflammatory drugs**

Inflammation is crucial for the pathogenesis of acquired neurosensory hearing loss, but the precise mechanism involved remains unknown.

**Steroids** are otoprotective, but can also decrease the antitumour effectiveness of platinum-based drugs when administered systemically, and they pose safety concerns in long or chronic doses, particularly in children, so their utility is very limited (Ramaswamy *et al.*, 2017: 268).

A prospective, randomised, double-blind study with 195 patients demonstrated a protective effect of **acetyl salicylic acid (ASA)** on ototoxicity caused by gentamicin (Sha *et al.*, 2006: 1856-1857), although high-dose ASA is known to be ototoxic. ASA has not been shown to be useful for otoprotection against cisplatin (Crabb *et al.*, 2017: 75-83).

However, among a number of inflammatory mediators, tumour necrosis factor alpha (TNF- $\alpha$ ) plays a key role in cisplatin ototoxicity. The combination of (interferon) IFN- $\gamma$  and TNF- $\alpha$  appears to increase the cytotoxicity of cisplatin to *ex vivo* cochlear sensory cells, opening up a whole path to using **anti-TNF and anti-IFN drugs** in the prevention of cochlear damage.

**Statins** could also be otoprotective agents based on their antioxidant effect, as well as their anti-inflammatory properties (Prayuenyong *et al.*, 2020: 21-31).

Table 4 shows some of the main otoprotective drugs discussed, with their corresponding target action.

Otoprotective drugs may be administered by several routes. Systemic administration has the advantage of being a common and simple form, with easy to determine pharmacokinetics because it does not require specialist equipment. However, the main disadvantage is the potential of the drug to inhibit the antitumour function of other treatments. In addition, the amount of drug that reaches the inner ear is questionable and difficult to determine, as it is not currently possible to obtain a patient's perilymph or endolymph without damaging the structures of the inner ear. Transtympanic administration, on the other hand, may prevent systemic side effects and potentially reach the inner ear more easily; however, perilymph or endolymph concentrations may be unpredictable.

### **Protocols for the management of ototoxicity in the hospital setting are recommended**

Other factors that may also affect the permeability of the drug in the inner ear include viscosity, pH, molecular weight, use of facilitators, and thickness of the round window.

Important aspects to consider are also the time and equipment required, as it requires administration by an otolaryngologist, as well as an examination microscope, and can be difficult to perform in a paediatric patient.

Finally, side effects may occur as a result of the drug itself, such as inflammation of the middle ear mucosa or vertigo, and perforation of the tympanic membrane. The main advantage of this route is to avoid large concentrations of the product in blood (Waissbluth, 2020: 2413-2422).

The inhalation route could also be used. Inhaled **aqueous and gaseous hydrogen (H<sub>2</sub>)** has effects on the prevention of ischemia in several ototoxicity and nephrotoxicity models, allegedly reducing oxidative stress (Fransson *et al.*, 2017: 280; Kros and Steyger, 2019: a033548).

It is important to point out a number of medical and ethical issues regarding otoprotection in clinical practice (Laurell, 2019: 434-439). These include:

- Otoprotection measures should not cause any decrease in the effectiveness of the ototoxic drug in the treatment setting for which it is indicated.

### **The family of the child treated with ototoxics should receive information and guidance on the possibility of developing early and long-term hearing difficulties**

- The risk of drug-induced hearing loss from a drug therapy should be substantial enough to motivate the administration of otoprotectors.
- The otoprotective measure should cause minimal side effects.
- Otoprotection must have a reasonable cost-benefit ratio.

In conclusion, the search for drugs that can reduce hearing damage from ototoxic compounds is still an ongoing challenge, and their resolution would lead to significant improvements in patients' quality of life.

There are several challenges regarding the prevention of ototoxicity, such as ignoring the mechanisms of ototoxicity for each individual, knowing which otoprotection strategy is best for each ototoxic, and translating this knowledge into an effective therapeutic intervention.

No definitive conclusions can currently be drawn on the benefits and risks of otoprotection; however, it must be considered that the fact that there is no evidence on its effect does not mean that it does not exist ("no evidence of effect" is not the same as "evidence of no effect"). Therefore, more high-quality research is needed (Van As *et al.*, 2019: CD009219).

## 6. CODEPEH RECOMMENDATIONS 2020

It is advisable to implement protocols for the management of ototoxicity in the hospital environment, as their existence is currently minority (some extensive studies show that they are missing in 72% of hospitals in developed countries) (Maru and Malky, 2018: S76-S88).

CODEPEH recommendations for early detection, prophylaxis, otoprotection, monitoring, and treatment of ototoxicity due to AG antibiotics and platinum-based anticancer agents in the paediatric population are presented below and summarised graphically in *Figure 3*.

- 1. The complete audiological monitoring protocol** for ototoxicity in the paediatric population should include a pre-treatment baseline assessment followed by audiological testing during the course of treatment (platins) and audiological testing at the end of treatment.
- 2. The reference technique for audiological monitoring** during treatment with ototoxic drugs is **tonal audiometry**, although the use of objective evidence is essential in patients who are unable to cooperate while it is being performed.
- 3. The standardised criteria for grading hearing loss due to ototoxicity** are listed on the SIOP-Boston grading scale, so their use for monitoring ototoxicity is recommended.
- 4. The determining of blood markers of cochlear damage**, such as proteins in the inner ear or miRNA, may anticipate lesions secondary to the use of ototoxic drugs.
- 5. Genetic testing** may help detect at-risk patients, such as mutations in the MT-RNR1 gene, which are responsible for aminoglycoside-induced hearing loss.
- 6. The main preventive measure** is to strictly comply with the indications of ototoxic drugs, avoiding their use when it is not absolutely necessary.
- 7. Other simple** and useful measures to prevent further injury by the drug are to reduce its dose, change its dosage, and/or control its levels, as well as the development and use of less toxic drug variants.
- 8. Otoprotective substances are a very interesting therapeutic option** based on using drugs with anti-oxidant potential or other mechanisms that can prevent the ototoxicity of several compounds.
- 9. It is advisable to inform and guide the patient and his/her family** about the possibility of developing early and long-term hearing difficulties, which may occur as a result of receiving treatment with ototoxic drugs, in order for them to request a specialist assessment.
- 10. Any child who has received ototoxic treatment**, regardless of his or her hearing status, must be monitored for ten years. If hearing loss is detected, it must be addressed early with audiological treatment and speech therapy intervention.

TABLE 1. Selection of Ototoxic Medicinal Products (Cianfrone *et al.*, 2011)

Ototoxic Drugs		
Drug class	Drug	Site of action
Aminoglycosides	Streptomycin Gentamicin	Cochlea - Vestibule → Vestibule
	Dihydrostreptomycin Amikacin Kanamycin Tobramycin Neomycin	→ Cochlea
Macrolides		Cochlea
Glycopeptides		Auditory N. - Vestibule
Other antibiotics	Minocycline Chloramphenicol Cephalexin	Cochlea - Vestibule
Loop diuretics		Cochlea
Antimalarials		Cochlea and/or Lobby
Salicylates		Cochlea
Platinum derivatives		Cochlea and/or Lobby

**TABLE 2. SIOP-Boston Ototoxicity Grading Scale**  
(Brock et al., 2012)

<b>SIOP-Boston Ototoxicity Grading</b>	
<b>GRADE</b>	<b>AUDIOMETRIC THRESHOLD</b>
<b>0</b>	<b>≤ 20 dB HL at all frequencies</b>
<b>1</b>	<b>&gt; 20 dB HL at 6 kHz or 8 kHz</b>
<b>2</b>	<b>&gt; 20 dB HL at 4 kHz and above</b>
<b>3</b>	<b>&gt; 20 dB HL at 2 kHz or 3kHz and above</b>
<b>4</b>	<b>&gt; 40 dB HL at 2 kHz and above</b>

**TABLE 3. Severity Rating Scale for Ototoxic Hearing Loss** (King and Brewer, 2018)

*(0.5 to 4 kHz tone burst stimuli are used, assuming normal middle ear function)*

<b>Severity of ototoxic hearing loss</b>	
<b>GRADE</b>	<b>PEA THRESHOLD 0.5 4 KHz)</b>
<b>1</b>	<b>Threshold change &gt; 10 to ≤ 20 dB at 4 kHz in at least one ear</b>
<b>2</b>	<b>Threshold change &gt; 20 dB at 4 kHz in at least one ear</b>
<b>3</b>	<b>Threshold change &gt; 20 dB at 2 kHz in at least one ear</b>
<b>4</b>	<b>Absolute thresholds &gt; 80 dB at 1 to 4 kHz in both ears (not present at baseline assessment)</b>

TABLE 4. Some Recognised Otoprotective Drugs (Adapted from av)

Otoprotective Drugs		
TARGET	DRUG	
Alpha-lipoic acid	Aminoglycosides Carboplatin Cisplatin	(Hussain et al., 2005: 198-206)
Amifostine	Cisplatin	(Duval and Daniel., 2012: 309-315)
Coenzyme Q 10	Gentamicin Cisplatin	(Astolfi et al., 2016: e0162106)
D-methionine	Aminoglycosides Carboplatin Cisplatin	(Hamstra et al., 2010: 2666-2676) (Fox et al., 2016: 518-530)
Ebselen	Gentamicin Tobramycin Carboplatin Cisplatin	(Kil et al., 2017: 969-979)
Gingko Biloba	Aminoglycosides	(Ma et al., 2015:949-959)
N-acetyl-cysteine	Aminoglycosides Cisplatin	(Kranzer et al., 2015:1070-1077)
Pantoprazole	Cisplatin	(Huang et al., 2013: 585-592)
Aspirin	Gentamicin	(Crabb et al., 2017: 75-82)
Sodium thiosulphate	Gentamicin Cisplatin	(Freyer et al., 2017: 63-74)
Steroids	Gentamicin Cisplatin	(Özel et al., 2016: 225-234)
Vitamins with Magnesium	Aminoglycosides Cisplatin	(Villani et al., 2016: E2118.
Avocado oil	Aminoglycosides Cisplatin	(Pham et al., 2020: 947)
Astaxanthin	Aminoglycosides Cisplatin	(Gu et al., 2020: 53)
Pentoxifylline	Amikacin	(El-Anwar et al., 2018: E8-E12.
Paeoniflorin	Neomycin	(Yu et al., 2018: 9-19)
Misoprostol	Aminoglycosides Cisplatin	(Dogan et al., 2017: 140-144)
Curcumin Ferulic acid	Cisplatin	(Paciello et al., 2020: 1063)
Rapamycin Pasireotide	Gentamicin	(Guo et al., 2019: 475-487) (Kucharava et al, 2019: 110)

**FIGURE 1. Diagram of the Minimum Audiometric Test Battery**(Fligor, 2019)

*(This test needs only two or three frequencies to apply the SIOP-Boston ototoxicity severity grading scale)*

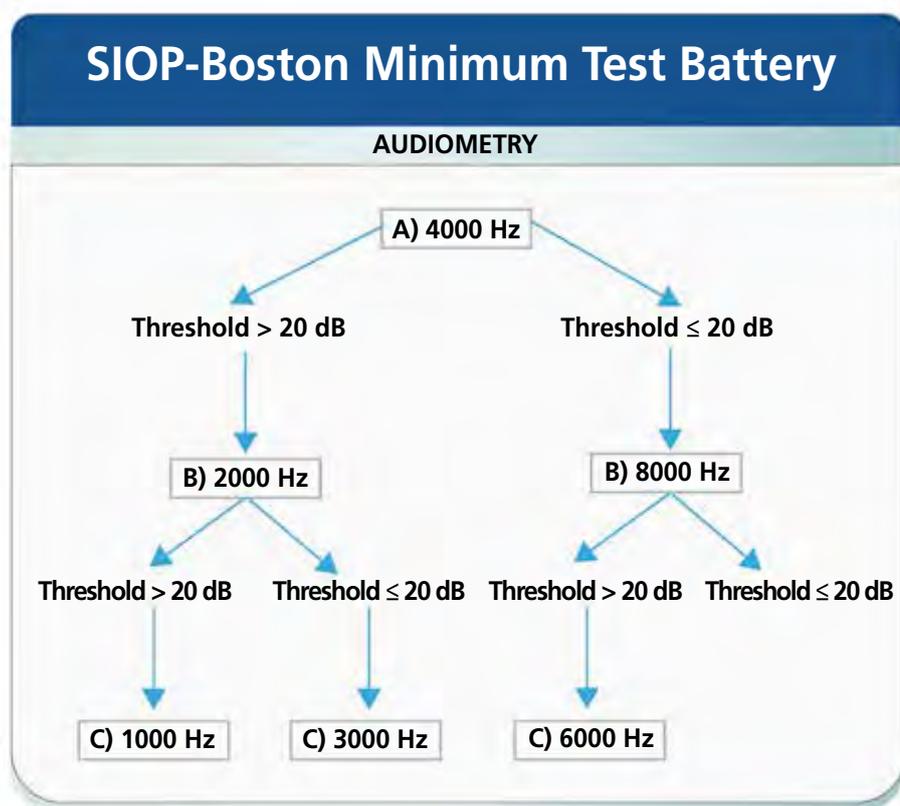
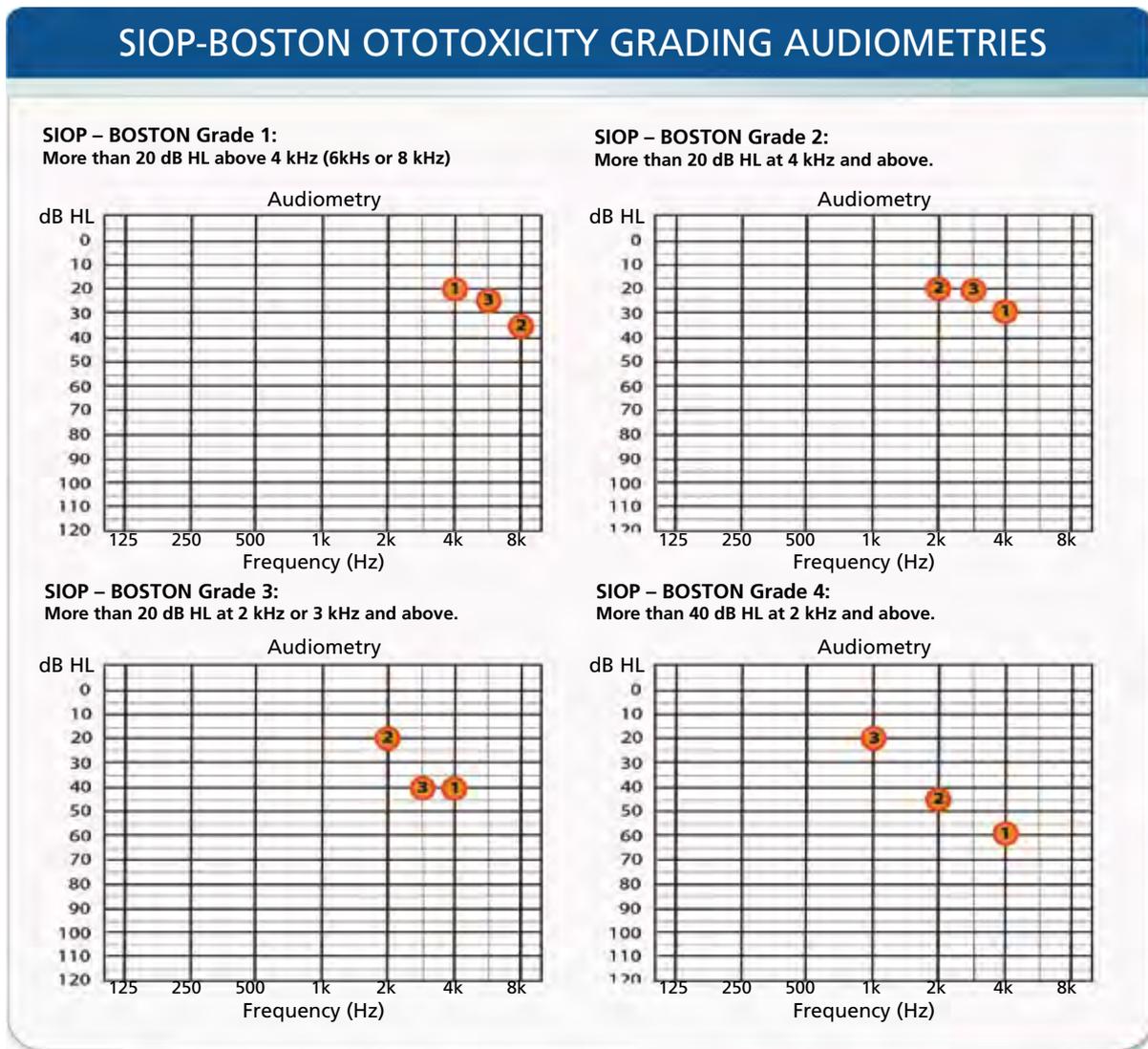


FIGURE 2. SIOP-Boston Audiometry Graphs (Fligor, 2019)



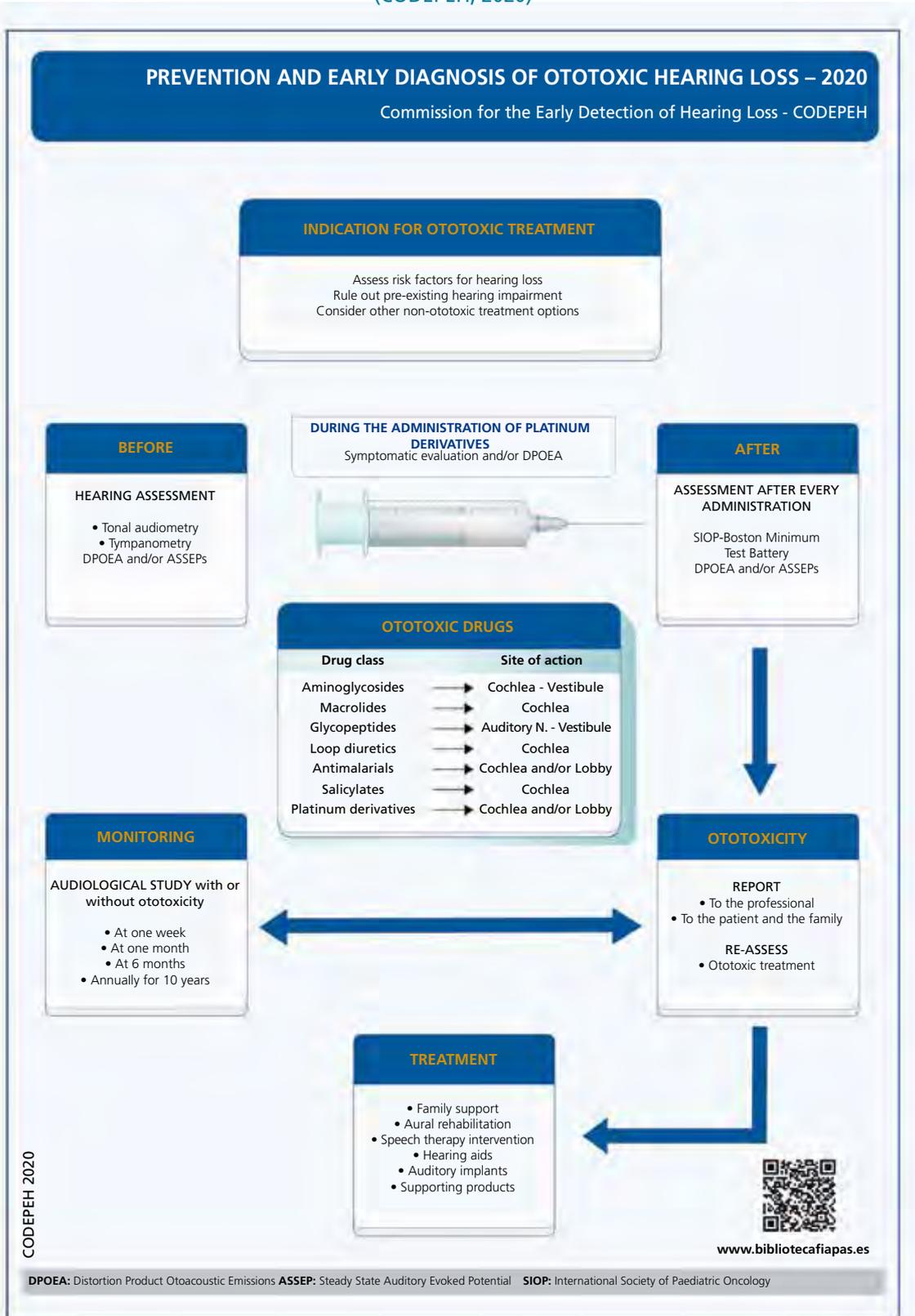
**Grade 1 (A).** According to the minimum audiometric battery test, the threshold is first determined at 4 kHz (marked with 1) and at a threshold of 20 dB, then the frequency threshold is determined at 8 kHz (marked with 2). If the threshold at 8 kHz is greater than 20 dB, the threshold at 6 kHz (marked with 3) is determined.

**Grade 2 (B).** The threshold is determined at 4 kHz (marked with 1), if the threshold is greater than 20 dB the threshold is determined at 2 kHz (marked with 2). If the threshold is 20 dB, 3kHz (marked with 3) is determined in third place.

**Grade 3 (C).** The threshold is determined at 4 kHz (marked with 1), if it is greater than 20 dB, then 2 kHz (marked with 2) is determined second. If the threshold at 2 kHz is 20 dB, the threshold at 3 kHz (marked with 3) is determined third.

**Grade 4 (D).** The threshold is determined at 4 kHz (marked with 1), if it is greater than 20 dB the threshold is determined at 2 kHz in second place (marked with 2). If it is greater than 20 dB, the threshold is determined at 1 kHz in third place (indicated with 3).

**FIGURE 3. Proposed Protocol for Early Detection, Prophylaxis, Otoprotection, Monitoring, and Treatment of Ototoxicity due to AG Antibiotics and Platinum-Based Anticancer Agents in the Paediatric Population (CODEPEH, 2020)**



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