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Platinum Induced Ototoxicity in Childhood Cancer Survivors

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Abstract: Cisplatin and carboplatin, the platinum compounds, are widely utilized towards a number of malignancies. Treatment with these compounds, despite their efficacy, frequently contributes to severe side impacts, like nephrotoxicity, neurotoxicity and ototoxicity. Ototoxicity caused by platinum is clinically expressed as bilateral, progressive and permanent sensory neural hearing loss, resulting in devastating effects on cancer survivors' quality of life. Tinnitus may also be shown in sufferers. Age, cumulative dosage, renal dysfunction, concomitant ototoxic drugs, and head (cochlear) radiotherapy are thought to play a function in its severity. Research has lately made progress in deciding if such genetic polymorphisms predispose patients to ototoxicity caused by platinum. This study aimed to assess the frequency of ototoxicity and associated risk factors in survivors of childhood cancer receiving platinum-based chemotherapy and to detect the relation between GSTP1 c.313A>G (rs1695) poleomorphism and ototoxicity.
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Introduction

Chemotherapy is a core component of treatment for pediatric cancer (Bertolini et al., 2004).

Unfortunately, the use of cisplatin and carboplatin can result in serious side effects, including nephrotoxicity, neurotoxicity, and ototoxicity. **(Ruggiero et al., 2013).**

Platinum- induced ototoxicity has been defined as a sensorineural hearing loss that is bilateral, progressive, and permanent. It has additionally been found that, years following finishing of their chemotherapy remedy, sufferers may experience hearing loss and may also show tinnitus. Hearing loss (HL) can be devastating, especially in children, as it could have a detrimental effect on their capacity to learn, develop, and communicate with their colleagues. It was demonstrated that even a mild degree of deafness will affect the growth and psychological condition of a child. It may also have distressing effects on the quality of life of survivors of childhood cancer. **(Waissbluth et al., 2018)**

For platinum-induced ototoxicity, numerous threat variables had been identified. Remedial age (patients under 5 years of age), excessive cumulative dosage, pre-present kidney impairment, pre-present deafness, consequent use of ototoxic medications, and cranial irradiation are thought to play a function in its seriousness **(Thiesen S et al., 2017)**

Increasing variety of research indicate that genetics can be a significant factor in ototoxicity. One of the cytotoxic mechanisms of cisplatin is to result in oxidant stress producing reactive oxygen species from which cochlea cells are blanketed through excessive levels of antioxidant enzymes, such as glutathione-S-transferases (GST), or superoxide dismutases (SOD). Deletion of 3 nucleotides in the GSTM3 gene was shown to have defensive function, while hearing loss was associated with the possession of the GSTT1 and GSTM1 and GSTP1 genes **(Lui et al., 2018)**

Glutathione S-transferases (GSTs), a metabolic phase II isoenzyme, have a major function in the protection of cells by scavenging cisplatin-induced free radicals and catalyzing cisplatin by combining it with glutathione **(Choeyprasert et al., 2013)**

(GSTs), a family of enzymes, the dominant member of which is the GSTP1 isoenzyme. **(Wang et al., 2015)**

The single nucleotide polymorphism of GSTP1 c.313A > G contributes to the replacement of isoleucine for valine (p.Ile105Val) resulting in a hypoactive enzyme and hence the synthesized enzyme's ability to detoxify and reduce the rate of its biological effect. **(Wang et al., 2018)**

For better regulation of cancer care in pediatric patients, the elucidation of correlations among genetic factors and the risk of ototoxicity are essential.

This study hypothesizes that genetic variant of GSTP1 (rs1695) gene can lead to the susceptibility to hearing loss caused by cisplatin and carboplatin in children treated for a range of malignancies.

Pediatric Cancer

A term used to identify cancers that happen among birth and 15 years of age is pediatric cancer. Childhood cancers are uncommon, and the way they develop and propagate, how they are handled, and how they react to treatment can vary from adult cancers (**National Cancer Institute, 2018**).

Incidence of pediatric cancer:

There is a great difference of incidence and mortality rates of childhood cancers worldwide and this great variation occurs with comparison of high-income countries to low-income ones, **(Torre et al, 2016)**. This can be attributed to variations in the ability to detect cancer, variations in threat among different subgroups of the ethnic or racial community, as well as variations in risk factors. Examples of different threat factors include pediatric Burkitt lymphoma, a type of non-Hodgkin lymphoma which affects 6 to 7 of every 100,000 children per year in parts of sub-Saharan Africa in which both the Epstein-Barr virus and malaria have a history of infection. Burkitt lymphoma is not correlated with these contagious conditions in developed nations **(Lima et al, 2013)**.

According to study at the South Egypt Cancer Institute's (SECI) Department of Pediatric Oncology, Assiut University, pediatric tumor constituted 11.1% of the total cancer cases admitted to SECI **(Ali et al., 2016).**

And this is comparable to the findings of National Cancer Institute (NCI) Egypt during the period from 2002 to 2005 (10.2%) **(El-Attar., 2004)** and higher than other studies reported5% in Aswan **(Ibrahim and Mikhail, 2010)**

The maximum number of pediatric malignancy cases in that study was observed between the first and the fifth age groups (42.8%), 30.1% of instances were in the age group 5-10 years and 27.1% was older than 9 years **(Ali et al., 2016).**

In Aswan, Egypt, the highest prevalence was 1-4 years of age (44.4 % for men, 52.2 % for women and 47.5 % for both genders) **(Ibrahim and Mikhail, 2010)**

Less than 1% of all cancers diagnosed per year globally are childhood cancers. Around 10,590 children under the age of 15 in the United States were diagnosed with cancer in 2018. In the last few decades, childhood cancer rates have increased marginally **(Howlader, 2017**).

More than 80 %of children with cancer are now living for 5 years or more due to major medical advancements in recent decades. Overall, since the mid-1970s, when the five-year survival rate was about 58%, there has been significant improvement. However, survival rates differ depending on the specific of cancer and other variables **(kassam et al., 2018**).

After accidents, in children aged 1 to 14, cancer is the second major reason of death. In 2018, around 1,180 children under the age of 15 are projected to die from cancer (**American Cancer Society, 2016**).

Ototoxicity

Ototoxicity refers to the harm caused by exogenous agents including pharmaceuticals, chemicals and ionizing radiation, heavy metals and solvents to the structure and functions of the auditory-vestibular system **(Steyger et al, 2018).**

Ototoxicity encompasses cochleo- toxicity, vestibulotoxicity, and neurotoxicity. **(Watts, 2019).**

There are between 200 and 600 drugs which may trigger hearing and/or balance damage. **(Cianfrone et al., 2011).**

Platinum-Based Antineoplastic Drugs

In 1978, the launch of the first anti-cancer drug based on platinum, cisplatin, revolutionized the management of some cancers. Cisplatin has been extremely effective in the management of testicular cancer, according to Cancer Research UK, and currently, with surgery and combined chemotherapy therapy, there is a cure rate nearing 100% for this disease **(Gomez- Ruiz et al., 2012).** Cisplatin is a platinum compound which, when delivered directly into the bloodstream by an intravenous injection, it acts to kill cancer cells and avoid their multiplication by reacting with DNA (**Johnstone et al., 2014**)

An unintended discovery was the capacity of platinum compounds to destroy off cancer cells. US biochemist Barnett Rosenberg performed research in 1965 into the impact of an electrical field on the growth of bacteria. Inexplicably, by failing to split and dying off, the bacteria cells responded **(Oun et al., 2018)**

Rosenberg originally assumed this was due to the impacts of the electrical field, but subsequent studies led to the assumption that the platinum electrodes used to build the electrical circuit reacted to the test solution themselves. This reaction formed a platinum compound, which was ultimately responsible for the cells being destroyed **(Gomez-Ruiz et al., 2012)**

Researchers have found that cancer cells act in a similar way on the basis of this information: the platinum compound that causes them to die. From here, several years of comprehensive studies contributed to the development of cisplatin, which started clinical studies in the United Kingdom in 1971, selected from a range of possible molecular combinations to achieve an optimal balance between

toxicity and effectiveness **(Johnstone et al., 2014)**

Platinum Induced Ototoxicity in Children

The incidence in children and adults

The prevalence of cisplatin-induced ototoxicity is approximately 63–77% in paediatric patients. **(Brock et al., 2018 - Rybak et al., 2019).**

Carboplatin is much less ototoxic, but with high-dose treatment, hearing loss can happen. **(Brook et al., 2018)**.

Ototoxicity reaches 80-90 % if both medications are being used in combination (Landier et al, 2014**).**

Although there are several reports that report ototoxicity correlated with platinum-based chemotherapy, limited sample sizes, insufficient baseline measurements and non-standard audiometric measurement reporting characterize the literature. The incidence of ototoxicity dependent on platinum in adults recorded in the literature is about 50-80% **(Frisina et al., 2016 – Skalleberg et L., 2017)** and 60–90% in children **(Van As et al., 2016 – Baguley et al., 2020)**.

The occurrence of ototoxicity of cisplatin in children and adults is variable. Differences can be attributed to a variety of variables, like dosage variations, both within a cycle and the overall amount of multi-cycle administration, the time period between courses, the method of administration and the period of therapy, as well as disparities in the population of patients. Therefore, further exploration in this respect is required **(paken et al., 2019)**

Clinical presentation

Platinum associated with platinum typically presents as permanent, progressive, bilateral, high-frequency sensorineural tinnitus deafness. **(Waissbluth et al., 2017**). Tinnitus may occur even without hearing loss **(Baguely et al., 2020)** and can be irreversible or temporary. A little hours following therapy, or instead a week after therapy, often disappears **(Arora et al., 2009)**. Due to the lack of studies in this field, the incidence of tinnitus correlated with ototoxicity caused by platinum is uncertain in the literary works, but it is probably to be underreported and underappreciated **(Van As et al., 2016)**.

Although much of the hearing loss is irreversible, intermittent and partial recovery often occurs. Moreover, rare instances of unilateral hearing loss, typically explained by the location of the tumor and by surgical or therapeutic interventions on the affected side, have been identified. **(2016, Paken et al.).** In addition, hearing loss is not necessarily symmetrical **(Jenkins et al., 2009**)

Risk factors for platinum ototoxicity

With the amount of the person single dosage as well as the combined cisplatin dosage of > 400 mg / m2, the risk of cisplatin-induced ototoxicity rises **(Rybak et al., 2019)**. Furthermore, age ≤ 4 years, male age, combined cranial irradiation, noise exposure **(Lanvers-kaminsky et al., 2017),** co-medication with other ototoxic and nephrotoxic medicines, such as loop diuretics or aminogylcosides, extra carboplatin therapy, pre-existing hearing loss or kidney deficiency, pose a hazard of ototoxicity caused by cisplatin. **(Waissbluth et al., 2018)**.

Genetic and pathophysiology

While treatment-related risk factors have been reported for hearing loss following treatments for childhood cancer, in some people, in which other children may not suffer hearing loss following multiple and elevated dose of platinum agents, irreversible hearing loss can happen following a single dose of platinum medication. **(Thiesen et al., 2017)**

Therefore, several studies suggest a role for genetic susceptibility, but, the findings that were released were not reliable, with several of the studies documenting conflicting findings. **(Drogmemoller et al., 2019)**

Here the most common genes mentioned in the literature and associated with platinum ototoxicity in pediatric:

Glutathion-S-Transferases (GST) genes

(GST) are antioxidant enzymes which, through scavenging unfastened oxygen radicals, protect the cell **(Sheth et al, 2017)**

Single nucleotide proteins (SNPs) in various GST (GSTM, GSTP, GSTT) isoforms contribute to a decrease in enzyme activity that may contribute to ototoxicity **(Mukherjea et al, 2013).**

This gene on chromosome 11q13 with respect to GSTP1 and shows polymorphisms. An A/G single nucleotide mutation at rs1695 leads in an isoleucine-to-valine amino acid replacement (p.rs1695). In the encoded GSTP1 protein, this leads in reduced substrate specificity, catalytic activity, and thermal stability in the encoded GSTP1 protein. **(Lv et al., 2018)**

Several researches have recently investigated the relationship among the GSTP1 rs1695 gene polymorphism and ototoxicity caused by platinum-based drugs. Four additional studies reported association between SNP of GSTP1 (rs 1695) with cisplatin caused ototoxicity (CIO). **(liberman et al,2019 - Lui et al,2018 - Olugen et al, 2016 - Oldenburg et al,2007).** On the other side, two studies did not identify significant association **(peters et al., 2000 – Jurajda, 2012)**

According to studies conducted on different SNPs of GST, a deletion of 3 nucleotides on the GSTM3 gene was shown to have a defensive function, while hearing loss has been correlated with having the GSTT1 and GSTM1 genes and the A / A genotype at rs1695 in GSTP1**(Langer et al, 2013)**. In other

studies, the presence of GSTT1 **(Choeyprasert et al, 2013)**, and the AG or GG genotypes of rs1695 were associated with a higher risk of serious hearing impairment **(Rednam et al, 2013).**

Superoxide dismutase (SOD)

(SOD) another antioxidant enzyme encoded by the SOD2 gene**. (Sheth et al, 2017)**

SNP rs4880, that results in valine to alanine exchange, raises the catalytic activity of SOD2, resulting in hydrogen peroxide accumulation and secondary generation of ROS. Consequently, it is probable that the changed mitochondrial role in cochlea can raise the susceptibility of cisplatin to ototoxicity **(Tserga et al., 2019).**

SNP rs4880 in SOD2 was associated with ototoxicity in adults in a medulloblastoma sample. **(brown et al., 2015)**

The solute carrier (SLC) Genes

Cisplatin and carboplatin are transferred by various family genes coded by (SLC) influx transporters **(Ciarimboli et al., 2010).** Several studies have linked SLC genes and ototoxicity. It was shown that the T allele in SLC22A2 at rs316019 protects against hearing loss **(Lanvers et al., 2015).** There was an elevated sensitivity to ototoxicity in the C allele carriers at rs10981694 in SLC31A1 **(XU et al., 2012).** In SLC16A5, rs4788863 was also associated with hearing loss in adults **(Drogemoller et al., 2017).**

TPMT & COMT Genes

Thiopurine S- methyltransferase (TPMT) and catechol methyltransferase (COMT) genes with a lesser-understood biologic role in CIO. TPMT and COMT are both methyltransferases based on S-adenosylmethionine, a substrate reported to amplify the toxicity of cisplatin **(Ochoa et al., 2009)**

Consequently, a decrease in the activity of TPMT and COMT can lead to an elevated in S-adenosyl methionine that may in turn raise the toxic response to cisplatin. **(Bhavasar et al, 2017)**

Multiple cohorts were examined by the TPMT and COMT correlations, even though a few research have repeated these correlations **(Ross et al,2009 – Pussegoda et al,2013 – Tef et al, 2019),** others were unable to validate these results **(Wheeler et al,2018 - Drogemoller et al, 2017 – Talach et al, 2016 - Thiesen et al,2017).**

Acylphosphatase 2 (ACYP2) Gene

ACYP2 was shown to engage in homeostasis of calcium and hair cell disruption has been associated with calcium signaling **(Thomas et al., 2013)** In addition, ACYP2 is expressed in murine ear cells**. (Shen et al., 2015)** and reduced ACYP2 expression is linked with increased cisplatin induced cytotoxicity, Multiple variants contribute to CIO development in the ACYP2 region. While the most strongly linked variant remains rs1872328 **(Drogmoller et al., 2019)**

The correlation with ACYP2 and CIO was replicated by three independent studies **(Thiesen et al, 2017 - Drogemoller et al, 2018 –Vos et al,2016)** However, two studies were unable to replicate these findings. **(wheeler et al., 2017 – Tef et al., 2019)**

Excision repair cross-complementation group (ERCC)

ERCC is a gene for DNA repair which, through single nucleotide excision, inhibits DNA damage induced by cisplatin. Gene polymorphisms involved in the repair of cisplatin-DNA adducts (ERCC1, ERCC2) will raise the risk of toxicity associated with cisplatin **(Turan et al., 2019)**

In a research performed by Caronia et al. (2009) on 91 patients with osteosarcoma, it has been found that only SNP of XPC had a major relationship with cisplatin ototoxicity among the SNPs of 5 DNA repair genes, comprising ERCC1, ERCC2, XPC, XPA, ERCC4 and ERCC. **(Olgun et al, 2016)** This study, no substantial association among the SNPs of ERCC and cisplatin ototoxicity was also found.

Another research did not report any association between ERCC1 C8092 A genotypes and hearing loss**. (Obiedat et al., 2018)**.

Mechanisms of platinum ototoxicity

Dose-dependent death of cochlear hair cells is caused by platinum agents, with outer hair cells in some animal samples more prone to cisplatin and inner hair cells more prone to carboplatin **(Brock et al., 2012).** Even so, carboplatin mainly targets outer hair cells in Guinea pigs. Death of cochlear hair cells is first visible at the cochlear base and develops apically with continued drug use **(Dalian et al., 2012).**

Unlike cisplatin and carboplatin, that mostly impact hair cells, oxaliplatin is usually not toxic to cochlear hair cells, but tends to cause substantial degeneration of the auditory nerve **(Campbell et al., 2018)**.

Cisplatin ototoxicity, as shown **in Figure (VI)**, is produced by several different mechanisms. One such mechanism, the antioxidant model, includes the formation within the cochlea of reactive oxygen species (ROS) and the consequent reduction of antioxidant enzymes after cisplatin chemotherapy exposure **(Sheth et al., 2017).**

The important contribution of nicotinamide adenine dinucleotide phosphate oxidase 3 isoform (NOX3) to the production of reactive oxygen species inside the cochlea when activated by cisplatin is another mechanism of cisplatin ototoxicity **(Rybak et al., 2019)**.

The third mechanism concerns to the stimulation of transient receptor potential vanilloid 1 channel (TRPV1) **(Karasawa & Steyger 2015)**.

Consequently, the molecular mechanisms of cisplatin ototoxicity include the following: **(Paken et**

al., 2019).

1- Formation of oxygen reactive species,
2- Depletion of antioxidant glutathione and its regenerative,
3- Increased lipid peroxidation rate,
4- Proteins oxidative modifications,
5- Damage to nucleic acids by activation of the caspase system and
6- S-Nitrosylation of cochlear proteins.

Cellular mechanisms of cisplatin-associated ototoxicity, involving damages to external hair cells, supportive cells, marginal stria vascularis cells, spiral ligament, and spiral ganglion cells **(Chirtes & Albu, 2014**). It is clear that the inner ear structures are most vulnerable to damage by cisplatin chemotherapy, with the most notable being apoptotic degeneration of the hair cell in Corti 's organ **(Callejo et al., 2015)**. Outer hair cells at the basal turn of the cochlea are most impacted **(Paken et al., 2016).**

This contributes to an initial increase of high-frequency audiometric thresholds, accompanied by a gradual loss to lower frequencies with continuing treatment **(Lanvers et al., 2016).**

For health care practitioners, knowledge of the various mechanisms of cisplatin ototoxicity is significant as it will generate an understanding of its complexities and the resulting clinical presentation.

Table 1: Meta-analysis of the outcomes of studies investigating variants correlated with CIO from pharmacogenomic correlation analysis (Drogemoller BI et al., 2019)

SNP	Gene	Effect allele	Alternate allele	Directiona	Meta *P*	No. of samples	Cohorts
rs1872328	*ACYP2*	A	G	+ + + + − +	6.3 × 10−8	1,322	Xu *et al.* (2015) (two cohorts), Vos *et al.* (2016),Thiesen *et al.* (2017), Wheeler *et al.* (2017), Drögemöller *et al.* (2018).
rs62283056	*WFS1*	C	G	+ + +	1.1 × 10−9	978	Xu *et al.* (2015), Wheeler *et al.* (2017) Drögemöller *et al.* (2018).
rs4788863	*SLC16A5*	T	C	− − − −	9.6 × 10−5	805	Drögemöller *et al.* (2017), Wheeler *et al.* (2017), Lui *et al.* (2018).
rs9332377	*COMT*	T	C	+ + + − + − + + + +	1.3 × 10−3	1,761	Ross *et al.* (2009), Pussegoda *et al.* (2013), Yang *et al.* (2013), Hagleitner *et al.* (2014),Talach *et al.* (2016),Wheeler *et al.* (2017), Thiesen *et al.* (2017),Drögemöller *et al.* (2017),Teft *et al.* (2019)
rs12201199	*TPMT*	T	A	All studies + + + − − − − + −	0.03	1,500	Ross *et al.* (2009),Pussegoda *et al.* (2013), Yang *et al.* (2013),Hagleitner *et al.* (2014) Wheeler *et al.* (2017) Thiesen *et al.* (2017) Drögemöller *et al.* (2017)
				Pediatric, noncranial irradiation studies + + + − +	1.7 × 10−6	478	Ross *et al.* (2009) Pussegoda *et al.* (2013),Yang *et al.* (2013) Thiesen *et al.* (2017)

CIO cisplatin- induced ototoxicity**.** **(+)** associated with increased risk of CIO. **(−)** associated with decreased risk of CIO.

Impact of hearing loss on children

Ototoxicity presents a significant issue for cancer patients, as hearing loss can adversely affect the quality of life after undergoing platinum chemotherapy, leading to social, emotional and occupational difficulties, as successful communicating is often impeded. Tasks taken for granted by normal-hearing people can be daunting and stressful. **(Paken et al., 2019)**.

Furthermore, a person's protection can be impaired because of deafness, as an effective response to alarm and alert signals can be delayed. In addition, psychosocial and physical health conditions may also arise from hearing loss, as well as depression and social isolation. Hearing deficiency, also known as "the invisible disease," thus has important observable effects for the quality of life of a person with hearing impairment **(Tye-Murray et al., 2014**).

This is especially important unless a person has indeed entered the world of hearing; the ability to hear has never been went back to normal, although the usage of assistive hearing aids, like hearing aids and cochlear implants, can benefit patients (**Yorgason et al., 2006**).

The consequences of ototoxic hearing loss can be more profound for infants and young children who are at a crucial stage in their speech and language development **(Nielsen et al., 2010**).

In addition, the high-frequency aspect of ototoxic hearing loss can impair speech recognition and understanding (**Langer et al., 2013**), resulting in possible neurocognitive dysfunction **(Olivier et al., 2019)**.

In school-aged children and adolescents, there is also a high risk of academic learning issues and psychosocial problems **(Waissbluth et al., 2018)**.

The effect of hearing loss not only impacts sufferers and family members, but also contributes to societal costs of millions of dollars, like medical costs and lost productivity **(Waissbluth et al., 2017)**.

Ototoxicity monitoring

Advances in medical education and technology, such as screening and early identification of many cancers, have contributed to substantial increases in cancer's relative five-year survival rates **(Siegel et al., 2015)**. Improving the quality of life after platinum-based chemotherapy is therefore becoming increasingly necessary and, if proper monitoring is in place, subsequent comorbidities, like ototoxicity, may be handled adequately and immediately.

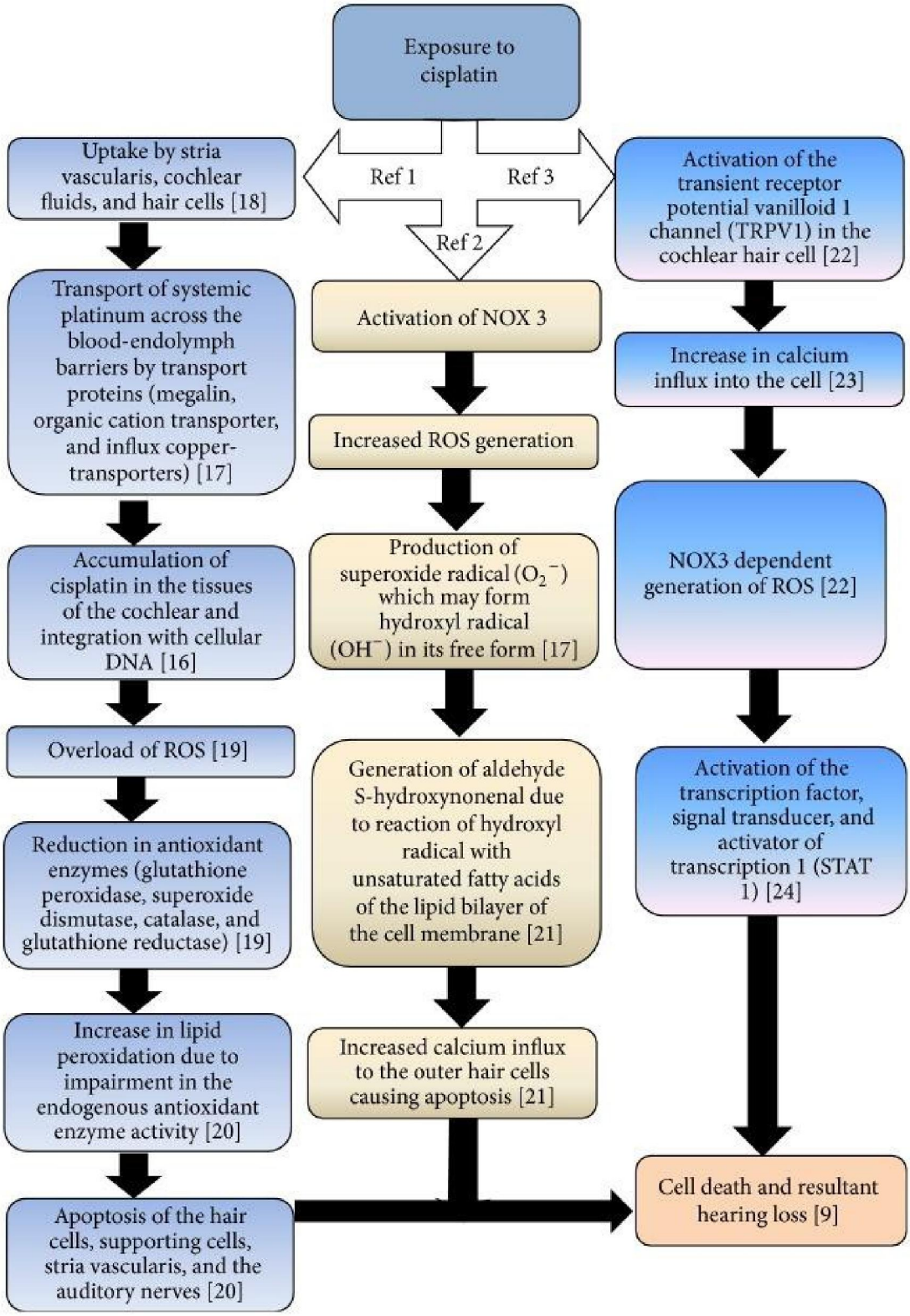

Figure 1: Mechanisms of cisplatin ototoxicity (Karasawa & Steyger 2015)

The essence of ototoxicity is such that before speech intelligibility is impaired, it frequently goes undetected **(Konrad-Martin, 2005)** and is normally identified when a communication issue is apparent. Communication issues like continuously asking for repetition or not answering when spoken to, suggest that hearing loss has advanced to frequencies that are critical for understanding speech **(Baguely et al., 2020).**

In this case, the decreased quality of life as a result of hearing loss can be prevented by an audiological surveillance program, as patients on platinum-based chemotherapy could be detected early, informed, monitored, and controlled appropriately by treatments in a rational, systematic, and coherent way. Audiological testing should seek to detect early hearing loss and decrease its effect on the life of the person through appropriate medical and hearing intervention **(Jacob et al., 2006)**.

The only effective technique for identifying ototoxicity before it is symptomatic remains prospective audiological assessments. A health care team containing an oncology nurse, oncologist, audiologist, and pharmacist should be part of an ototoxicity surveillance network to ensure successful continuity of such a program if introduced, with the patient becoming the central focus. The audiologist is interested in detecting ototoxic hearing loss, advising the oncologist of such a development, recommending and prescribing amplification devices, like hearing aids and cochlear implants, to the patient and family members **(Paken et al., 2019)**

Early detection of ototoxic hearing loss offers an opportunity for oncologists to change the chemotherapy protocol to minimize or avoid further hearing impairment. In an attempt to brace patients for clinical results and help them set reasonable standards, oncologists and nurses can also educate patients on the adverse effects of platinum-based chemotherapy, including ototoxicity **(Paken et al., 2016)**

Oncologists and audiologists can also be notified by pharmacists who have access to a patient's prescription list of others who are on other ototoxic drugs and are also at higher danger of ototoxicity. Effective treatment of these patients may enhance the treatment of cancer patients using evidence-based methods **(Schellack et al., 2015**).

Monitoring is used to alert families, caregivers and medical personnel to changes in the hearing so that coping strategies can be recommended and action can be taken as soon as possible. With family approval, children can also be told about improvements in their hearing, the effect on their comprehension and the realistic methods they can use to enhance communication.

Our experience has generally been that promoting interaction among parents and children, often as young as four or five years of age, about the communication frustrations they can encounter, helps them be educated observers of different listening environments and gives them a common understanding of problem-solving skills **(Brooks et al., 2018)**.

As a result, the guidelines established by the American Association of Speech-Language-Hearing Association (ASHA) for the Audiological Management of Individuals Receiving Cochleotoxic Drug Therapy in Countries Lacking Ototoxicity Management Guidelines would direct the audiologist to introduce a monitoring program for ototoxicity in a local, regional, or national setting. Ototoxicity surveillance systems need to implement reliable and cost-effective ototoxicity detection techniques for widespread adoption and use **(paken et al., 2019)**.

Ototoxicity is detected clinically by comparing functional status pre and post ototoxic drug administration; baseline assessment is therefore necessary. This avoids the erroneous diagnosis of iatrogenic ototoxic hearing loss due to prior hearing impairment, like noise-induced hearing loss, previous to chemotherapy treatment.

Pre- and post-treatment hearing evaluations also endorse basic and clinical research on medications or therapies which can neutralize ototoxicity whilst not interfering with the effectiveness of chemotherapy's antineoplastic capability. Pre-existing hearing status can be useful in predicting the degree of ototoxic hearing loss in conjunction with the combined dose of cisplatin. **(Dille et al., 2012)**.

Drug-induced hearing loss is usually permanent and happens in both cumulative and dose-related ways **(Trendowski et al., 2019)** consequentially, for the early detection of ototoxicity, a routine surveillance program is important, providing valuable information to reduce permanent hearing loss and timely treatments. After administration of platinum-based compounds, hearing deterioration may also be ongoing for years following discontinuation of therapy **(Frisina et al., 2016)**, suggesting that hearing loss can not only be evident in sufferers who have undergone ototoxicity throughout care. Moreover, recent research indicates that in patients treated with cisplatin, platinum is retained indefinitely **(Bregilo et al., 2017)**.

Consequently, due to the potential for gradual or delayed-onset hearing loss, long-term monitoring is required.

Depending on the sort of cancer, the rate and dosage of chemotherapy used, the required time periods for audiological evaluations can vary (**Figure VII**). **(Paken et al., 2016).**

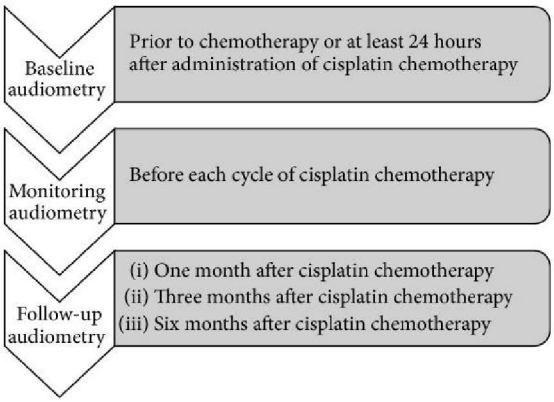

Figure 2: Timelines for audiological assessments (Paken et al., 2016)

The American Speech-Language-Hearing Association (ASHA) suggests that assessments should be carried out between 1 and 3 months after discontinuation of ototoxic therapy **(Baguely et al., 2020).** Latest evidence-based guidance on adolescent and young adult ototoxicity surveillance indicated continuing 5-year **(Clemen E, Van de et al., 2019).**

The significance of accurate and proper hearing measurements prior, during and after chemotherapy to assess the occurrence and prevalence of hearing deterioration correlated with platinum-based chemotherapy is emphasized in all the available information. Even so, despite the presence of clinical guidelines and recommendations for ototoxicity surveillance, monitoring programs are not consistently enforced **(Clemen, Van den et al., 2019)**.

Speech audiometry, behavioral pure tone audiometry, auditory reflexes, extended high-frequency audiometry, immittance, otoacoustic emissions, and electrophysiological testing are the techniques for ototoxicity monitoring in children. **(Brooks et al., 2018)**.

Tympanometry must be involved in each assessment to evaluate the role of the middle ear. In the pediatric population, otitis media is relatively common, and the incidence of middle ear impairment is elevated in patients who receive cranial radiation and are immunosuppressed **(Grewal et al, 2010)**. The pathology of the middle ear may confuse audiometric outcomes and prevent accurate OAES measurements.

The fundamental basis for the detection and categorization of hearing impairment in several ototoxicity grading schemes remains traditional pure tone audiometry (PTA) **(Crundwell et al., 2016)**.

PTA could be all the tests that can be tolerated by chemotherapy patients, and this may be particularly true of the paediatric population **(Clemen, Van den et al., 2019).** Otoacoustic emissions can present an opportunity for some younger children to evaluate cochlear health in an ear and frequency-specific manner **(Brooks et al., 2018).**

Audiological evaluations for ototoxicity can vary in the importance of test frequencies and sequence of tests from the standard hearing assessment **(Brooks et al., 2018).**

High-frequency audiometry (HFA) is a more sensitive method than the standard PTA for early detection of ototoxic changes **(Abujamra et al., 2013)**. Even so, HFA needs specialised instrumentation and extra time to be tested and, in practice, a change in hearing greater than 8 kHz do not generally affect the continuity of treatment regimens. Researches have shown the ability to identify early drug-induced cochlear damage across a limited frequency range of behavioral tests called the sensitive range of ototoxicity (SRO) **(Baguely et al., 2020)**.

For grading platinum-induced hearing loss in adults and children, a number of standards have been used globally, such as the criteria of the National Cancer Institute, Brock's grading system, the criteria of the American Speech-Hearing-Language Association, the criteria of the World Health Organization, the criteria of the Pediatric Oncology Group, and the classification of Muenster. The Chang classification, the Functional Hearing Loss Scale, the HIT (German Hirntumor Research Grading System) and, most lately, the Boston International Pediatric Oncology Society for Ototoxicity Grading Scale are less widely used criteria **(Waissbluth et al., 2017)**

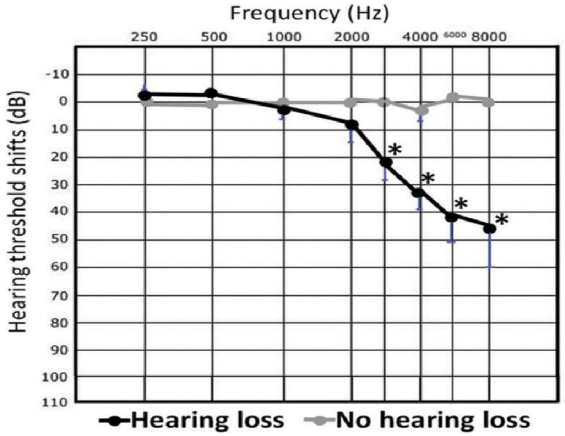

Figure 3: This audiogram showed an example of hearing loss induced by cisplatin.

While all criteria utilized to grant grades of hearing loss on scales varying from no hearing loss to extreme hearing loss, as shown in **Figure VIII**, there is substantial variation in design and criteria included in grading systems and **Table I. (Celemens, Brooks et al., 2019)**.

There were decreases in hearing level detected at

3,4,6 and 8 KHz. The degree of hearing loss differed according to the grading and classification system used. To clarify, the degree of hearing loss would be grade (3) by CTACEV4.03, grade (2a) by Munester, grade (1) by SIOP, grade (1) by Brock and grade (1b) by Chang.

Table 2: Hearing assessments used for ototoxicity monitoring (Minasian et al,.2018)

Test	Test description	Age	Research application
Pure tone audiometry (PTA)	. Behavioral measurement of hearing thresholds in decibels (dB) for the speech frequency range250-8000 Hz) . Testing requires participation and cooperation of the subject. . Assessment methods for young children include visual reinforcement audiometry (VRA) and conditioned play audiometry.	8 mo and older	Standard method for hearing measurement, detection of ototoxic damage and identification of communicatively significant hearing loss.
Extended high frequency audiometry (HFA)	• Behavioral measurement of hearing thresholds in decibels (dB) for frequencies above the speech range. • Test frequencies include 9000 Hz up to 20 000 Hz. • Testing requires participation and cooperation of the subject. • Not available at all institutions.	4-5y and older	Provides a more sensitive and earlier signal of ototoxic damage because ototoxicity initially occurs at the highest audible frequencies.
Otoacousemissions (OAEs)	• Objective measurement of cochlear outer hair cell function. • Does not require active subject participation. • In the presence of normal middle ear function, loss of OAEs suggests outer hair cell damage but additional testing is needed to quantify change in hearing sensitivity. • Available at most institutions.	Any age	Typically provides a more sensitive and earlier signal of ototoxic damage. Available at most institutions.
Auditory brainstem response (ABR)	• Objective measurement of neural responses to sound stimuli (auditory evoked potentials). • For ototoxicity monitoring, tone burst stimuli are used to estimate hearing thresholds when behavioral audiometry is not possible due to age, development or medical condition. • The subject must be sleeping or lying completely still during testing. • Useful for very young, medically debilitated or uncooperative patient (who may be sedated).	Any age.	Standard method for hearing measurement, ototoxicity detection, and identification of communicatively significant hearing loss when behavioral testing is not possible.
Tympanometry	• Objective measurement of middle ear pressure and function. • Used to determine middle ear status.	Any age	Necessary for valid interpretation of OAEs and to identify conductive middle ear pathology.

Table 3: Ototoxicity classification systems. (Celemens, Brooks et al.,2019)

CTCAEv4.03 (NCI)	Muenster	SIOP	Brock	Chang	Deleterious hearing loss
Grade 0: <20 dB all	**Grade 0**: ≤ 10 dB all	**Grade 0**: ≤ 20 dB all	**Grade 0**: <40 dB all	**Grade 0**: ≤ 20 dB at 1, 2 and 4 kHz	**No**
Grade 1: >20 dB at 8 kHz	**Grade 1**: >10 dB at ≤ 2 kHz	**Grade 1**: >20 dB at >4 kHz	**Grade1**: ≥ 40 dB at 8 kHz	**Grade 1a**: ≥ 40 dB at 6–12 kHz	
	Grade 2a: >20 ≤ 40 dB at ≥ 4 kHz			**Grade 1b**: >20 dB and <40 dB at 4 kHz	
Grade 2: >20 dB at ≥ 4 kHz (if 6 kHz measured, use 6 kHz)	**Grade 2b**: >40 ≤ 60 dB at ≥ 4 kHz	**Grade 2**: >20 dB at ≥ 4 kHz	**Grade 2**: ≥ 40 dB at ≥ 4 kHz	**Grade 2a**: ≥ 40 dB at ≥ 4 kHz	**Yes**
Grade 3: >20 dB at ≥ 3 kHz (if 3 kHz not measured, use 2 kHz)	**Grade 2c**: >60 dB at ≥ 4 kHz	**Grade 3**: >20 dB at 2 or 3 kHz	**Grade 3**: ≥ 40 dB at ≥ 2 kHz	**Grade 2b**: >20 and <40 dB at 1, 2 or 3 kHz	
Grade 4: Audiological indication for cochlear implant: ≥ 50 dB at ≥1 kHz	**Grade 3a**: >20 ≤ 40 dB at <4 kHz	**Grade 4**: >40 dB at ≥ 2 kHz	**Grade 4**: ≥ 40 dB at ≥ 1 kHz	**Grade 3**: ≥ 40 dB at ≥ 2 or 3 kHz	
	Grade 3b: >40 ≤ 60 dB at <4 kHz			**Grade 4**: ≥ 40 dB at ≥1 kHz	
	Grade 3c: >60 <80 dB at <4 kHz				
	Grade 4: ≥80 dB at <4 kHz				

The decibel (or dB): is the unit of intensity used describe hearing sensitivity.
The hertz (or Hz): is used for measurement of sound frequency (pitch).
SIOP: the International Society of Pediatric Oncology.
CTCAEv4.03: National Cancer Institute **(NCI)** Common Adverse Effects Technology Standards Version 4.03.

Prevention of ototoxicity

Monitoring during treatment

The introduction of standard audiologic surveillance protocols allows early diagnosis of ototoxicity in sufferers undergoing cancer treatment and, if necessary, can provide a chance to alter treatment before significant auditory damage occurs. Even if there is no appropriate alternative and ototoxic agent treatment must proceed, surveillance can still be useful in facilitating early intervention and auditory recovery **(landier, 2016).**

2- Otoprotective agents

Research methodology for evaluating new agents to prevent cisplatin- induced hearing loss (CIHL) is fraught with challenges. These involve the discovery of otoprotective agents that do not interact with the chemotherapy's anticancer impacts and are safe for patients, the use of suitable preclinical models to improve the translation of the agent into human studies, and the design of pediatric medical studies which may be carried out with acceptable specimen size **(Minasian et al., 2018)**.

Many studies have tested the usage of cisplatin otoprotectants over the years, aimed at shielding the inner ear from any damage although not interacting with cisplatin's antitumor impacts. Otoprotective methods involve minimizing free radical formation by preserving the level of glutathione and antioxidant activity **(Paken et al., 2019)**.

Novel strategies for preventing cisplatin ototoxicity may be provided by future advances in drug delivery to the cochlea. This is an exciting clinical research area and further advancements are expected to occur in the immediate future. **(Rybak et al., 2019)**

Otoprotective agents –clinical studies.

Sodium Thiosulfate

The most promising protection agent against CIHL appears to be sodium thiosulfate as free radical scavenger. The efficacy of sodium thiosulfate against cisplatin ototoxicity was reported in two Phase 3 clinical trials. A phase 3 open-label study comparing sodium thiosulfate with observation in pediatric cisplatin-treated cancer patients showed a decreased incidence of hearing loss in sodium thiosulfate-treated patients. Nevertheless, survival in high-risk patients with spread cancer who obtained sodium thiosulphate decreased (**Freyer et al., 2017**)

Children treated with cisplatin for hepatoblastoma who obtained intravenous sodium thiosulfate 6 hours later were shown to have a lower occurrence of hearing loss in a randomized phase 3 study compared to those who obtained cisplatin alone. No obvious interference with the efficacy of antitumor has been shown (**Brock, Maibach et al., 2018**)

N-acetylcysteine

N-acetylcysteine is an antioxidant and, by scavenging free radicals, may be efficient **(Freyer et al., 2019)**

Transtympanic injections of N-acetylcysteine appeared to protect against CIHL in cisplatin-treated sufferers in a double-blinded comparison with injections of dexamethasone. Less effective than N-acetylcysteine was the latter drug (**Sarafraz et al., 2018**)

The feasibility of intratympanic administering drugs is not known in the pediatric population, especially for very young children, due to the limited number of children involved.

One prior research demonstrated protection only at 8 kHz, while another research did not demonstrate substantial protection (**Yoo et al., 2014**)

Amifostine

Mixed findings have been demonstrated by clinical trials using amifostine as a putative protective agent **(Rybak LP et al., 2019).** However, future research to assess the possible protective impacts of amifostine as a free radical scavenger against could be suggested (**Hazlitt et al., 2018**)

The effectiveness of amifostine in minimizing cisplatin-induced ototoxicity in pediatric medulloblastoma patients has been demonstrated in two clinical trials.

Thirteen patients (37.1 %) in the control group against nine (14.5 %; p 1⁄4 0.005) of the amifostine treated patients had at least grade 3 ototoxicity one year after start of therapy, needing hearing aid in at least one ear. These researchers concluded that in patients with medulloblastoma, amifostine can lower the risk of serious ototoxicity (**Fouladi et al., 2008**)

A second clinical research showed that amifostine was only effective as a protective agent against cisplatin-induced severe hearing loss in average-risk medulloblastoma patients, but did not demonstrate substantial protection toward hearing loss in high-risk tumor patients (**Gurney et al., 2014**)

Other research in patients with medulloblastoma, pediatric germ cell tumors, head and neck cancer, melanoma and in patients with hepatoblastoma have not shown substantial protection against cisplatin ototoxicity (**Katzenstein et al., 2009**)

Dexamethasone

Dexamethasone is the second intratympanically administered drug to be studied in randomized trials. By reducing the generation of reactive oxygen species caused by cisplatin and related inflammation, the drug could be efficient **(Freyer et al., 2019)**

In addition to the study comparing intratympanic N-acetylcysteine with dexamethasone **(Sarafraz et al., 2018),** two studies, both of which enrolled adult patients, compared intratympanic dexamethasone without medication.

In these experiments, in the control ears, but not in the intervention ears, a substantial raise in thresholds was found at 6 kHz, suggesting an advantage of dexamethason **(Marshak et al., 2014 & Nasr et al., 2018)**

Vitamin E

A randomized, placebo-controlled oral vitamin E trial showed substantial 2 and 8 kHz hearing safety in patients treated with cisplatin relative to placebo-treated subjects. (**Villani et al., 2016**)

Management of an Ototoxic Hearing Loss

The aim of ototoxicity management is to reduce or avoid communication impairment and to plan suitable rehabilitation measures **(Ganesan et al., 2018)**.

Hearing aids

Hearing aids are a vital part of the treatment of severe hearing loss in both adults and children, but it is important to recollect that although hearing aids amplify sound, they do not restore normal hearing. Therefore, hearing quality will be distorted to some degree in patients with hearing aids, resulting in a decreased capacity to differentiate towards speech in noisy environments. The regular use and caring of hearing aids can also be difficult, especially for young children. **(Munoz et al., 2015)**.

Nonetheless, various types and styles of hearing aids are available, such as behind-the-ear, in-the-ear, and in-the-canal models, and continuing developments in digital technology have led to enhanced programmability and improved speech recognition in newer models **(landier, 2016)**.

Cochlear implants

For sufferes with bilateral severe to profound sensorineural HL, cochlear implants are an alternative that cannot be fixed by hearing aids **(Bass, Knight et al., 2016)**.

Cochlear implants are instruments that are surgically implanted in the cochlea that specifically activate auditory neural pathways. Cochlear implant has a mechanism for transferring sound waves to the brain through bypassing damaged sensory hair cells **(Pepsin et al., 2007)**.

The Federal Drug Administration (FDA) has recently approved an implant overview for patients' ≥18 years of age in 2014. **(Bass, Knight et al., 2016)**.

For patients with severe to serious hearing loss, hybrid cochlear implants are restricted to high frequencies and combine both auditory and electrical stimulus **(landier, 2016)**.

In recent decades, successful promotion of cochlear gene therapy and stem cells transplation that differentiated in to functional hair or spiral ganglion cells have been thoroughly demonstrated as preclinical trials **(Ralli et al., 2017)**. These methods will be clinically appropriate over the coming decades, with further improvement.

Assistive devices

While hearing aids and implantable hearing devices are of great benefit to people with hearing impairments, they do not often function well in every situation, particularly in loud environments such as meetings, cafes, workplaces and classrooms. **(Bass, Knight et al., 2016)**

In challenging listening conditions, assistive listening devices like frequency-modulation (FM) systems and audio streamers may minimize the adverse impacts of range, resonances, and ambient noises **(Liu et al., 2019)**

In addition, for patients with significant hearing loss, devices such as auditory coaches, telephone amplifiers, and telephone systems for deaf people and, more lately, the widespread use of text messages and social networks offer alternative means of communication. In challenging listening conditions, these assistive tools can be used with appropriate hearing aids to enhance the transmission of sound directly to the impacted patient **(landier, 2016)**

Accommodation and adjustment of classrooms will help survivors with HL do better in the learning environment. These include communication and/or teaching techniques specific to favorable classroom seating, the avoidance of external noise, and the use of hearing aid technologies such as frequency-modulation (FM) or induction loop systems for student needs; **(Bass, Knight et** al., 2016).

Rehabilitation

Rehabilitation must be dependent not on audiological findings but on communication difficulties **(Ganesan et al., 2018)**

Therefore, minimizing the disability by speech and language therapy, occupational therapy is recommended. Vestibular therapy is also prescribed in order to assist a person in promoting central compensation. Balance management, involving balance preparation, vestibular rehabilitation and security of alternative balance data sources, like the recommendation of annual ophthalmological examinations **(Maru et al, 2018).**

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