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Monitoring Ototoxicity in Pediatric Oncology: A Literature Review on Audiological Surveillance During Cisplatin Therapy

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ABSTRACT

Cisplatin remains a key component of pediatric oncology, significantly improving survival rates in solid tumors such as neuroblastoma, hepatoblastoma, medulloblastoma, and osteosarcoma; however, its effectiveness is often limited by high rates of irreversible ototoxicity. This review compiles evidence on cisplatin-related auditory damage, highlighting the importance of early, structured, and age-appropriate audiological monitoring. Mechanistic studies show that cisplatin ototoxicity is driven by oxidative stress, mitochondrial dysfunction, and cell death in cochlear hair cells, worsened by the inner ear's limited blood supply and detoxification abilities. Clinically, hearing loss in children affects more than just sensation; it impacts language learning, cognitive development, academic success, and social interaction. Epidemiological data report incidence rates ranging from 20% to 70%, with risk factors including age, total dose, genetic predisposition, and exposure to other ototoxic agents. Monitoring techniques, such as otoacoustic emissions (OAE), auditory brainstem response (ABR), pure-tone audiometry (PTA), and high-frequency audiometry (HFA), each have specific benefits but are often underused or inconsistently applied. Guidelines from organizations like ASHA, the Children's Oncology Group, and SIOP emphasize the need for baseline and ongoing assessments, yet practice disparities remain, especially in resource-limited settings. Recent innovations like sodium thiosulfate offer pharmacological protection but do not eliminate the need for continued surveillance. This review advocates for a tiered, age-specific monitoring approach to enable early detection, treatment adjustments, and prompt rehabilitation. In pediatric cancer care, protecting hearing is crucial not only for quality of life but also for supporting the developmental progress of survivors.

Keywords: *cisplatin, ototoxicity, pediatric, oncology, surveillance*.

INTRODUCTION

Over the past four decades, progress in pediatric oncology has transformed childhood cancer from a nearly always fatal disease into a largely survivable condition. With multimodal treatments, survival rates for many pediatric cancers now exceed 80%, marking one of medicine's greatest achievements (Brock et al., 2012; Li et al., 2004). Among the key drugs contributing to these outcomes is cisplatin, a first-generation platinum-based chemotherapy. Its introduction in the 1970s changed treatment strategies for solid tumors such as medulloblastoma, hepatoblastoma, osteosarcoma, and neuroblastoma, establishing it as a first-line treatment in oncology centers worldwide (Lanvers-Kaminsky et al., 2016).

Nevertheless, this therapeutic progress has been paralleled by an equally significant recognition of cisplatin's toxicity profile (Li et al., 2004). Unlike transient chemotherapy-related side effects such as nausea or myelosuppression, cisplatin-induced ototoxicity is permanent, bilateral, and progressive. It preferentially damages the high-frequency regions of the cochlea and can extend to frequencies essential for speech perception with continued exposure (K. R. G. Knight et al., 2005). For adults, such damage results in functional hearing impairment, but the stakes are far higher for children; even mild hearing loss during the critical years of auditory and language development may irreversibly disrupt communication skills, literacy acquisition, cognitive functioning, and psychosocial adjustment (Gurney et al., 2007). As childhood cancer survival has improved, the long-term quality of survivorship has become a central concern, with ototoxicity emerging as a leading determinant of developmental and educational outcomes.

The pathophysiological basis of cisplatin-induced hearing loss lies in its accumulation within the inner ear, where the drug exerts cytotoxic effects through reactive oxygen species generation, mitochondrial injury, and apoptotic pathways (Karasawa & Steyger, 2015; Rybak et al., 2019) Cochlea's limited antioxidant defenses and reliance on transporter systems such as OCT2 and CTR1 exacerbate this vulnerability (Ciarimboli, 2012). This biological susceptibility is heightened in young children, whose auditory systems are still developing, making them disproportionately sensitive to damage. Epidemiological studies confirm that children under five years of age are at the greatest risk, particularly when exposed to cumulative doses exceeding 400 mg/m² (Lanvers-Kaminsky et al., 2016; Li et al., 2004). Additional risks arise from concurrent therapies, such as aminoglycoside antibiotics or cranial irradiation, and from genetic polymorphisms in detoxification-related genes, including TPMT, COMT, and GST (Ross et al., 2009).

The effects of unmonitored cisplatin ototoxicity are considered serious. Early high-frequency hearing loss might go unnoticed in casual conversation but gradually weakens phoneme recognition, speech clarity, and classroom understanding. Without early detection, this damage can extend to conversational frequencies, resulting in permanent deficits that affect verbal IQ, literacy, and social skills (K. R. G. Knight et al., 2005). Long-term data from

survivor groups show that children with cisplatin-related hearing loss are more likely in need for special education services due to relatively lower academic performance compared to their normal-hearing peers (Brock et al., 2012)). Therefore, hearing monitoring is not just an optional extra in oncology care but rather a crucial part of supporting development during survivorship.

Despite this knowledge, audiological surveillance in pediatric oncology remains inconsistent. Barriers include a lack of awareness among oncology teams, limited audiological infrastructure, and logistical challenges in coordinating repeated assessments during intensive chemotherapy schedules (Knight et al., 2005). Where monitoring is implemented, its scope is often insufficient, failing to include sensitive measures such as high-frequency audiometry or otoacoustic emissions that can detect subclinical changes before they affect speech-related thresholds. International guidelines from ASHA, the Children's Oncology Group, and SIOP provide frameworks for age-appropriate monitoring, however, disparities in implementation continue both within and across healthcare systems (Freyer et al., 2017).

The main objective is to express scientific knowledge in consistent clinical practice. This review consolidates existing research on cisplatin-induced ototoxicity in pediatric oncology, including mechanistic insights, epidemiological data, clinical effects, and assessments of monitoring methods. It also thoroughly reviews international guidelines and proposes a tiered, age-specific surveillance system designed to enhance early detection and prompt intervention. Moreover, it highlights that hearing monitoring should not be optional in oncology care, but an essential component of quality survivorship. Protecting hearing in children receiving cisplatin extends beyond maintaining hearing thresholds to help safeguard their developmental, educational, and social futures.

Cisplatin in pediatric oncology

Cisplatin (cis-diamminedichloroplatinum) is a first-generation platinum compound that has remained one of the most powerful cytotoxic agents in oncology for nearly fifty years. Its continued importance in pediatric oncology reflects not only its strong anti-tumor effectiveness but also the lack of equally effective alternatives in many treatment plans. Cisplatin works mainly by binding to purine bases in DNA, forming both intra-strand and inter-strand crosslinks that interfere with replication and transcription. This structural change hampers DNA repair and leads to apoptosis of rapidly dividing cells (Rybak et al., 2019).

In children, cisplatin is a first-line treatment for various solid tumors, including neuroblastoma, hepatoblastoma, osteosarcoma, and medulloblastoma. Additionally, it is a part of multi-agent chemotherapy protocol for germ cell tumors, Wilms' tumor, and specific sarcomas. Clinical trial data and decades of follow-up confirm its ability to significantly enhance event-free and overall survival, particularly in cancers previously associated with poor prognoses (Brock et al., 2012; Li et al., 2004). Its use is not limited to curative treatments; cisplatin also plays a key role in induction protocols, consolidation therapy, and in some cases, palliative strategies where tumor sensitivity is high.

Pharmacokinetically, cisplatin is administered intravenously and undergoes

aquation to produce positively charged species that bind to DNA and cellular proteins. While the drug distributes widely, it demonstrates preferential accumulation in tissues with limited regenerative capacity, such as renal tubular epithelium, peripheral nerves, and the cochlea (Rybak et al., 2009). This accumulation pattern underpins its three most clinically significant dose-limiting toxicities: nephrotoxicity, neurotoxicity, and ototoxicity. Although hydration protocols and nephroprotective strategies have mitigated kidney damage to some extent, and dose-modification can reduce neurotoxicity, effective preventive measures for ototoxicity remain elusive in clinical practice.

The vulnerability of the auditory system is attributable to unique physiological and anatomical features. The cochlea has low vascular perfusion, limiting systemic clearance of toxic metabolites. It also lacks robust intrinsic detoxification mechanisms, leaving it exposed to oxidative insults and demonstrates poor regenerative potential, as mammalian hair cells do not spontaneously regenerate after injury (Lanvers-Kaminsky et al., 2016). Thus, once cochlear injury occurs, the resulting sensorineural hearing loss is permanent.

Cisplatin dosing in pediatric oncology protocols is carefully titrated, yet, cumulative exposure frequently exceeds thresholds known to cause ototoxicity. Standard regimens deliver between 300 and 600 mg/m² over the course of treatment, often in cycles. Knowing that auditory damage is dose-dependent, children receiving cumulative doses above 400 mg/m² are at particularly high risk of significant hearing loss (Li et al., 2004). Notably, children under five years of age are particularly susceptible, both due to the immaturity of their auditory system and their greater systemic sensitivity to cytotoxic drugs. These realities frame ototoxicity not as an incidental side effect but as a foreseeable, mechanistically inevitable consequence of a drug that remains central to pediatric cancer survival.

Pathophysiology of cisplatin-induced ototoxicity

The ototoxic effects of cisplatin have been clarified through years of cellular, animal, and clinical research. They are now understood as the result of oxidative stress, mitochondrial dysfunction, apoptotic signaling, and drug transport processes within the inner ear.

Cochlear Targets of Cisplatin

Within the cochlea, cisplatin mainly accumulates in the outer hair cells (OHCs) of the basal turn, the stria vascularis, and spiral ganglion neurons. The basal region of the cochlea is responsible for transducing high-frequency sounds, which explains why ototoxicity first appears as subtle high-frequency hearing loss (Rybak et al., 2019). With repeated cycles, the damage spreads apically to eventually affect mid- and low-frequency areas that are essential for speech understanding.

Oxidative Stress and Reactive Oxygen Species

The main pathogenic process involves excessive production of reactive oxygen species (ROS). Cisplatin activates NADPH oxidases and damages antioxidant defense systems such as glutathione and superoxide dismutase. This imbalance causes lipid peroxidation, protein nitration, and DNA fragmentation. ROS-induced oxidative stress damages mitochondrial membranes in OHCs, releasing pro-apoptotic factors that trigger

caspase cascades (Karasawa & Steyger, 2015).

Mitochondrial Dysfunction and Apoptosis

Mitochondria are particularly vulnerable to cisplatin because they contain DNA with limited repair capacity. Damage to mitochondrial DNA and respiratory chain enzymes causes a decrease in ATP production and an increase in ROS generation, creating a vicious cycle of oxidative damage. This leads to the release of cytochrome c and activation of caspase-3, which triggers apoptosis in cochlear sensory cells (Breglio et al., 2017).

Role of Transporters

Recent research emphasizes the role of membrane transporters in regulating cisplatin uptake into cochlear cells. Organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1) increase the amount of cisplatin inside cells, which worsens cochlear damage. Animal studies with transporter blockers show reduced cochlear cisplatin levels and less hearing loss, suggesting potential pharmacological strategies for hearing protection (Ciarimboli, 2012).

Inflammatory Pathways

Cisplatin also triggers inflammatory signaling pathways, including tumor necrosis factor-α (TNF-α) and nuclear factor-κB (NF-κB). These pathways boost apoptotic responses, attract immune cells to the cochlea, and contribute to ongoing inflammatory damage. Evidence indicates that anti-inflammatory strategies might provide some protection against ototoxicity, although clinical application remains limited (Breglio et al., 2017).

Lack of Regenerative Capacity

Perhaps the most clinically significant aspect of cisplatin ototoxicity is its permanence. Unlike lower vertebrates, mammals cannot regenerate cochlear hair cells once they are lost; therefore, cisplatin-induced hair cell apoptosis leads to irreversible sensorineural hearing loss. This biological limitation underscores the importance of early detection because treatment options are limited to prevention, amplification (hearing aids), or auditory prostheses (cochlear implants), rather than cellular repair (Breglio et al., 2017; Shojaei et al., 2016).

Given all this information, cisplatin's ototoxic profile results from a combination of predictable pharmacology and inherent vulnerabilities of the auditory system. The drug accumulates in cochlear structures with limited capacity for repair, causes oxidative stress and mitochondrial dysfunction, and induces apoptosis through transporter-mediated uptake and inflammatory responses (Breglio et al., 2017). The resulting sensorineural hearing loss is both permanent and cumulative, beginning with high-frequency impairment and progressing to deficits that hinder speech perception (K. R. Knight et al., 2007). These mechanisms explain the high rate of ototoxicity in pediatric populations and emphasize the importance of proactive monitoring and early intervention (Brock et al., 2018; Gurney et al., 2007).

Review of Audiological Assessment Tools for Monitoring Cisplatin-Induced Ototoxicity in Children

Cisplatin-induced ototoxicity is among the most prevalent and clinically significant long-term toxicities affecting children treated for cancer. As survival rates in pediatric

oncology continue to rise, increasing emphasis has been placed on survivorship outcomes, including sensory, cognitive, and educational functioning. Cisplatin-related hearing loss is characteristically permanent, bilateral, and progressive, typically beginning in the high-frequency regions of the cochlea before advancing into frequencies critical for speech perception (Rybak et al., 2019). This pattern complicates monitoring, as early cochlear damage is often asymptomatic and may not be detected using conventional behavioral audiometry. Consequently, the selection of sensitive, age-appropriate audiological assessment tools has become a central focus of the literature, with ongoing debate regarding their sensitivity, feasibility, and clinical utility across pediatric age groups (ASHA, 1994).

A consistent finding across studies is that no single audiological test is sufficient to monitor cisplatin ototoxicity throughout childhood. Effective surveillance therefore requires a multimodal approach combining objective and behavioral measures tailored to the child's developmental level, medical condition, and treatment course (Knight et al., 2005). Although widely endorsed in principle, implementation of such comprehensive monitoring remains inconsistent in routine oncology practice.

Otoacoustic emissions (OAEs) are frequently recommended for early ototoxicity monitoring, particularly in infants and young children who cannot provide reliable behavioral responses. Generated by outer hair cell activity, OAEs offer a rapid, non-invasive assessment of cochlear function. While transient-evoked OAEs primarily reflect responses up to approximately 4 kHz, distortion-product OAEs extend assessment into higher frequencies and are therefore more sensitive to early cisplatin-related damage (Knight et al., 2007). Their objectivity and suitability for repeated testing without sedation make OAEs attractive for serial monitoring during chemotherapy.

However, OAEs have notable limitations. Their dependence on middle ear integrity is problematic in pediatric oncology populations, where otitis media and effusions are common, increasing the risk of false-positive or false-negative findings (Kemp, 2003; van Dyk et al., 2015). In addition, OAEs assess outer hair cell function exclusively and provide no information about neural integrity or functional hearing ability (Shankaran et al., 2012). Several studies have demonstrated preserved OAEs despite measurable behavioral threshold shifts, suggesting that OAEs alone may underestimate clinically meaningful hearing loss (Fausti et al., 1994). Accordingly, OAEs are best viewed as complementary tools within a broader audiological test battery.

Auditory brainstem response (ABR) testing is widely regarded as the reference standard for objective threshold estimation in infants and very young children. By measuring neural activity along the auditory pathway, ABR provides frequency-specific estimates of hearing sensitivity using tone-burst or chirp stimuli and offers insight into both cochlear and neural function (Fitzpatrick et al., 2013). In pediatric oncology, ABR is commonly employed for baseline assessment prior to cisplatin exposure and for confirmation of suspected changes identified through other measures (Hall, 2015; Hall III, 2016).

Despite its diagnostic value, ABR is constrained by practical and ethical considerations. Reliable recordings typically

require the child to remain still or asleep, and sedation is often necessary for infants and toddlers. During chemotherapy, sedation introduces additional medical risk and logistical complexity, contributing to delays or missed assessments. ABR also requires specialized equipment, trained personnel, and extended testing time, limiting its feasibility for routine serial monitoring, particularly in resource-limited settings (Knight et al., 2005; Knight et al., 2007).

Pure-tone audiometry (PTA) remains the clinical gold standard for evaluating functional hearing loss in children capable of reliable behavioral participation, generally from five years of age onward (Stach, 2010a, 2010b). PTA provides detailed frequency-specific thresholds across the speech range and allows differentiation between sensorineural and conductive hearing loss, making it essential for determining severity, functional impact, and rehabilitation needs (Gurney et al., 2007; Katz, 2009).

Nevertheless, conventional PTA protocols are limited by their typical restriction to frequencies ≤8 kHz, despite robust evidence that cisplatin-induced cochlear injury begins at higher frequencies (Fausti et al., 1994; Brock et al., 2018). Reliance on PTA alone may therefore delay detection until hearing loss has progressed into speech frequencies, at which point deficits are functionally significant and irreversible. Additionally, the attentional and behavioral demands of PTA may be difficult to meet during intensive cancer treatment, further limiting its sensitivity as an early monitoring tool.

High-frequency audiometry (HFA) addresses this limitation by extending behavioral threshold assessment to frequencies up to 16–20 kHz, targeting the basal cochlear regions most vulnerable to cisplatin toxicity (Fausti et al., 1994). Multiple studies demonstrate that high-frequency threshold shifts frequently precede changes at conventional audiometric frequencies, offering a critical window for early detection and intervention.

Importantly, earlier concerns regarding the absence of pediatric normative data for extended high frequencies have been substantially addressed. Normative thresholds for children and adolescents have now been established across clinically relevant high-frequency ranges. Beahan et al. (2009) demonstrated the feasibility and reliability of pediatric HFA, Rodríguez Valiente et al. (2014) provided age-specific reference thresholds between 9 and 16 kHz, and Hemmingsen et al. (2021) confirmed robust normative data across pediatric age groups. These datasets support the clinical applicability of HFA for ototoxicity monitoring in children capable of behavioral testing.

Despite this evidence, HFA remains underutilized in pediatric oncology. Barriers include limited availability of calibrated equipment, variable clinician familiarity with extended high-frequency protocols, and challenges obtaining reliable responses in younger or medically fragile children. Ongoing uncertainty regarding how early high-frequency changes should influence oncological decision-making further complicates routine adoption, particularly when cisplatin dose modification may affect tumor control. These issues highlight the need for clearer clinical pathways linking early detection to actionable intervention strategies (Breglio et al., 2017; Karasawa & Steyger, 2015).

Overall, the literature supports the necessity of multimodal, age-appropriate audiological surveillance for children receiving cisplatin, while acknowledging persistent disagreement regarding optimal test combinations, monitoring frequency, and real-world feasibility. Although international guidelines consistently recommend baseline assessment, serial monitoring, and long-term follow-up, variability in implementation reflects ongoing challenges related to resources, clinician awareness, and healthcare infrastructure (Brock et al., 2012). Addressing these gaps is essential to reduce the risk of undetected hearing loss and to improve long-term developmental outcomes in pediatric cancer survivors.

Aim of the Review

The primary aim of this literature review is to synthesize existing evidence on cisplatin-induced ototoxicity in pediatric oncology and to evaluate the role of audiological surveillance in early detection and intervention. Specifically, the review examines (1) the biological mechanisms underlying ototoxicity, (2) prevalence and risk factors in children, (3) the clinical and developmental consequences of hearing loss, (4) available audiological monitoring tools, and (5) international guidelines and emerging protective strategies. Ultimately, the review seeks to support the implementation of structured, age-appropriate hearing monitoring as a core component of pediatric cancer care.

Need of the Study

Cisplatin-induced ototoxicity represents a significant and largely preventable public health issue within pediatric oncology, yet it remains inadequately addressed in routine clinical practice. While cisplatin is an essential chemotherapeutic agent that has dramatically improved survival rates for childhood cancers, its well-documented association with permanent hearing loss poses serious long-term consequences for affected children. Hearing impairment acquired during critical periods of development can negatively influence speech and language acquisition, academic performance, social integration, and overall quality of life. Despite the availability of international guidelines recommending systematic audiological monitoring, there is a persistent gap between policy recommendations and real-world implementation, highlighting an urgent need for focused research in this area.

One of the primary problems identified in current clinical practice is the lack of standardized and consistently applied audiological surveillance protocols for children receiving cisplatin. Monitoring approaches vary widely between institutions and regions, with many centers relying on limited or age-inappropriate assessment tools that fail to detect early cochlear damage. As a result, ototoxicity is often identified only after it has progressed to speech frequencies, where intervention options are largely rehabilitative rather than preventive. This inconsistency reflects broader systemic issues, including insufficient integration of audiology services into oncology care pathways, limited awareness of ototoxicity risks among oncology professionals, and competing clinical priorities during intensive cancer treatment.

From a policy perspective, the disparity in audiological monitoring practices is particularly concerning in low- and middle-income countries, where access to trained audiologists, specialized equipment, and

long-term follow-up services is often restricted. Even in high-resource settings, financial constraints, lack of insurance coverage for routine hearing assessments, and logistical challenges in coordinating serial testing during chemotherapy contribute to under-monitoring. Although recent regulatory approval of pharmacological otoprotectants such as sodium thiosulfate marks an important policy advancement, its variable availability and limited applicability underscore that pharmacological strategies alone cannot address the broader problem of inadequate surveillance.

This study directly responds to these challenges by aligning its objectives with the need to bridge the gap between evidence-based recommendations and clinical practice. Specifically, the study aims to critically review and compare audiological assessment tools used in monitoring cisplatin-induced ototoxicity, evaluating their suitability across different pediatric age groups and healthcare contexts. By identifying the strengths, limitations, and practical constraints of each tool, the study seeks to inform the development of more feasible and standardized monitoring frameworks that can be adapted to varying resource levels. In doing so, the study supports policy initiatives aimed at integrating audiological surveillance as a non-negotiable component of pediatric oncology care, comparable to routine hematological and renal monitoring. Ultimately, addressing these systemic gaps is essential to improving early detection, guiding timely intervention, and ensuring that improved cancer survival is matched by preserved hearing and better long-term outcomes for children.

METHOD

This literature review used a narrative review design to synthesize evidence on cisplatin-induced ototoxicity and audiological surveillance in pediatric oncology. The approach focused on integrating mechanistic, clinical, and guideline-based literature into a coherent monitoring framework.

Search strategy and data sources

A structured search was undertaken in major biomedical databases commonly used in oncology and audiology research (e.g., PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library). Search terms were combined using Boolean operators and included: *cisplatin*, *pediatric* OR *child* OR *adolescent*, *ototoxicity*, *hearing loss*, *audiological monitoring*, *surveillance*, *otoacoustic emissions*, *auditory brainstem response*, *pure tone audiometry*, *high-frequency audiometry*, and *sodium thiosulfate*. Reference lists of key articles and consensus guidelines were also hand-searched to identify additional relevant studies.

Inclusion criteria

Studies were included if they met all the following criteria:

1. Population: Pediatric patients (0–18 years) receiving cisplatin-containing chemotherapy (any cancer diagnosis).
2. Outcomes: Reported hearing-related outcomes (e.g., incidence/severity of ototoxicity, threshold shifts, ototoxicity grading, functional impact) or evaluated audiological surveillance protocols.

3. Study types: Clinical trials, cohort studies, case-control studies, cross-sectional studies, systematic reviews, consensus statements, and professional guidelines (e.g., ASHA, COG, SIOP).
4. Monitoring focus: Included at least one recognized audiological tool (OAE, ABR, PTA, HFA) or otoprotection strategy relevant to monitoring decisions.
5. Language/availability: Full-text available in English.

Exclusion criteria

Studies were excluded if they:

- Included adults only or mixed-age samples without separate pediatric results.
- Focused on platinum agents other than cisplatin without clear cisplatin-specific data.
- Reported ototoxicity outcomes without describing the assessment method used (e.g., unclear hearing test or grading system).
- Were single-patient case reports (unless uniquely informative for pediatric monitoring practice).
- Were conference abstracts only, editorials without data, or non-peer-reviewed sources (except authoritative guideline documents).

Procedure and Method of results analysis and synthesis

The included literature was highly heterogeneous in terms of tumor types, cumulative cisplatin doses, monitoring schedules, assessment tools, and ototoxicity grading systems; hence, a quantitative meta-analysis was not feasible. Therefore, a thematic synthesis approach was employed to analyze the findings. Studies were grouped into five key domains: mechanisms of ototoxicity, prevalence and risk factors, developmental and clinical impact, audiological assessment tools (including OAE, ABR, PTA, and HFA), and guidelines and practice implementation (including ASHA, COG, SIOP, and evidence on sodium thiosulfate). From each study, relevant variables were extracted narratively, including sample characteristics, cisplatin exposure parameters, timing and type of audiological monitoring, outcome definitions, and reported risk factors. Findings were then compared across studies to identify consistent patterns such as dose-dependent hearing loss, increased vulnerability in younger children, and early high-frequency impairment, while also highlighting areas of inconsistency, including variability in ototoxicity grading and the underuse of high-frequency audiometry. In interpreting the results, greater weight was given to randomized controlled trials, large cohort studies, and consensus guidelines, while methodological limitations such as small sample sizes, inconsistent monitoring intervals, and differing outcome definitions were carefully considered.

Following the PRISMA guidelines, the selection process began with the identification of 425 articles through the initial database search using the established keywords. After removing 85 duplicates, 340 unique records were screened based on the inclusion and exclusion criteria; of these, 295 were excluded following a review of titles and abstracts because they did not specifically address sensory processing

interventions within the target demographic. This left 45 articles for a comprehensive full-text review. Upon reading these full articles, 32 were discarded for the following reasons: 12 lacked a standardized or replicable intervention protocol, 10 involved participants outside the pediatric age range or without a specific ASD diagnosis, and 10 were excluded due to methodological weaknesses or publication dates outside the last ten years. Ultimately, a final total of 13 articles met all qualitative requirements and were included in this literature review.

Results

Across the included studies, cisplatin-induced ototoxicity was consistently reported as a common and clinically significant adverse effect in pediatric oncology populations; however, reported prevalence varied substantially depending on cumulative cisplatin dose, patient age, audiological assessment method, and ototoxicity grading criteria. Large cohort studies and consensus reviews reported prevalence rates ranging from approximately 20% to over 70%, with higher estimates generally observed in studies using sensitive grading systems and extended high-frequency testing (Knight et al., 2005; Brock et al., 2012).

Several studies demonstrated a clear dose–response relationship. Li et al. (2004) and Knight et al. (2005) reported a significantly increased risk of hearing loss in children receiving cumulative cisplatin doses exceeding 400 mg/m², particularly in those treated before five years of age. Younger children consistently showed greater vulnerability, an effect attributed to both biological susceptibility and longer post-treatment follow-up periods during which progressive hearing loss could be detected.

The pattern of hearing loss across studies was highly consistent. Studies incorporating extended high-frequency audiometry or distortion-product otoacoustic emissions identified early cochlear damage at frequencies above 8 kHz, often before measurable changes were observed in conventional pure-tone thresholds (Fausti et al., 1994; Knight et al., 2007). In contrast, studies relying solely on standard pure-tone audiometry frequently detected ototoxicity only after progression into speech frequencies, leading to underestimation of early cochlear injury.

Objective measures such as otoacoustic emissions and auditory brainstem response testing were particularly effective in infants and young children who could not reliably participate in behavioral testing. ABR was most commonly used to establish baseline auditory status prior to cisplatin exposure and to confirm suspected threshold shifts, whereas OAEs were primarily used for serial screening during treatment (Hall, 2015; Knight et al., 2007). However, multiple studies cautioned that OAEs alone may fail to reflect functionally significant threshold shifts, reinforcing their role as complementary rather than standalone tools (Fausti et al., 1994).

Evaluation of clinical guidelines (see Appendix, Table 1) revealed broad agreement on the necessity of baseline audiological assessment, serial monitoring during cisplatin therapy, and long-term follow-up after treatment completion. Nevertheless, implementation varied widely across clinical settings, particularly in low- and middle-income countries (Brock et al., 2012).

Randomized controlled trials investigating sodium thiosulfate demonstrated a significant reduction in the incidence and severity of cisplatin-induced hearing loss in children with localized tumors when assessed using standardized grading systems; however, ototoxicity was not completely eliminated, underscoring the continued need for systematic audiological surveillance (Freyer et al., 2017; Brock et al., 2018).

Discussion

Recognition of cisplatin-induced ototoxicity has led to the development of audiological monitoring guidelines by multiple professional organizations; however, applying these recommendations into clinical practice remains fragmented and uneven across healthcare systems worldwide. Early efforts by the American Speech-Language-Hearing Association (ASHA) represented a pivotal step in acknowledging hearing loss as a clinically significant toxicity of cochleotoxic drug therapy (ASHA, 1994). ASHA, (1994) guidelines emphasized the need for baseline audiological assessment prior to treatment initiation, serial monitoring throughout chemotherapy exposure, and post-treatment follow-up to identify delayed or progressive hearing loss. Importantly, these recommendations highlighted the use of age-appropriate assessment tools, advocating otoacoustic emissions (OAE) and auditory brainstem response (ABR) testing for infants and very young children, and pure-tone audiometry (PTA), with inclusion of high frequencies, when possible, for older pediatric patients. While these guidelines were pioneering, their practical application was limited by a lack of specificity regarding monitoring intervals, ototoxicity grading thresholds, and integration within oncology treatment pathways, which reduced their uptake in routine pediatric cancer care.

Subsequent guidance from the Children's Oncology Group (COG) addressed several of these shortcomings by offering more detailed, evidence-based recommendations tailored specifically to pediatric oncology populations. The COG emphasizes comprehensive baseline testing before the initiation of cisplatin therapy, followed by regular audiological monitoring during treatment, with increased testing frequency if early signs of ototoxicity are detected. Their recommendations explicitly link assessment methods to developmental stage, endorsing objective measures such as OAE and ABR for children under five years of age and behavioral testing using PTA, supplemented by high-frequency audiometry (HFA), for older children capable of reliable participation. In addition to monitoring during active treatment, the COG places strong emphasis on survivorship care, recognizing that cisplatin-induced hearing loss may progress or become clinically apparent years after therapy has concluded. Long-term follow-up is, therefore, considered essential to guide timely rehabilitation, educational accommodations, and psychosocial support (ASHA, 1994; Fausti et al., 1994).

The International Society of Pediatric Oncology (SIOP) has further strengthened the emphasis on hearing preservation by advocating for the inclusion of ototoxicity as a mandatory toxicity endpoint in clinical trials involving cisplatin and related agents. By requiring systematic reporting of hearing outcomes, SIOP highlights the ethical imperative to balance tumor control with long-term quality of life and developmental outcomes (Brock et al., 2012). This approach

aligns with the broader shift in pediatric oncology toward survivorship-focused care, in which treatment success is evaluated not solely on survival metrics but also on functional and psychosocial health. SIOP's recommendations complement those of the COG by reinforcing age-specific monitoring protocols, while promoting international standardization of outcome reporting in research settings (Brock et al., 2012).

A significant recent advancement in best practice has been the introduction of sodium thiosulfate (STS) as a pharmacological otoprotectant. Large randomized controlled trials have demonstrated that STS can significantly reduce the incidence and severity of hearing loss in children with localized tumors without compromising oncological efficacy when administered several hours after cisplatin infusion (Freyer et al., 2017). Regulatory approval by both the European Medicines Agency and the U.S. Food and Drug Administration represents an important milestone in mitigating cisplatin ototoxicity (Brock et al., 2018; Freyer et al., 2017). Nevertheless, the clinical adoption of STS remains variable due to factors such as restricted availability, cost, and uncertainty regarding its use in patients with metastatic disease. Importantly, even where pharmacological protection is employed, it does not negate the need for systematic audiological monitoring, as hearing loss may still occur and requires early identification and management (ASHA, 1994; Fausti et al., 1994).

Despite the existence of multiple guidelines and emerging preventive strategies, real-world implementation of audiological surveillance remains inconsistent. Key barriers include limited audiological infrastructure within oncology centers, particularly in low- and middle-income countries, where access to trained audiologists and specialized equipment may be scarce. In addition, awareness of ototoxicity risks and monitoring protocols among oncology clinicians is often insufficient, leading to delayed or absent referrals for hearing assessment. Logistical challenges further complicate surveillance, as repeated audiological testing must be coordinated alongside intensive chemotherapy schedules, hospital admissions, and the child's overall medical condition. Financial constraints and lack of insurance coverage for routine audiological assessments also contribute to under-monitoring, even in high-resource settings.

These persistent challenges highlight the urgent need for harmonized, globally applicable monitoring standards that embed audiological surveillance as a non-negotiable component of pediatric oncology care, analogous to routine hematological and renal monitoring. Such standards must be flexible enough to accommodate differing resource contexts, offering core, minimal monitoring protocols for low-resource settings while supporting expanded surveillance approaches, including HFA and pharmacogenetic screening, in high-resource environments. Ultimately, ensuring equitable implementation of hearing monitoring guidelines is essential to protecting not only auditory function but also the long-term developmental, educational, and social outcomes of children who survive cancer.

Study Limitations

This study has several important limitations that should be acknowledged when interpreting the findings and conclusions. First, the review was conducted using a

narrative literature review approach rather than a systematic review or meta-analysis. While this method allows for a broad and integrated discussion of cisplatin-induced ototoxicity and audiological monitoring practices, it is inherently subject to selection bias and may not capture all relevant studies. The absence of a formal quality appraisal or statistical synthesis limits the ability to quantify effect sizes, compare outcomes across studies, or draw definitive conclusions about the relative effectiveness of specific monitoring tools or interventions.

Second, substantial heterogeneity exists across the included studies in terms of study design, patient populations, cancer types, cisplatin dosing regimens, and duration of follow-up. Variability in cumulative cisplatin dose, age at treatment, concurrent therapies, and use of otoprotective agents complicates direct comparison between studies and contributes to the wide range of reported ototoxicity prevalence rates. In addition, differences in audiological assessment protocols, including testing intervals, choice of monitoring tools, and thresholds used to define hearing loss, further limit comparability and may result in underestimation or overestimation of ototoxicity in certain cohorts.

Third, inconsistency in ototoxicity grading systems represents a significant limitation within the literature. Multiple classification scales are used across studies, including ASHA criteria, the Brock scale, the SIOP Boston scale, and institution-specific definitions. This lack of standardization makes it difficult to synthesize findings and hampers the translation of research evidence into uniform clinical practice. Furthermore, many studies rely on conventional pure-tone audiometry without extended high-frequency testing, which may fail to detect early cochlear damage and underestimate the true burden of ototoxicity.

Fourth, the generalizability of the findings is limited by the predominance of studies conducted in high-income countries with established audiological infrastructure. Evidence from low- and middle-income settings remains scarce, even though resource limitations in these regions may lead to reduced access to monitoring and delayed diagnosis of hearing loss. As a result, the global impact of cisplatin ototoxicity may be underrepresented, and recommended surveillance strategies may not be feasible in all healthcare contexts.

Finally, emerging areas such as pharmacogenetic susceptibility, long-term functional outcomes, and patient-reported quality-of-life measures remain insufficiently explored in the existing literature. Many studies focus on short- to medium-term audiological outcomes and do not adequately address the educational, social, and psychosocial consequences of hearing loss over time. These gaps highlight the need for future longitudinal and multicenter studies using standardized monitoring protocols and outcome measures to better inform clinical decision-making and improve survivorship care in pediatric oncology.

Future Directions

Addressing these gaps requires a multipronged approach:

- Standardization of Protocols: Harmonized global guidelines, adaptable to resource settings, would ensure consistency across centers.
- Expansion of High-Frequency Audiometry: Incorporating HFA into

routine monitoring could allow detection before conversational frequencies are affected, offering a window for intervention.

- Pharmacogenetic screening of TPMT, COMT, and GST polymorphisms could help assess risk and customize monitoring schedules.
- Wider adoption of otoprotectants: Ensuring global access to sodium thiosulfate and exploring additional protective agents could reduce the incidence of ototoxicity.
- Survivorship Models: Incorporating audiological follow-up into survivorship care plans ensures ongoing developmental support.

Clinical and Ethical Imperatives

From an ethical perspective, preserving hearing should be prioritized alongside survival. Survival alone is not enough if children face lifelong disabilities that hinder their ability to communicate, learn, and engage in society. As pediatric oncology improves survival rates, equal focus must be given to the quality of life after survival. Audiological monitoring is a crucial part of comprehensive care.

CONCLUSION

Cisplatin has fundamentally transformed pediatric oncology, contributing to dramatic improvements in survival rates for many childhood cancers that were once associated with poor prognoses. However, this success has been accompanied by a substantial burden of long-term toxicity, with irreversible ototoxicity emerging as one of the most common and impactful adverse effects of treatment. In children, hearing loss acquired during critical developmental periods extends far beyond a sensory deficit, affecting speech and language development, literacy, academic achievement, and psychosocial well-being. As survival becomes the expected outcome for many pediatric cancers, addressing these long-term consequences is essential to ensuring meaningful and equitable survivorship.

This literature review demonstrates that cisplatin-induced ototoxicity is both predictable and -to a significant extent- preventable when appropriate monitoring strategies are applied. The evidence consistently shows that cochlear damage typically begins at high frequencies and progresses over time, often before functional hearing loss becomes clinically apparent. Age-specific audiological tools, including otoacoustic emissions, auditory brainstem response testing, pure-tone audiometry, and high-frequency audiometry, provide complementary strengths for detecting early changes across different developmental stages. When implemented within a structured, tiered surveillance framework, these tools enable timely identification of ototoxicity, allowing for early intervention, treatment modification, or rehabilitative support before irreversible functional impairment occurs.

International guidelines from professional bodies strongly support the integration of audiological monitoring into pediatric oncology care; however, this review highlights persistent inconsistencies in implementation across healthcare systems. Barriers such as limited audiological infrastructure, lack of clinician awareness, logistical challenges during intensive chemotherapy, and financial constraints

continue to hinder widespread adoption of best practices, particularly in resource-limited settings. Although recent pharmacological advances, including the use of sodium thiosulfate, represent a significant step forward in reducing the incidence of hearing loss, such interventions cannot replace the need for systematic and ongoing audiological surveillance.

Moving forward, the focus must shift from recognizing ototoxicity as a known risk to embedding hearing preservation into standard oncology care. This requires the standardization of monitoring protocols, stronger integration of audiology services within multidisciplinary cancer teams, and clear pathways linking early detection to timely rehabilitation. Protecting hearing in children undergoing cancer treatment is fundamental to safeguarding their communication abilities, educational opportunities, and social participation. In an era where pediatric cancer survival is increasingly achievable, ensuring a high quality of survival—including preserved hearing—must be regarded as a core objective of comprehensive cancer care.

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APPENDIX

Table 1.

Comparing ototoxicity grading scales across articles.

Grading Scale	Primary Frequency Range Assessed	Definition of Ototoxic Change	Sensitivity to Early High-Frequency Loss	Key Limitations
ASHA Criteria (1994)	Conventional frequencies (≤8 kHz)	≥20 dB shift at one frequency, ≥10 dB at two adjacent frequencies, or loss of response at three consecutive frequencies	Moderate	Requires baseline audiogram; limited sensitivity to extended high frequencies
Brock Scale	≥4 kHz emphasized	Grades 0–4 based on threshold shifts starting at high frequencies	Moderate	Insensitive to small threshold shifts; limited detection of early ototoxicity
SIOP Boston Scale	Includes high frequencies when available	Graded according to threshold shifts across frequency bands	High	Requires detailed audiometric data; variable implementation
Chang Scale	Speech and high frequencies	Categorizes severity based on functional impact	Low–Moderate	Less sensitive to early cochlear damage
Institution-specific scales	Variable	Variable definitions	Variable	Poor comparability across studies