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Auditory monitoring in childhood cancer: an integrative review

Monitoramento auditivo no câncer infantojuvenil: uma revisão integrativa

Monitorización auditiva en cáncer infantil: una revisión integradora

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Abstract

Introduction: Chemotherapy drugs are widely used to treat neoplasms and can lead to ototoxicity, damaging auditory cells and causing hearing loss. That is why some groups suggest hearing monitoring protocols to identify any alterations at an early stage. **Aim:** To identify auditory monitoring routines implemented at national and international level. **Methods:** Integrative literature review to synthesize results of independent studies about auditory monitoring in children and adolescents diagnosed with cancer. PubMed/Medline, EMBASE and Virtual Health Library databases were searched with terms from Emtree and Medical Subject Headings metadata systems. **Results:** 1504 articles were found, of which 11 were appraised. Evoked Otoacoustic Emissions were frequently cited and most of the studies performed monitoring at the beginning and throughout treatment to identify ototoxicity. **Conclusions:**

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National and international auditory monitoring practices vary on procedures and frequency between assessments.

Keywords: Ototoxicity; Hearing Disorders; Antineoplastic Protocols; Child; Adolescent.

Resumo

Introdução: Amplamente utilizados para o tratamento de neoplasias, os fármacos quimioterápicos podem desencadear ototoxicidade, lesando as células auditivas e podendo ocasionar perdas auditivas. Por isso, alguns grupos sugerem protocolos de monitoramento auditivo para identificar quaisquer alterações de forma precoce. **Objetivo:** Identificar a rotina de acompanhamento auditivo utilizada nos âmbitos nacional e internacional. **Métodos:** Revisão integrativa da literatura para sintetizar resultados de estudos independentes sobre a temática do monitoramento auditivo em crianças e adolescentes diagnosticados com câncer. Foram pesquisados descritores em inglês nos sistemas de metadados Emtree e Medical Subject Headings e as buscas foram realizadas nas bases de dados PubMed/Medline, EMBASE e Portal da Biblioteca Virtual em Saúde. **Resultados:** Foram detectados 1504 artigos, dos quais 11 foram incluídos na revisão. A avaliação auditiva mais utilizada foi o exame de Emissões Otoacústicas Evocadas, e a maioria dos estudos realizou monitoramento com avaliação ao início do tratamento oncológico e em diferentes momentos do tratamento, para verificar a ototoxicidade. **Conclusões:** As práticas de monitoramento auditivo nacional e internacional são variáveis quanto aos métodos utilizados e a frequência entre as avaliações.

Palavras-chave: Ototoxicidade; Transtornos da Audição; Protocolos Antineoplásicos; Criança; Adolescente.

Resumen

Introducción: Los fármacos quimioterápicos son muy utilizados para tratar neoplasias y pueden desencadenar ototoxicidad, dañando las células auditivas y causando una posible pérdida de audición. Por esta razón, algunos grupos sugieren protocolos de vigilancia auditiva para identificar cualquier alteración en una estadio precoz. **Objetivo:** Identificar la rutina de vigilancia auditiva utilizada a nivel nacional e internacional. **Métodos:** Revisión bibliográfica integradora para sintetizar los resultados de estudios independientes sobre el tema de la vigilancia auditiva en niños y adolescentes diagnosticados de cáncer. Se utilizaron descriptores en inglés en los sistemas de metadatos Emtree y Medical Subject Headings y se realizaron búsquedas en las bases de datos PubMed/Medline, EMBASE y Virtual Health Library. **Resultados:** Se encontraron 1504 artículos, de los cuales 11 se incluyeron en la revisión. La evaluación auditiva más utilizada fue la prueba de Otoemisiones Acústicas Evocadas, y la mayoría de los estudios realizaron un seguimiento con evaluación al inicio del tratamiento oncológico y en diferentes momentos durante el tratamiento para comprobar la ototoxicidad. **Conclusiones:** Prácticas nacionales e internacionales de vigilancia auditiva varían en cuanto a los métodos utilizados y la frecuencia entre evaluaciones.

Palabras clave: Ototoxicidad; Trastornos de la Audición; Protocolos Antineoplásicos; Niño; Adolescente.

Introduction

Childhood cancer is one of the leading causes of disease-related morbidity and mortality. In Brazil, it is the primary cause of death among children and adolescents aged 1 to 19, accounting for around 8% of all deaths in this age group[1]. The prevalence of cancer diagnoses in children ranges from 1% to 4% of all cancer diagnoses reported worldwide. Nationally, the reported prevalence ranges from 2% to 3% of registered cancer cases[2]. Early diagnosis increases the potential for a cure, estimated at around 70%[2], and treatment may involve chemotherapy, radiotherapy, and/or oncological surgery to remove the tumor. The probability of a cure also increases when multiple therapeutic modalities are combined, but this can also lead to severe side effects[3,4].

Chemotherapy drugs, widely used for cancer treatment—especially in the pediatric population—are highly effective against cancer. However, one of the most well-known side effects is ototoxicity, which damages auditory cells and can cause hearing loss[3]. Hearing disorders caused by exposure to ototoxic drugs begin in the basal portion of the cochlea, initially affecting high frequencies, and then progress to the apical portion, impacting middle and low frequencies, thus compromising speech intelligibility[4]. It is worth noting that these hearing losses are typically classified as sensorineural, bilateral, symmetrical, and irreversible, and can be triggered immediately after the first dose of chemotherapy[4,5].

Given the increased risk of ototoxicity, some international multi-professional hearing healthcare teams recommend hearing monitoring protocols, which include a baseline hearing assessment, followed by periodic assessments and patient counseling throughout the period of exposure to ototoxic drugs. The goal of monitoring is to identify any disorders as early as possible in order to minimize the impact of hearing loss on the patient's quality of life[6]. However, despite the availability of such protocols, information on their implementation in cancer care services indicates that the practice has not yet been integrated into routine care. One study reported that 50% of the professionals on the team carried out the assessments routinely[7], while another study found that only 20% of professionals performed monitoring regularly, and approximately 80% of oncologists were unclear about the referral process required for their patients to have their hearing assessed[8].

It is worth mentioning that there is no established national auditory monitoring protocol. One study analyzed the medical records of patients treated at a children's cancer care center to assess its auditory monitoring routine. The study identified a lack of audiological and otorhinolaryngological follow-up and reported that only one patient had a hearing assessment, though it was not specified when during the cancer treatment the assessment occurred[9].

Due to the scarcity of information about the auditory monitoring practices adopted for this population, and considering the clinical relevance of the topic, this integrative review aims to identify the best practices and outcomes of auditory monitoring used both nationally and internationally.

Methods

This is an integrative literature review, conducted following the recommendations of Cronin and George (2023)[10], aimed at identifying, analyzing, and synthesizing the results of independent studies on auditory monitoring in children and adolescents diagnosed with cancer. The review seeks to assess what the scientific community has reported about the practices adopted in cancer care services.

The first stage involved formulating the guiding question using the Population (P), Exposure (E), Comparison (C), and Outcome (O) (PECO) components. The review's question was: "What are the findings on hearing monitoring in children undergoing chemotherapy and radiotherapy?" Accordingly, the search included keywords for: children (P), chemotherapy and radiotherapy (E), and brainstem auditory evoked potential and evoked otoacoustic emissions (O). Keywords for Comparison were not included in the searches, as pilot searches showed that their inclusion limited the results. Therefore, to obtain broader results, descriptors related to this component were excluded.

Based on the criteria defined by the PECO components, selected keywords were searched in English within the Emtree and Medical Subject Headings (MeSH) metadata systems. The terms were combined using the Boolean operator OR to create groups, which were then interrelated with the operator AND, resulting in the final search strategy

in the format (P) AND (E) AND (O), as shown in Figure 1. In addition to the keywords, MeSH-suggested terms and synonymous text words were used to conduct broad searches.

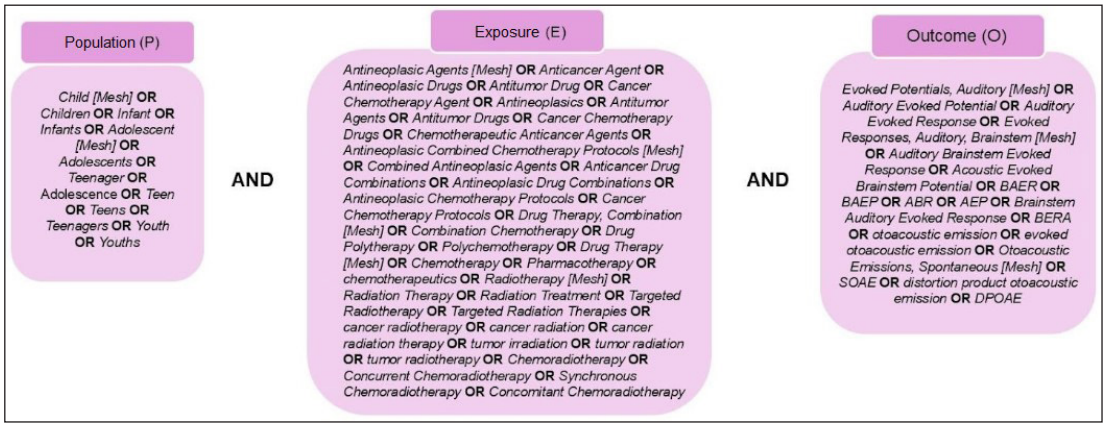

Figure 1. Search strategy

Searches were conducted in July 2024 across the following databases: PubMed/Medline, EMBASE, and the Virtual Health Library Portal (VHL), which includes the electronic libraries Índice Bibliográfico Español en Ciencias de la Salud (IBECS) and Literatura Latino-Americana del Caribe en Ciencias de la Salud (LILACS). The following inclusion criteria were applied for the selection and appraisal of the studies: publications from the year 2000 onwards, observational studies and clinical trials involving human participants, with the aim of assessing hearing in patients diagnosed with cancer aged 0 to 17 years and 11 months. Studies were excluded if the patient group had a concomitant diagnosis that could contribute to hearing loss (such as a history of hearing loss prior to cancer treatment, genetic syndromes, or other risk factors for hearing loss), as well as systematic literature reviews, animal studies, letters to the editor, book chapters, abstracts of scientific events, and case reports.

After filtering the results by study type, population, and excluding duplicates, two reviewers screened the identified records by checking the titles and abstracts of studies that seemed to meet the predetermined eligibility criteria. Subsequently, the records selected by the same reviewers were read in full for final inclusion. The necessary information and data were extracted from the selected articles in a standardized manner and recorded in a Microsoft Excel® spreadsheet. The data were analyzed descriptively.

Results

The search in the electronic databases detected 1,504 articles: 256 in PubMed, 1,148 in VHL, and 100 in EMBASE. Of these, 87 duplicates were removed. After reading the titles and abstracts of the remaining studies, 64 were selected for full appraisal, and 13 articles were deemed eligible for this review.

Brazil had the highest number of publications, with three articles included in the analysis[11,12,13]. The United States, Germany, and Mexico each had two articles included, covering the topic in question[14-19]. The other publications were from Chile[20], Italy[21], the United Kingdom[22], and Saudi Arabia[23].

In terms of sample size, the studies ranged from 10[15,16] to 104[21] subjects. The participants' ages ranged from 1[15,16] to 17[21] years. All the studies had paired samples for the gender variable, with no differences in the percentage of boys and girls in the samples. In Chart 1, the ages are presented as they appear in the article, i.e., by mean or minimum and maximum values.

As for the hearing assessment methods, 10 of the 13 articles used transient (TEOAE)[11,13-17,19,20,22,23] or distortion product (DPOAE)[11,12,17-23] evoked

otoacoustic emissions (EOAE). Nine studies analyzed the results of pure-tone audiometry, and three used Brainstem Auditory Evoked Potential (BAEP)[11,20,21]. One study investigated the cortical auditory response using the Long Latency Auditory Evoked Potential (LLAEP)[11]. With the exception of one study[19], the other studies performed acoustic immittance measurements before each assessment to rule out middle ear hearing disorders. Additionally, with the exception of one study, which only assessed patients at the end of treatment[19], the others performed more than one assessment over the course of antineoplastic treatment. The data from the included articles are shown in Chart 1.

Chart 1. Data from the included studies

Author (country)	Sample (age in years)	Hearing tests and time between assessments	Pros and Cons
Al-Noury, 2011 (Saudi Arabia)	26 (mean of 11,3)	Pure tone audiometry, TEOAE, DPOAE and tympanometry before and after the first dose of cisplatin.	Pros: The combination of pure tone audiometry, OAEs, and tympanometry contributed to the assessment of early hearing alterations, providing more comprehensive information about the hearing of these children. Cons: The data were collected before and after one dose of cisplatin, which does not allow for an evaluation of the deleterious effects of treatment with higher cumulative doses.
Bhagat et al, 2010 (USA)	10 (mean of 1,14)	DPOAE and tympanometry, before chemotherapy and after 3 months of cancer treatment	Pros: Observing a reduction in DPOAE response can serve as an early marker of cochlear alterations. Cons: The absence of pure tone audiometry results prevents analysis of the degree of ototoxicity, as well as the extent to which these disorders have impacted psychoacoustic thresholds.
Bhagat et al, 2013 (USA)	10 (mean of 1,15)	TEOAE and tympanometry. before chemotherapy and after 3 months of cancer treatment	Pros: The absence of pre- and post-exposure differences in TEOAE response may be useful in identifying the extent of cochlear damage early on, as the tests were carried out at frequencies up to approximately 5 kHz, which are less affected by ototoxicity. Cons: The absence of pure tone audiometry results prevents analysis of the degree of ototoxicity, as well as the extent to which these disorders have impacted psychoacoustic thresholds.
Caldas et al, 2015 (Brazil)	12 (minimum: 2; maximum: 12)	TEOAE, DPOAE and tympanometry. before cancer treatment and after 6 months of cancer treatment	Pros: OAEs can be useful in identifying cochlear damage at an early stage. Cons: The absence of pure tone audiometry results prevents analysis of the degree of ototoxicity, as well as the extent to which these disorders have impacted psychoacoustic thresholds. Furthermore, although a high prevalence of alterations was not observed at the conclusion of the study, retrocochlear losses cannot be ruled out.
Fetoni et al, 2016 (Italy)	104 (mean of 8,7)	BAEP, pure tone audiometry and tympanometry. First assessment two weeks after starting treatment and follow-up after each cycle for two years	Pros: The study aims to evaluate both the peripheral and central auditory pathways, allowing for the analysis of cochlear and retrocochlear alterations. In addition, monitoring was conducted over two years, with assessments performed after each cycle, enabling the analysis of the long-term impact and cumulative doses on hearing.
Pecora Liberman et al, 2011 (Brazil)	32 (mean of 1,7)	Pure tone audiometry, TEOAE and tympanometry. Hearing was assessed before and after cancer treatment.	Pros: The combination of pure tone audiometry, OAEs, and tympanometry contributed to the assessment of early hearing alterations, providing more comprehensive information about the hearing of these children. Cons: Assessments were performed before and after treatment, which interferes with the analysis of the doses at which chemotherapy begins to affect hearing.

Author (country)	Sample (age in years)	Hearing tests and time between assessments	Pros and Cons
Schmidt et al, 2008 (Germany)	55 (mean of 10,06)	Pure tone audiometry, TEOAE, DPOAE and tympanometry, at the start of treatment then 6 weeks after the end of treatment	Pros: The combination of pure tone audiometry, OAEs, and tympanometry contributed to the assessment of early hearing alterations, providing more comprehensive information about the hearing of these children. In addition, a significant difference was observed between the left and right ears at 4, 6, and 8 kHz, suggesting that the hearing losses may also be asymmetrical. Cons: Assessments were performed before and after treatment, which interferes with the analysis of the doses at which chemotherapy begins to affect hearing.
Stavroulaki et al, 2001 (United Kingdom)	12 (mean of 8,7)	Pure tone audiometry, TEOAE, DPOAE and tympanometry, before chemotherapy and after first infusion	Pros: The combination of pure tone audiometry, OAEs, and tympanometry contributed to the assessment of early hearing alterations, providing more comprehensive information about the hearing of these children. Cons: The data were collected before and after one dose of cisplatin, which does not allow for an evaluation of the deleterious effects of treatment with higher cumulative doses.
Toral-Martiñón et al, 2003 (Mexico)	16 (minimum: 2; maximum: 15)	DPOAE and tympanometry. Hearing was assessed after cancer treatment and results were compared to a control group	Pros: The study identified the progression of hearing loss, with worsening DPOAE responses over time. In addition, long-term follow-up was carried out, allowing the impacts of cancer treatment to be analyzed after its completion. Cons: The children were compared with a control group, which excluded baseline data on their hearing assessments. In addition, the absence of pure tone audiometry results prevents analysis of the degree of ototoxicity, as well as the extent to which these disorders have impacted psychoacoustic thresholds
Toral-Martiñón et al, 2003 (Mexico)	26 (minimum: 2; maximum: 15)	Pure tone audiometry and DPOAE, between the second and eighth doses of cisplatin	Pros: The combination of pure tone audiometry, OAEs, and tympanometry contributed to the assessment of early hearing alterations, providing more comprehensive information about the hearing of these children. DPOAEs showed 100% sensitivity and 82% specificity in identifying alterations at the 4 kHz frequency, related to the increase in hearing thresholds observed in pure tone audiometry. Cons: There were no baseline data on their hearing assessments (before treatment was administered).
Vosgrau et al, 2023 (Brazil)	17 (minimum: 3; maximum: 16)	Pure tone audiometry, tympanometry, BAEP and LLAEP. Assessments were conducted at three time points: before starting chemotherapy, 3 months after starting, and 6 months after starting.	Pros: The study aims to evaluate both the peripheral and central auditory pathways, allowing for the analysis of cochlear and retrocochlear alterations. In addition, monitoring was conducted over six months, enabling the analysis of the impactof cumulative doses on hearing. Another highlight is the finding of altered LLAEP, which suggests neurotoxic effects of the treatment.
Waissbluth et al, 2018 (Chile)	28 (mean of 7,2)	BAEP, TEOAE, DPOAE, pure tone audiometry and tympanometry. Assessments were performed before each cycle of chemotherapy and after the completion of treatment.	Pros: The study aims to evaluate both the peripheral and central auditory pathways, allowing for the analysis of cochlear and retrocochlear alterations. In addition, monitoring was conducted over one year and nine months, with assessments performed after each cycle, enabling the analysis of the long-term impact and cumulative doses on hearing.
Weissenstein et al, 2012 (Germany)	27 (mean of 9,84)	Pure tone audiometry and tympanometry. Assessments were conducted at three time points: before starting chemotherapy, 6 weeks after starting, and 6 months after completion of treatment.	Pros: The analysis of pure tone audiometry results allows for the determination of the type and degree of hearing loss. In addition, monitoring was conducted six months after the completion of treatment, enabling the analysis of the impact of cumulative doses on hearing. Cons: OAEs are more sensitive in identifying cochlear alterations early on and could provide additional information about the damage chemotherapy causes to the peripheral auditory pathway.

Legend: USA: United States of America; BAEP: Brainstem Auditory Evoked Potential; LLAEP: Long Latency Auditory Evoked Potential; TEOAE: Transient Evoked Otoacoustic Emissions; DPOAE: Distortion Product Otoacoustic Emissions; OAE: Otoacoustic Emissions

Discussion

The definition of auditory monitoring is to conduct regular follow-up assessments of hearing function, beginning with a baseline assessment, preferably before the first exposure to the drug, and repeating the same assessment at various times throughout the course of treatment. However, it is not always possible to perform an assessment before the first exposure due to the urgency of starting antineoplastic treatment. Therefore, it is recommended that the first hearing assessment be performed soon after the first exposure to the drug[8]. In this context, the scientific literature reviewed shows that most studies analyze OAE findings as a method for assessing hearing in children with cancer. OAEs are widely recommended for the early identification of cochlear alterations, especially DPOAEs, as they do not depend on the patient's voluntary response, making them suitable for use in children and in situations where bedside assessment is necessary, as is often the case in this population at the start of treatment[6].

Despite their advantages, such as high specificity and sensitivity for early detection of changes in outer hair cells, OAEs also have limitations. They do not provide information on the hearing threshold at each frequency, unlike pure tone audiometry, which is considered the gold standard test for hearing assessment[6,24]. Of the studies that performed OAEs, four[13-16] did not test patients with pure tone audiometry. Most available guidelines recommend combining both methods, and for pure tone audiometry, the recommendation is to investigate thresholds at high frequencies, as these are the first to show abnormalities due to the physiological mechanism of action of ototoxic drugs[6,25]. When audiometry is not possible, as it depends on the patient's voluntary response, an alternative is the Brainstem Auditory Evoked Potential (BAEP) test. The BAEP can even be carried out during preparatory procedures for chemotherapy, such as sedation for the insertion of the peripherally inserted central venous catheter[6,25], and allows for the investigation of thresholds in certain frequencies, both by air and bone conduction.

With the exception of one study, the others followed the guidelines of conducting a baseline assessment either before exposure to the drug or after one or two doses. The study that did not conduct a baseline assessment included a control group with no cancer diagnosis from the same age group to compare the results[14]. The adopted protocols varied in both the methods and timing of hearing assessments, with some performing tests after each chemotherapy session, while others only had retests at one point during treatment. Additionally, two studies[15,18] extended the follow-up to periods after the end of exposure to the antineoplastic drug to check for late-onset impairments.

This variability can be explained by the differences between the guidelines adopted by healthcare teams. Although there is some agreement, such as the recommendation of OAEs as an assessment method, the length of patient follow-up varies according to each guideline. In this review, 10 of the included studies evaluated patients exposed to platinum derivatives but did not consider the effects of other medications included in the treatment protocol, such as antibiotics and corticosteroids. It should be noted that the main guidelines available were published before 2010, including documents from the American Academy of Audiology and the American Speech-Language-Hearing Association[26,27], which only mentioned this group of drugs widely recognized as ototoxic. However, recently, the groups responsible for these publications have observed in clinical practice that other chemotherapy drugs, as well as combinations with other medications, can have ototoxic or neurotoxic effects, or a combination of both, impacting hearing in the long term[28,29].

One of the antineoplastic agents currently being investigated for ototoxicity is methotrexate, which is used to treat acute lymphoblastic leukemia, which is very prevalent in childhood[1]. Methotrexate was part of the treatment for the samples in two studies included in the review[11,13], and no significant changes were observed in OAE responses after six months of cancer treatment. However, changes were observed in central auditory pathway assessments, with altered BAEP and LLAEP results. More recent studies have shown that children exposed to methotrexate can experience hearing loss even up to 2 years after the end of treatment[29,30]. Additionally, methotrexate has been identified as neurotoxic, meaning that although it doesn't cause hearing loss, it can affect the speed of information processing in the auditory cortex. For this reason, updates to the guidelines suggest that children exposed to substances considered to have low ototoxic risk should receive long-term

monitoring, with annual hearing assessments to identify late ototoxic or neurotoxic effects[29-31].

It should be emphasized that all the included studies monitoring pure tone audiometry results identified sensorineural hearing loss after exposure to platinum derivatives[11,12,17-23]. It is important to emphasize that any type of hearing loss in childhood can have deleterious effects on child development, as observed in a study that assessed the impact of hearing loss on the quality of life of children who had undergone chemotherapy. The study identified greater difficulty in communicating with family and peers, in their independence, in interactions with peers, and in emotional well-being[32]. This reinforces the need to identify and rehabilitate hearing loss early and highlights the importance of monitoring these patients with a multidisciplinary team after cancer treatment.

Furthermore, the scarcity of studies specifically focused on children and adolescents is noteworthy, given that the adult population of childhood cancer survivors is more widely studied in relation to ototoxicity and auditory monitoring. This highlights a significant gap in the literature and underscores the need for more research aimed at children and adolescents.

As for the limitations of the findings of this review, it is important to note the heterogeneity of the data, due to the high variability in monitoring practices both nationally and internationally, especially regarding the tests used for auditory diagnosis. It was also observed that groups of patients exposed to the same chemotherapy had their hearing assessed in different ways, which interferes with the synthesis of the data. The integrative nature of this review is also emphasized. Although it allows for a comprehensive analysis of the literature, it has some limitations, such as not evaluating the methodological quality of the studies included or applying a meta-analysis.

However, the data from this review have important implications for research, highlighting the need for studies that analyze auditory function in children exposed to antineoplastic treatment to monitor its possible ototoxic effects, as well as studies that examine the effects of each chemotherapeutic agent independently to assess the risk of ototoxicity associated with each drug. In terms of clinical practice, the findings reinforce the importance of healthcare professionals paying close attention to possible hearing alterations in this population, given the evidence of this phenomenon and its impact on child development.

Conclusion

It was observed that international and national hearing monitoring practices vary in terms of the methods used and the frequency of assessments. The most commonly used test was OAE at the beginning and during treatment. The findings highlight the need for more studies on this subject, both to identify the adopted protocols and to understand the main difficulties in implementing them. Additionally, it should be noted that good hearing requires both peripheral and central pathways to be intact, so both auditory pathways should be assessed, taking into account the specificities of each case in order to rule out alterations that could impact child development.

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