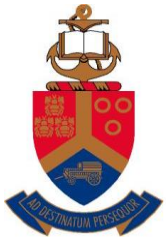

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A protocol for the identification and monitoring of aminoglycoside-induced cochleotoxicity: A systematic literature review

A dissertation in partial fulfilment of the requirements for the degree (MA) Audiology in the Department of Speech-Language Pathology and Audiology, Faculty of Humanities, University of Pretoria.

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DECLARATION

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I, Larraine (van Schalkwyk) Botha, hereby declare that this dissertation is my own work. Where secondary material was used it has been carefully acknowledged and referenced in accordance with the University of Pretoria and the Department of Speech-Language Pathology and Audiology's requirements. I understand what plagiarism is and am aware of the University of Pretoria's policy regarding this matter. No part of this may be produced in any form without written permission from the author.

30 October 2020

Signature

Date

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Abbreviations and Acronyms

AAA	American Academy of Audiology
ABR	Auditory Brainstem Response
AC	Air conduction

AG/s	Aminoglycoside/s
APA	American Psychological Association
ASHA	American Speech-Language Hearing Association
BC	Bone conduction
BKB	Bamford-Kowal-Bench
BMF	Berlin-Frankfurt-Munster
BOA	Behavioural observation audiometry
dB	Decibel
CF	Cystic Fibrosis
CRD	Centre for Reviews and Dissemination
DIN	Digits-in-noise
DPOAE/s	Distortion Product Otoacoustic Emission/s
EHF	Extended High Frequencies
HL	Hearing Level
HPCSA	Health Professions Council of South Africa
Hz	Hertz (Frequency)
IHC/s	Inner Hair Cell/s
kHz	Kilohertz
MDR-TB	Multidrug-Resistant Tuberculosis
MeSH	Medical Subject Headings
MOCB	Medial Olivocochlear Bundle
NIHL	Noise-Induced Hearing loss
OAE/s	Otoacoustic Emission/s
OHC/s	Outer Hair Cell/s
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PTA	Pure Tone Audiometry
PTT/s	Pure Tone Threshold/s
ROS	Reactive Oxygen Species
SNHL	Sensorineural Hearing Loss
SNR	Signal-to-Noise Ratio
SPIN	Speech-in-Noise
TB	Tuberculosis
TEOAE/s	Transient Evoked Otoacoustic Emission/s

UTI	Urinary Tract Infection/s
VRA	Visual Response Audiometry

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Abstract

Objective: This study aimed to examine the current available peer-reviewed evidence in order to gain insight into the most effective procedures used for the early identification and monitoring of aminoglycoside (AG)-induced cochleotoxicity and to suggest a protocol based on these findings. **Method:** Several databases were sourced with a comprehensive search conducted on Pubmed, Scopus and Medline (Ovid) to identify peer-reviewed studies published in English up until March 2020. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were adhered to. Studies were subjected to pre-set inclusion and exclusion criteria in order to eliminate the possibility of effects other than AG/s influencing auditory functioning. The reference lists of the included studies were also screened. **Results:** Twenty-one studies met the inclusion criteria for the systematic review and were analysed. The majority of the studies used conventional pure tone audiometry (PTA) with only a few studies using extended high frequencies (EHF/s) and otoacoustic emission (OAE) testing. **Conclusion:** Since the damaging effect of AG/s is evident at the outer hair cells (OHC/s) of the basal end of the cochlea first, EHF audiometry and distortion product otoacoustic emissions (DPOAE/s) testing seems more promising for the early detection and monitoring of AG-induced cochleotoxicity. For effective and efficient identification and monitoring of AG-induced cochleotoxicity, a test battery comprising of a combination of subjective and objective measures, specifically aimed at the OHC/s by means of EHF audiometry and OAE-testing (DPOAE specifically) and possibly speech-in-noise (SPIN) tests such as the digits-in-noise (DIN) / SPIN-tests, is recommended as a standard protocol.

Key words: Aminoglycosides, auditory function, cochleotoxicity, cochleotoxicity monitoring, distortion product otoacoustic emissions, extended high frequencies, ototoxicity, systematic review, pure tone audiometry

A protocol for the identification and monitoring of aminoglycoside-induced cochleotoxicity: A systematic literature review

Aminoglycosides (AG/s) are a group of potent antibiotics (Krause et al., 2016) commonly used to treat a variety of life-threatening bacterial infections such as sepsis, multidrug-resistant (MDR) tuberculosis (TB) (MDR-TB), endocarditis, respiratory infections in patients with cystic fibrosis (CF) and complex urinary tract infections (UTI/s) (Krause et al., 2016; Jiang, Karasawa & Steyger, 2017). There are more than 600 categories of drugs, such as AGs, available (Cianfrone et al., 2011), which have the potential to cause temporary or permanent damage to the inner ear, known as ototoxicity (Roland & Pawlowski, 2009). There are two broad categories of ototoxicity namely cochleotoxicity and vestibulotoxicity, with the former referring to damage occurring to the organ of hearing, known as the cochlea, and the latter to damage to the vestibular system responsible for balance (Roland & Pawlowski, 2009). Cochleotoxicity presents as hearing loss, tinnitus (Cianfrone et al., 2011) and hyperacusis (increased sensitivity to ordinary environmental sounds) (Ganesan et al., 2018). Even though the toxic side effects of AG/s are well known, they are still being prescribed and administered due to their efficient effect, broad antimicrobial coverage (Krause et al., 2016), lower cost compared to new non-ototoxic medications, lower incidence of resistance and chemical stability in higher temperatures in sub-Saharan Africa (Harris et al., 2012; Jiang et al., 2017). Estimations of the degree of hearing loss caused by AG/s vary as a result of different testing methods, the criteria used to classify a cochleotoxic threshold shift, as well as the dosage and type of AG administered (Stavroulaki et al., 2002). Rybak and Ramkumar (2007) and Jiang et al. (2017) stated that amikacin, kanamycin and neomycin are known to have a greater impact on the cochlea, while gentamicin, streptomycin and tobramycin affect the vestibular system more, although both sensory systems are affected to some degree by all of the AG/s (Jiang et al., 2017).

There is currently no treatment or medication available to reverse the damaging effects that cochleotoxic medication has on the auditory system. However, it can be managed in various ways such as through cochleotoxicity monitoring which enables early identification and consequently alterations in the drug dose and duration, which subsequently may lessen the adverse effects on hearing. Once a hearing loss has developed, hearing cannot be restored, but assistance can be provided by fitting the patient with a hearing aid or other assistive device (Ramma, Schellack & Heinze, 2019). Cochleotoxicity monitoring entails the serial

testing of the functioning of the auditory system in patients receiving cochleotoxic medication. The aim of performing cochleotoxicity monitoring is to identify changes in auditory function as early as possible (Konrad-Martin et al., 2005) in order to reduce the effects that it may have on an individual's hearing and consequently, the quality of life and communication abilities (American Speech-Language Hearing Association [ASHA], 2006). Effective cochleotoxicity monitoring is only possible with an interdisciplinary team of healthcare practitioners such as the audiologist, physician, pharmacist, nurse, psychologist, patient and family members. The major symptom of cochleotoxicity, hearing loss, is not a life-threatening condition, but it has a negative impact on a person's quality of life (Guinand et al., 2012; Sun et al., 2014; Stevenson et al., 2015). A hearing loss negatively affects a person's everyday communication which in turn, influences their socializing, employment and/or academic performance, cognitive and mental development, self-esteem, as well as general well-being (van de Berg, van Tilburg & Kingma, 2015). Individuals with hearing loss are more likely to suffer from loneliness (Weinstein, Sirow & Moser, 2016), anxiety and depression (Cohen et al., 2004).

Important elements of a cochleotoxicity monitoring program include timely identification of a hearing loss, the type and nature of monitoring evaluations, and determining the presence of an ototoxic hearing threshold shift and the grading thereof. The first ototoxicity monitoring protocol 'Guidelines for the Audiologic Management of Individuals Treated with Cochleotoxic Drug Therapy' was developed by ASHA in 1994 and is today, more than 20 years later, still considered the standard protocol to be followed in most settings. This protocol includes the following procedures as part of a baseline evaluation: case history, otoscopic examination, immittance testing (tympanometry and acoustic reflexes), pure tone audiometry (PTA) in the conventional air conduction (AC) frequencies of 125 Hz to 8 kHz and bone conduction (BC) 250 Hz to 4 kHz, as well as determining the thresholds at extended high frequencies (EHF/s) 9 kHz to 20 kHz and speech audiometry. Objective measures such as otoacoustic emission-testing (OAE) and/or auditory brainstem response (ABR) testing is recommended for patients with limited concentration and/or the difficult-to-test population. ASHA recommends that the following procedures be included in the follow-up monitoring evaluations: otoscopic examination, AC in the conventional frequencies, as well as EHF audiometry and, if a decrease in auditory function is observed, speech audiometry, immitance testing and BC PTA should be performed. International governing bodies such as the American Association of Audiologists (AAA) and

the Health Professions Council of South Africa (HPCSA) have made certain changes to the original ASHA 1994 protocol in their own versions, i.e. the 'AAA Position Statement and Clinical Practice Guidelines on Ototoxicity Monitoring' (2009) and 'HPCSA Audiological Management of Patients on Treatment that includes Ototoxic Medications' (2018). However, there is no consensus on which procedures are considered the most effective and efficient to be included for the monitoring of ototoxicity. The majority of the procedures are still the same, despite new research suggesting the use of different procedures such as speech-in-noise (SPIN) and digits-in-noise (DIN) tests.

Extended high frequency audiometry evaluates the air-conduction thresholds at the extended frequency range between 9 kHz and 20 kHz. According to Campbell (2004); Fausti et al. (2007) and Durrant et al. (2009) EHF audiometry is able to detect damage to the cochlea, caused by ototoxins such as AG/s at an early stage, which specifically targets the outer hair cells (OHC/s) at the basal region of the cochlea. An advantage of using EHF audiometry for cochleotoxicity monitoring is that it can detect the slightest changes in auditory function before the conventional frequencies between 125 Hz and 8 kHz are affected (Jacob et al., 2006; Knight et al., 2007), as well as that EHF audiometry is able to detect ototoxic changes earlier than is evident from the distortion product otoacoustic emission (DPOAE) test results (Knight et al., 2007). One of the disadvantages of using EHF audiometry is that the EHF thresholds cannot be obtained, and are often absent in patients with hearing thresholds greater than 60 decibels (dB) hearing level (HL) prior to the ototoxic treatment and/or in patients with noise induced hearing loss (NIHL) (AAA, 2009). Another disadvantage is that active participation and concentration are required from the patient in order to obtain reliable results. Lastly, the equipment needed to perform EHF audiometry is not available in many audiology centres.

Otoacoustic emissions are sounds emitted either spontaneously or evoked by an auditory stimulus, by the OHC/s located in the cochlea (Oostenbrink & Verhaagen-Warnaar, 2004) and provide information regarding the functioning of the OHC/s (Stach, 2003). The two most common types of OAE/s are DPOAE/s which occur in response to two simultaneous tones of different frequencies presented into the ear canal (Abdala & Visser-Dumont, 2001) and transient evoked OAE/s (TEOAE/s) which occur in response to single repeated stimuli such as clicks (Campbell, 2011). OAEs can be useful for cochleotoxicity monitoring because they are quick to perform (Campbell, 2004; Durrant et al., 2009) and objective, meaning they do not require a response from the patient. Therefore it is possible to

perform the tests on infants and patients who are non-responsive or not able to participate using behavioural audiometric methods (AAA, 2009). It has been determined by previous research that OAE-testing may be used to identify even very slight ototoxic related changes in OHC-functioning effectively (Konrad-Martin et al., 2016) prior to changes in behavioural (pure tone) thresholds (Lonsbury-Martin & Martin, 2001; Stavroulaki et al., 2001) as they are more sensitive than conventional PTA and/or ABR (Leigh-Paffenroth et al., 2005; Knight et al., 2007; Reavis et al., 2008). According to Konrad-Martin et al. (2005), DPOAE/s are particularly more effective for the early identification of ototoxicity as they are more frequency sensitive (Stavroulaki et al., 2002) and can be measured at higher frequencies and over a broader frequency range, which enables them to detect "warning signs" of ototoxicity earlier than TEOAE/s (Lonsbury-Martin & Martin, 2001; Konrad-Martin et al., 2016).

Disadvantages of using OAE-testing for cochleotoxicity monitoring are that they require a normal functioning outer and middle ear to be able to record the OAE (Campbell, 2011) and their results could be significantly affected and/or even be absent in the case of middle ear pathologies (Park et al., 2007) and a pre-existing hearing loss greater than 40 dB HL, due to damage to the cochlear OHC/s prior to the ototoxic treatment (Leigh-Paffenroth et al., 2005). A major disadvantage of using OAE/s as part of a cochleotoxicity monitoring protocol is the fact that there are no universally accepted and validated criteria to determine and grade a significant ototoxic threshold shift (Campbell, 2011).

Another measure which is recommended as part of an ototoxicity monitoring protocol is ABR-testing, which measures the neural responses from the cochlea to the upper brainstem (Katz, Medwetsky & Burkard, 2009) and generates a series of waves at different points in time in response to stimuli presented as clicks or tones (Rosa et al., 2014). Advantages of using ABR-testing is that it is also an objective and non-invasive procedure which has proven to be reliable and sensitive in detecting early signs of ototoxicity (Leigh-Paffenroth et al., 2005) and can be used to estimate thresholds in young infants and patients who are unable to cooperate (AAA, 2009). Conflicting evidence regarding its usefulness exists as it is time-consuming (Dille et al., 2013) and expensive to perform. Additional disadvantages of using ABR-testing are that it requires special equipment and training to perform the procedure and often requires the patient to be sedated, sometimes repeatedly (AAA, 2009). ABR-test results are sensitive to various artefacts such as electrical interference, muscle movement and noise (Polonenko & Maddox, 2019). An additional disadvantage of ABR compared to DPOAE is its relatively high measurement failure rate (Dille et al., 2013).

The majority of cells in the body absorb AGs and almost all of them are able to clear these drugs from their cytoplasm in a short period, except for the inner hair cells (IHC/s) and renal tubular cells, which keep these drugs in their cytoplasm for longer periods (Dai et al., 2006). The accumulation of AG/s inside the inner ear contributes to the formation of free radicals or reactive oxygen species (ROS) that activates cell death of sensory cells and neurons (Xing, Chen & Cao, 2007), resulting in irreversible hearing loss (cochleotoxicity) (Huth, Ricci & Cheng, 2011). It is suggested that the damage caused by AG/s in the cochlea disturbs the stereocilia (mechanosensing organelles of hair cells) in such a way that they become disorganized and eventually lead to apoptosis (cell death) of the OHC/s (Abi-Hachem, Zine & Van de Water, 2010). It is well established that many AG/s start by causing damage to the OHC/s at the basal turn of the cochlea, affecting the high frequencies first, followed by IHC loss at the apical region and low frequency hearing loss (Rizzi & Hirose, 2007; Bisht & Bist, 2011). Once the OHC/s at the basal turn of the cochlea are destroyed, it could cause a high frequency sensorineural hearing loss (SNHL) which in turn may affect speech comprehension (Duggal & Sarkar, 2007).

Cochlear toxicity due to AG antibiotics can result in a permanent SNHL, tinnitus, as well as difficulties understanding speech in the presence of background noise (Wium & Gerber, 2016). In a study by Einarsson et al. (2011), it was suggested that the use of standard speech recognition tests with words presented in a quiet setting may not accurately reflect the impact of ototoxic (cochleotoxic) hearing loss on auditory function, whereas speech-in-noise measures may more accurately reflect communication difficulties. It is for the abovementioned reasons that Smits, Kapteyn and Houtgast (2004), recommends the use of the SPIN test as a supplementary and/or alternative procedure for measuring functional hearing. Grant and Walden (2013) stated that the results of the SPIN test may provide more specific information about a person's hearing ability in everyday life situations. It has been proven that using the DIN test for the assessment of a SNHL is consistent with the results of PTA and a major advantage is that it no longer requires a soundproof booth, equipment that needs calibration and/or a person administering the tests, as it is computerised (Smits et al., 2004; Jansen et al., 2010; Potgieter et al., 2016; Koole et al., 2016). Neither of the governing bodies' ototoxicity monitoring protocols mentioned above currently recommends the use of the SPIN or the DIN test as ototoxicity monitoring procedure, despite evidence-based research done in this regard.

According to ASHA (1994), baseline evaluations should be conducted within 72 hours of the administration of AG/s, which is based on an animal study by Brummet and Fox (1982) who found evidence of ototoxicity occurring approximately 72 hours after the administration of AG/s. Cochleotoxicity monitoring should be done weekly or biweekly, as well as a few months and up to six months or longer after the treatment with AG/s (Konrad-Martin et al., 2005), as cochleotoxic threshold shifts can still occur after the completion of AG treatment (Bertolini et al., 2004).

In order to identify a cochleotoxic threshold shift, a criterion is needed to determine what is considered to be a significant change in hearing thresholds (King & Brewer, 2018). According to Jacob et al. (2006), Durrant et al. (2009) and Chang (2011), a universally accepted cochleotoxicity monitoring protocol and standard criterion to define cochleotoxicity do not currently exist. If there is no standardised, universally accepted criterion to follow, Audiologists would have difficulty in identifying a cochleotoxic hearing loss and will consequently not be able to manage a patient adequately if a change is detected concerning their auditory functioning. This will cause a lack of uniformity in the consistency and standard of services provided and clinicians will have difficulty in documenting the prevalence as well as any progression or regression of hearing loss due to cochleotoxicity. Standardised and universally accepted criteria will assist in providing a more efficient referral system for patients in need of ototoxicity monitoring (Govender & Paken, 2015). The ASHA (1994:6) criteria for determining a threshold shift are the most commonly used and accepted criteria and define a threshold shift as follows: (1) *a 20 dB decrease at any one test frequency, (2) a 10 dB decrease at any two adjacent test frequencies, or (3) no response at three consecutive frequencies where a response was previously reported.* These changes need to be confirmed by a follow-up test (ASHA, 1994) ideally performed within 24 hours (Konrad-Martin et al., 2005). Specific criteria to grade a cochleotoxic hearing loss are important, as it will allow the audiologist and/or clinician to identify and take the necessary steps when and if a change in hearing thresholds is observed (Govender & Paken, 2015). The abovementioned ASHA (1994) criteria include pure tone thresholds (PTT/s) as they are considered to be the "gold standard" for ototoxicity monitoring (King & Brewer, 2018). It was found that the ASHA criteria for identifying a cochleotoxic threshold shift are the most appropriate for the earliest identification of ototoxicity as it is the only available protocol emphasizing baseline evaluation (Ganesan et al., 2018). It is important to note that there is currently no consensus on criteria to grade a threshold shift when using objective measures

such as OAE-testing (DPOAE and TEOAE) and/or ABR-testing (AAA, 2009). Several significant change criteria for interpreting OAE/s have been put forward (Katbamna, Homnick & Marks, 1999; Lonsbury-Martin & Martin, 2001) although none have yet received universal consensus and acceptance, as accepted criteria for an ototoxic OAE shift has not yet been defined (Konrad-Martin et al., 2016).

Once a cochleotoxic threshold shift has been identified it is important to grade and describe the degree of the adverse event (hearing loss), which is useful in clinical trials (AAA, 2009) as it will ensure uniformity amongst clinicians (Govender & Paken, 2015). Uniformity in the interpretation of results will allow for effective communication of test results to various non-audiology stakeholders, and it will contribute to consistent data interpretation, as well as improved decision making regarding further management of each case (King & Brewer, 2018). A variety of validated adult and paediatric grading scales exist, such as the Brock scale by Brock et al. (1991), the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Ototoxicity Grades, the Chang scale by Chang and Chinosornvatana (2010), the TUNE scale by Theunissen et al. (2014) and the Boston International Society of Paediatric Oncology (SIOP) scale by Brock et al. (2012) which all have their differences and modifications such as the inclusion or exclusion of a baseline evaluation and EHF audiometry, as well as the sensitivity of the procedures (Crundwell, Gomersall & Baguley, 2016). While the majority of these scales use conventional PTA, a recent review on cochleotoxic classification systems by Crundwell et al. (2016) indicated that the Chang scale and the Tune scale were the only scales amongst those studied that included EHF audiometry into their grading systems (Ganesan et al., 2018). An adverse event grading scale using ABR thresholds were developed by King and Brewer (2018). However, it still has to be validated.

Research on the most effective and efficient procedures for the identification and monitoring of AG-induced cochleotoxicity should be collectively analysed to improve on current knowledge and practices of cochleotoxicity monitoring. A systematic literature review is an effective method for collectively analysing current knowledge and practices, as it aims to gather all relevant published evidence according to pre-selected criteria, in order to answer a specific research question (Higgins & Green, 2011). A systematic literature review uses systematic methods, specifically selected to minimize bias, to identify, select, analyse and summarise the findings of various studies, from which conclusions can be drawn and decisions can be made (Shamseer et al., 2015). Thus, a systematic literature review will aid in

identifying the most effective procedures recommended to identify and monitor AG-induced cochleotoxicity, by using the available evidence, as well as to identify in which area(s) a lack of knowledge is still present (Higgins & Green, 2011). This literature review aimed to examine the current available peer-reviewed evidence in order to gain insight into the most effective practices and/or procedures used for the early identification and monitoring of aminoglycoside-induced cochleotoxicity and to suggest the best protocol based on these findings.

Methodology

This section aims to provide comprehensive information on the methods used to perform this systematic review by elaborating on the aim of the study, the study design and the search strategies employed. Furthermore, in this chapter, the procedures used for data collection and analysis are described, as well as how quality control of the study was ensured.

Study aim

This study aimed to examine the current available peer-reviewed evidence in order to gain insight into the most effective practices and/or procedures used for the early identification and monitoring of aminoglycoside-induced cochleotoxicity and to suggest a protocol based on these findings.

Study design

By using a systematic literature review the researcher aimed to gather all relevant published evidence according to pre-selected criteria, in order to answer a specific research question (Higgins & Green, 2011). The researcher used systematic methods, specifically selected to minimize bias, to identify, select, analyse and summarize the findings of published literature, from which conclusions could be drawn and decisions be made (Shamseer et al., 2015). The researcher performed a systematic review in order to gain insight into the protocols and procedures considered to be the most efficient and effective for the identification and monitoring of AG induced cochleotoxicity. This systematic review identified the procedures and protocols followed by researchers and the areas where research is still needed for effective cochleotoxicity monitoring (Higgins & Green, 2011). Systematic reviews have recently become very popular with an estimated 22 new publications daily (Moher, Stewart & Shekelle, 2016) as they assist in the development of guidelines, as well as the identification of gaps in research (Shamseer et al., 2015).

Throughout this systematic review reference was made to the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) statement by Moher et al. (2009) in order to guide the research process. This PRISMA-P statement also recommends the use of the PRISMA-P checklist (Shamseer et al., 2015) which was

developed for the preparation of systematic review and meta-analysis protocols (Moher et al., 2015). This 17-item checklist, with 26 items in total, (Appendix A), consists of three main sections namely 'administrative information', 'introduction' and 'methods' to assist researchers in preparing and reporting scientifically accurate systematic reviews (Moher et al., 2016). During a period of just over a year after it was published, this checklist was downloaded about 45 000 times and cited on Google Scholar about 100 times with Google Scholar and other journals endorsing this PRISMA-P checklist (Moher et al., 2016). The duplication of existing published studies was avoided by the researcher by doing a thorough systematic review search on PROSPERO, as well as registering the protocol used in this study on the register (Stewart, Moher & Shekelle, 2012). The reference number is: 170142.

Data collection procedures

Data was collected by following a specific search strategy after which studies were subjected to specific inclusion and exclusion criteria in order for data extraction and analysis to commence.

Search strategy

In order to cover a wider variety of published research, a thorough literature search was conducted across the following three electronic databases namely Pubmed, Scopus and Medline (Ovid) during the month of April 2020, with the last search done on the 30th of April 2020. Internet sites from international and national scientific societies such as AAA, ASHA and HPCSA were also consulted. Specific search strategies for each database e.g. all fields and medical subject heading (MeSH) terms for Pubmed, title, abstract and keywords for Scopus, and keywords for Medline (Ovid) were applied. A variety of search terms were determined before the commencement of database searches and included the following: "aminoglycosides" OR "aminoglycoside-induced" AND "cochleotoxicity" OR "cochlear toxicity" OR "hearing" OR "hearing loss" AND "otoacoustic emissions" AND "auditory brainstem responses" AND "extended high frequencies" AND distortion product otoacoustic emissions" AND "transient evoked otoacoustic emissions" AND "speech" OR "speech in noise" OR "speech audiometry". Limiters were identified and set for each database to include English, peer-reviewed journal articles, in order to reduce the number of irrelevant articles.

No limitations were set in terms of the publication date. Table 1 below outlines the search strategies, search terms, limiters and results for each database searched.

Table 1

Search strategies

Database	Search strategy	Search terms	Limiters	Results
PubMed	All fields, MeSH terms	"aminoglycosides" OR "aminoglycoside-induced" AND "cochleotoxicity" OR "hearing" OR "hearing loss" AND "otoacoustic emissions" AND "auditory brainstem responses" AND "extended high frequencies" AND distortion product otoacoustic emissions" AND "transient evoked otoacoustic emissions" AND "speech" OR "speech in noise" OR "speech audiometry"	English, Journal articles, peer-reviewed	69
Medline (Ovid)	Keywords	"aminoglycosides" OR "aminoglycoside-induced" AND "cochleotoxicity" OR "hearing" OR "hearing loss" AND "otoacoustic emissions" AND "auditory brainstem responses" AND "extended high frequencies" AND distortion product otoacoustic emissions" AND "transient evoked otoacoustic emissions" AND "speech" OR "speech in noise" OR "speech audiometry"	English, Journal articles, peer-reviewed	41
Scopus	Title, abstract and keywords	"aminoglycosides" OR "aminoglycoside-induced" AND "cochleotoxicity" OR "hearing" OR "hearing loss" AND "otoacoustic emissions" AND "auditory brainstem responses" AND "extended high frequencies" AND distortion product otoacoustic emissions" AND "transient evoked otoacoustic emissions" AND "speech" OR "speech in noise" OR "speech audiometry"	English, articles, peer-reviewed	66

Inclusion and exclusion criteria

Prior to the commencement of the database searches strict inclusion and exclusion criteria were determined with reference made to the Population Intervention Comparison and Outcome (PICO) tool mentioned in the PRISMA-P checklist (Shamseer et al., 2015). This ensured the eligibility, reliability and validity of the included articles and reduced bias and irrelevant studies (Liberati et al., 2009). Table 2 below outlines the inclusion and exclusion criteria that studies had to adhere to in order to be included in this systematic review.

Table 2

Inclusion and exclusion criteria of studies for this systematic review

Inclusion criteria	
Criteria	**Rationale**
Studies published in English were included in this review	English is considered to be the 'universal language of science' (Drubin & Kellogg, 2012).
All studies published up until the end of March 2020 were included in this review	Ototoxicity has been researched since the discovery of streptomycin in the 1940's (Schatz, et al., 2005) and the American Academy of Audiology (AAA) as well as American Speech Language Hearing Association's (ASHA) ototoxicity guidelines which are still widely used, dates back to the 1990's. The literature search was conducted up until the end of March 2020 in order for data analysis to commence.
Peer-reviewed, case-controlled, cross-sectional and/or prospective cohort / longitudinal studies were included	To ensure that 'high quality research' articles were included in the study
Only studies done on human participants (paediatrics, adolescents and adults) until the age of 50 years, were included in the review	The aim of this study was to review the available research on cochleotoxicity monitoring procedures in humans. Cochleotoxicity is not specific to gender or race and occurs across all age ranges (Ganesan et al., 2018). Age has an influence on a person's hearing ability in the sense that certain changes occur in the perception of sound, which is related to aging and hearing loss (presbycusis) (Moore, 2014).
Only studies done on AG-induced cochleotoxicity and not on vestibulotoxicity were included	The aim of this review is to focus on cochleotoxicity due to the high incidence of patients receiving cochleotoxic medication such as AG/s for various conditions
Studies including AG induced cochleotoxicity as a major subject, topic or keyword were consulted	This correlates with the aim of this study
Only studies that had valid controls in terms of age, gender and audiometric procedures compared to the participants treated with aminoglycosides, were included	In order to make valid comparisons and conclusions
Exclusion criteria	
Criteria	**Rationale**
Systematic review articles were excluded from the study	In order to avoid bias by creating a new systematic review through the use of existing systematic reviews (Robinson et al., 2014) systematic review articles were excluded.
Editorials and chapters in a book were excluded from the study	In order to avoid non-scientific articles and studies, editorials were excluded from the study as these are merely the opinions and views of authors regarding a certain topic and not evidence based research (Stevens, Lynm & Glass, 2006).
Studies including participants with additional conditions or risk factors for hearing loss e.g. NIHL, middle ear pathologies, diabetes mellitus were excluded from the study	In order to draw conclusions on the effect of aminoglycosides on hearing abilities without having external influences influencing the search results.
Studies with animal participants were excluded from the study	The aim of this study was to review the available research on cochleotoxicity monitoring procedures in humans.

Study selection

Articles related to the title, aim and objectives of the study were carefully selected by using the PRISMA-P four-phase diagram (Figure 1) guiding the stages of data collection (Moher et al., 2009). The inclusion and exclusion criteria were also referred to during each phase to determine the relevance of each study.

During the initial phase, the articles were identified using the three electronic database searches (n = 176). Duplicate articles were excluded (n = 44). First, the titles and abstracts were screened (Moher et al., 2009) to determine its relevance to aminoglycoside-induced cochleotoxicity (n = 132). Sixty-eight articles were excluded for the following reasons: the study investigated animal participants (n = 10); the abstracts / full-texts were not available (n = 2); the study designs used were not relevant (n = 14); the articles were duplicates (n = 1); the study participants were older than 50 years of age (n = 7); the participants were at risk for hearing loss (n = 1); no audiological monitoring done (n = 4); the participants were not administered any AG/s and/or AG/s were administered in combination with other ototoxic drugs e.g. furosemide (n = 4) and the articles were not relevant to the aim of the current systematic review (n = 25). Articles with relevant titles and abstracts (n = 64) qualified for the full-text assessment as specified by the PRISMA-P four-phase diagram.

On the second phase of the PRISMA-P four-phase diagram the full texts (Moher et al., 2009) of articles were reviewed (n = 64) to determine their relevance to AG-induced cochleotoxicity and appropriateness for inclusion. Again, these articles were compared to the strict inclusion and exclusion criteria as set out in Table 2 that studies had to adhere to in order to be included in this systematic review. Forty-seven articles were excluded for the following reasons: the articles were not available (n = 11); the participants were older than 50 years of age (n = 15); the participants were not administered any AG/s and/or no audiological monitoring were done (n = 3); the participants were at risk for hearing loss (n = 6); the participants were given AG/s and other ototoxic medication (n = 8) and the studies were not relevant to the aim of the current systematic review (n = 4). Seventeen articles met the inclusion and exclusion criteria. A “hand search” of the reference list of these primary studies (Kitchenham, 2004) was done to ensure that no relevant studies were missed during the database search. During the “hand search” an additional (n = 4) articles were identified. A total of 21 articles met the inclusion and exclusion criteria of the study. A visual representation of the study selection procedure, guided by the PRISMA-P statement by

Moher et al. (2009), is presented in figure 1 below. Two independent reviewers reviewed the full articles and had an 85.71% agreement on the final included studies, indicating a good inter-rater reliability. Disagreements on articles (n = 3) were resolved by a discussion of each article.

Data management and data items

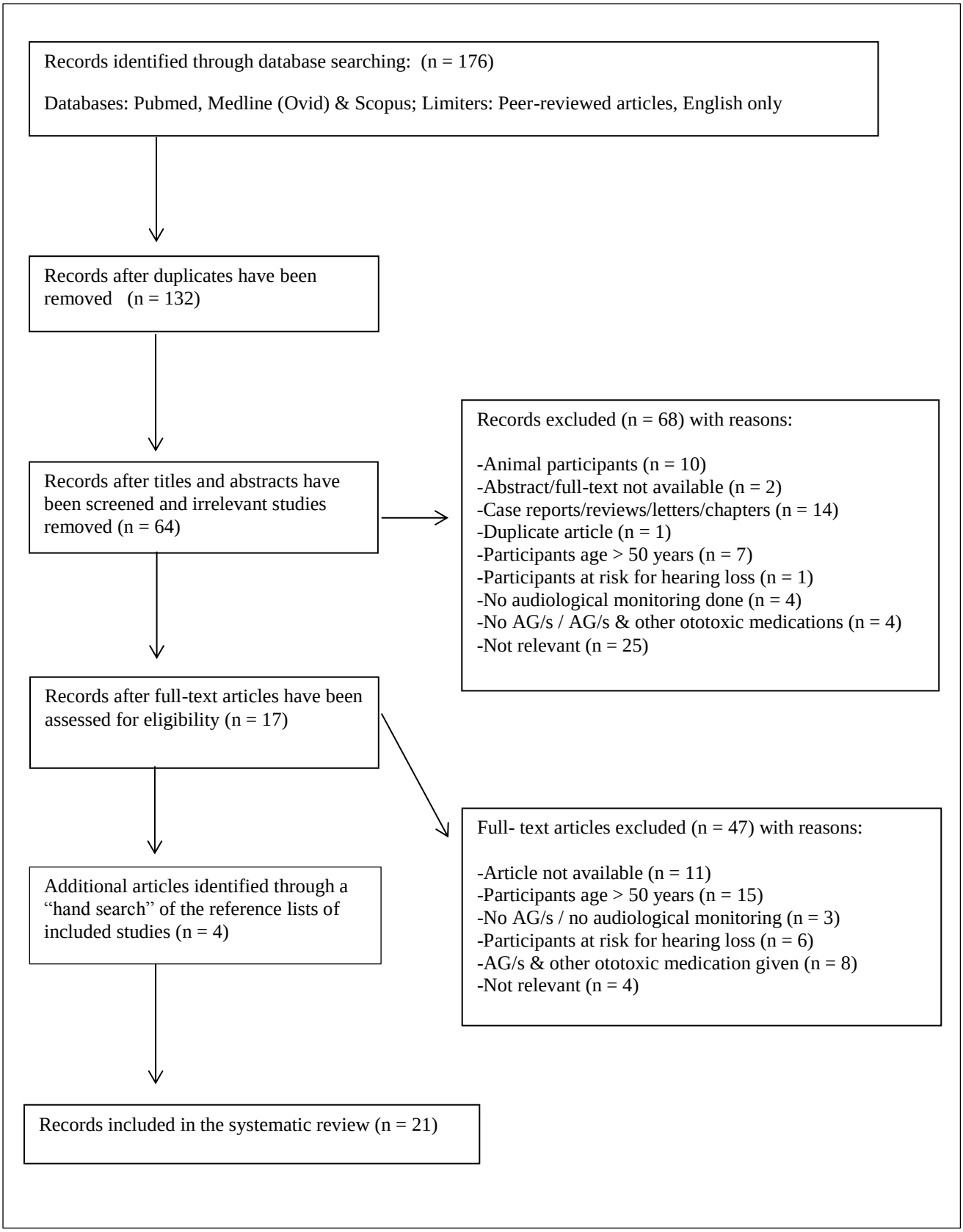
Rayyan web application software for systematic reviews, developed by the Qatar Computing Research Institute (QCRI) in 2016, was used to export the studies from the three selected databases. This software allowed efficient screening of the titles and abstracts, detection and exclusion of duplicate articles, reviewing of full-texts, as well as collaboration between the two reviewers. Mendeley Reference Manager was utilized to formulate citations and the reference list of the current systematic review by adhering to the American Psychological Association (APA) 7th edition referencing style.

The articles which were selected during the final phase of the study selection procedure were thoroughly reviewed in order to extract the relevant data items which were summarised and presented in table format on the data collection sheets. The data collection sheets with data items were formulated prior to the data collection process with reference made to the PRISMA-P Statement as a guide. The following data items were extracted from the articles and were included in the data collection sheets:

- The title of the study, name of authors and year published;
- The characteristics of the study participants such as group size, age, gender, diagnoses, as well as the type of AG/s administered and the duration of the administration;
- The procedures used for baseline evaluation and monitoring purposes, the timing of monitoring, as well as the criterion used to identify and diagnose cochleotoxicity;
- The results of each study and/or the correlation between the results of the study participants on AG treatment and the results of the control groups;
- The conclusions and recommendations of the included studies;
- The level of evidence of each study (CRD hierarchy of evidence);
- The test parameters of the objective measures used e.g. DPOAE, TEOAE and ABR.

Figure 1

Study selection procedure guided by the PRISMA-P statement Moher et al. (2009).



Study quality appraisal

According to the Centre for Reviews and Dissemination (CRD) and the Cochrane Reviewers' Handbook, study quality refers to the way in which a study limits biases and optimises internal and external validity (Higgins & Green, 2011). A total of 21 studies were accepted for the critical appraisal process which was done by two independent reviewers, to avoid bias, and who used the 'critical review form for quantitative studies' by Potvin (2007) which was modified from Law et al. (1998) (Appendix B). The abovementioned form focuses on areas such as the study purpose, literature, study design/s, sample size, outcomes, intervention and results, and allows the researcher/s to critically appraise each study in order to ensure that only valid and reliable studies of high quality are included in the systematic review. Any differences in opinions between the reviewers were resolved through discussions.

The included studies were rated on the CRD's Hierarchy of evidence scale (2009), as presented in Table 3 below, by the two independent reviewers in order to ensure that studies of high quality were included. This scale consists of five levels- the highest level 1 and the lowest level 5, in the following order: 1: experimental studies; 2: quasi experimental studies; 3: controlled observational studies; 3a: cohort studies; 3b: case control studies; 4: observational studies without a control group and 5: expert opinions based on theory, laboratory research or consensus.

Table 3

CRD hierarchy of evidence

Level	Description
1	Experimental studies i.e. RCT with concealed allocation
2	Quasi experimental studies i.e. studies without randomization
3	Controlled observational studies
3a	Cohort studies
3b	Case control studies
4	Observational studies without a control group
5	Expert opinions based on theories, laboratory research or consensus

Data analysis

Data analysis refers to the process of examining raw data in order to draw conclusions about the information gathered (Johnson & Christensen, 2010). The information obtained

from the systematic review was pooled and synthesized in a qualitative and narrative method and described in tables, graphs and paragraphs. This included information such as the characteristics of the participants, the timing of testing and procedures used to monitor for cochleotoxicity, the criterion used to identify and diagnose a cochleotoxic threshold shift, the test parameters, results, conclusions and recommendations. Qualitative data analysis assisted in summarizing the data and identifying common themes from each article, such as procedures used and their results and/or recommendations (Johnson & Christensen, 2010). The researcher expected diversity in the studies in terms of their research settings, interventions and outcome measures, thus a narrative approach making use of qualitative thematic analysis was considered to be appropriate.

Ethical considerations

Due to the nature of this study it wasn't necessary to adhere to ethical considerations typical in a human study, however, certain ethical considerations were still adhered to.

Research clearance

Ethical approval for this study was requested and obtained from the Faculty of Humanities Research Ethics Committee at the University of Pretoria. (Appendix C).

Plagiarism

Plagiarism was prevented in this study by strictly adhering to the American Psychological Association's (APA) 7th edition referencing style, by acknowledging all the information sources used, by means of citations and a comprehensive reference list. The researcher has signed a plagiarism declaration.

Reliability and validity

According to Kimberlin and Winterstein (2008), validity and reliability ensures the integrity and quality of a measurement instrument. High quality research requires that the measurement instrument or tool is both reliable and valid, which are the two most important

and fundamental features (Mohajan, 2017). Reliability refers to the degree to which a measurement instrument produces consistent, repeatable and trustworthy results (Chakrabartty, 2013). Validity is the degree to which the research results are presented in a truthful manner and the extent to which the instrument measures what it is meant to measure (Robson, 2011). The reliability and validity of the research data was ensured in the following ways:

- The PRISMA-P 2015 Statement checklist by Shamseer et al. (2015) was adhered to;
- The study aim and objectives were clearly defined;
- A thorough search on a variety of databases such as PubMed, Medline (Ovid) and Scopus were used in order to include all relevant data;
- The relevancy of each article was determined by means of comparing it to the inclusion and exclusion criteria of the study;
- Two external reviewers assisted in reviewing and critically appraising relevant articles.

Risk of bias

Bias refers to an error (intentionally or unintentionally) that can occur during any stage of the research process including the data collection phase, analysis and interpretation phase and/or publication phase, resulting in false conclusions (Simundic, 2013). As with any other study, there are a number of sources posing risks of bias to systematic reviews, which could be reduced and/or avoided in the following ways (Drucker, Fleming & Chan, 2016):

- By following the PRISMA-P guidelines (Moher et al., 2015);
- By registering the research protocol prior to conducting the review on PROSPERO;
- By performing a thorough literature search across various databases;
- By disclosing any competing interests;
- By assessing the risk of bias in the included articles.

In this study the abovementioned guidelines were followed to ensure transparency and to reduce the risk of bias. The Cochrane Collaboration tool for assessing risk of bias by Higgins, Altman and Sterne (2011) (Appendix D) was used to assess the risk of bias in each included study. This is a two-part tool which focused on six types of biases namely: selection,

performance, detection, attrition, reporting and ‘other’ and addresses seven specific domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and ‘other’ sources of bias (Higgins et al., 2011). This tool judged each domain as ‘low risk’, ‘high-risk’ or ‘unclear risk’ of bias. Reporting bias was reduced in this systematic review by reporting on all the relevant results and not only focusing on the positive findings (Chan & Altman, 2005).

Data storage

The data obtained from the study will be stored at the Department of Speech-Language Pathology and Audiology for 15 years, as per the regulations of the University of Pretoria.

Results

A total of 176 records were identified from the three electronic databases searched (Pubmed: 69; Medline [Ovid]: 41 and Scopus: 66) and narrowed down, by using strict inclusion/exclusion criteria, to a total of 17 studies that qualified for the critical appraisal process. A hand search of the reference list of these studies identified an additional four articles which resulted in a total of 21 studies that were included in this review.

Characteristics of the included studies

The 21 studies which met the criteria for the final study analysis consisted of randomized control trials (n = 5), a prospective cohort study (n = 1), retrospective cohort studies (n = 4), case control studies (n = 6) and observational studies without control (n = 5). According to the CRD hierarchy of evidence, the studies included were rated level 1 (n = 5); level 3 (n = 11) and level 4 (n = 5). The publication dates ranged from 1979 (Finitzo-Hieber, McCracken & Brown, 1979) to 2018 (Canet et al., 2018).

Characteristics of study participants

The sample size of the participants in the included studies varied from nine (Hotz, Harris & Probst, 1994) to 353 participants (Sagwa et al., 2015) with a total of 2066 participants and 1566 treated with AGs in the 21 included studies. The mean age of participants ranged from two days (Zorowka et al., 1993) to 36.08 years (Sagwa et al., 2015) with males (n = 890), females (n = 750) and unspecified gender (n = 426). The various conditions that AG/s were administered for were cystic fibrosis (n = 8), bacterial infections (n = 8), cancers (n = 3), MDR-TB (n = 1) and renal failure (n = 1). Gentamicin was the AG mostly used in the studies (n = 6), tobramycin (n = 5), amikacin (n = 2), netilmicin (n = 1), no specification given (n = 1) and a combination of AG/s (n = 6). A detailed description of the study characteristics of the 21 included studies is summarised in Table 4.

Table 4

Characteristics of studies included in the systematic review (n = 21)

Author (Year)	Participants (CG / SG)	Mean age (years)	Diagnosis	Type of AG
Finitzo-Hieber et al. (1979)	113 / 234	2.4 days	Systemic bacterial diseases	Gentamicin OR Kanamycin
Finitzo-Hieber et al. (1985)	51 / 99	27 – 41 weeks	Systemic bacterial diseases	Amikacin OR Netilmicin
Warady et al. (1993)	7 / 9	8.9 (± 4.0) years	Renal failure	Tobramycin
Zorowka et al. (1993)	45 / 59	2 days	Bacterial infections	Netilmicin
Hotz et al. (1994)	9 / 9	29.5 years	Malignant hematologic diseases	Amikacin
Wood et al. (1996)	29	27.7 (±8.9) years	Pulmonary infections	Tobramycin
Stavroulaki et al. (1999)	24 / 24	Median 6.7 years	Infections	Gentamicin
Katbamna et al. (1999)	10 / 8 5 / 10	7-14 years 15-23 years	CF	Tobramycin
Mulheran et al. (2001)	91 / 70	Young: median 14 years Adults: median 25 years	CF	Gentamicin
Stavroulaki et al. (2002)	19 / 12	8.3 years	CF	Gentamicin
Mulheran et al. (2006)	168	5-16 & 16+ years	CF	Tobramycin
Riga et al. (2007)	47	7.2 years	ALL	Gentamicin
Naeimi et al. (2009)	50 / 50	36 weeks	New-born infections	Gentamicin OR Amikacin
Scheenstra et al. (2010)	19	28.5 years	CF	Tobramycin
Al-Malky et al. (2011)	6 / 39	10.9 (±3.3) years	CF	Amikacin OR Tobramycin
Chen et al. (2013)	23	7 years	Cancer	Amikacin
Al-Malky et al. (2015)	7 / 63	10.7 (±3.5) years	CF	Amikacin, tobramycin & gentamicin
El-Barbary et al. (2015)	110 / 110	Neonates	Sepsis	Gentamicin
Geyer et al. (2015)	36 / 39	12.6 (±3.65) years	CF	Didn't specify
Sagwa et al. (2015)	353	36.08 (±10.56) years	MDR-TB	Amikacin OR kanamycin
Canet et al. (2018)	92	Young infants	Sepsis, septic shock, UTI	Gentamicin

ALL: acute lymphoblastic leukemia; CF: cystic fibrosis; CG: control group; MDR-TB: Multi-drug resistant tuberculosis; SG: study group; UTI: urinary tract infection

Timing of baseline and monitoring evaluations

In seven studies the hearing evaluations were performed once-off after at least one dose of AG treatment, at least five months after the last AG dose, one to three years after AG treatment, as well as up to five years after AG treatment (Katbamna et al., 1999; Mulheran et al., 2001; Riga et al., 2007; Al-Malky et al., 2011, 2015; Chen et al., 2013; Geyer et al., 2015). Thirteen of the 21 studies (62%) (Finitzo-Hieber, McCracken & Brown, 1985; Warady et al., 1993; Zorowka et al., 1993; Hotz et al., 1994; Wood et al., 1996; Stavroulaki et al., 1999, 2002; Mulheran et al., 2006; Naeimi et al., 2009; Scheenstra et al., 2010; Sagwa et al., 2015; El-Barbary, Ismail & Ibrahim, 2015; Canet et al., 2018) performed a baseline evaluation, either immediately after birth, before the start of treatment, within 24 hours of the onset of treatment, within 48 hours after initiation of treatment and/or within the first four days of life.

In the 14 studies in which monitoring or follow-up evaluations were performed as part of the procedures, the procedures were performed at six weeks, six months, 12 and 18 months post-treatment (Finitzo-Hieber et al., 1985), within 48 hours of completing therapy, four to six weeks and one-year post-therapy (Warady et al., 1993), within 24 hours of the last AG dose (Zorowka et al., 1993; Stavroulaki et al., 1999, 2002; Naeimi et al., 2009), before discharge or at the end of treatment (Wood et al., 1996; Mulheran et al., 2006; Scheenstra et al., 2010; El-Barbary et al., 2015; Canet et al., 2018), during the six to eight months intensive treatment phase and again during the 12 to18 month continuation phase (Sagwa et al., 2015). One study performed the follow-up evaluations on the last day of treatment if the treatment was administered for less than ten days, or a follow-up evaluation was done at three-day intervals after the tenth day of therapy and until three to six days after the end of therapy (Hotz et al., 1994) with another study (Finitzo-Hieber et al., 1979) monitoring the same group of participants annually for four years.

Criteria used to grade a cochleotoxic threshold shift

Six studies (Warady et al., 1993; Wood et al., 1996; Mulheran et al., 2001, 2006; Stavroulaki et al., 2002; Al-Malky et al., 2011) used the ASHA 1994 criteria for grading an ototoxic shift. In four studies (Finitzo-Hieber et al., 1979; Hotz et al., 1994; Stavroulaki et al., 1999; Scheenstra et al., 2010) it was not mentioned which criterion were used for grading a cochleotoxic hearing loss. In five studies (Finitzo-Hieber et al., 1985; Zorowka et al., 1993;

Riga et al., 2007; Naeimi et al., 2009; Canet et al., 2018) the measures performed namely ABR, TEOAE/s and DPOAE/s did not allow for a specific grading criterion to be used. One study (El-Barbary et al., 2015) used the Rhode Island criterion for TEOAE/s to indicate a change in auditory functioning due to cochleotoxic exposure. Two studies (Sagwa et al. 2015; Chen et al. 2013) mentioned the ASHA hearing loss classification, but not the ototoxicity grading criteria. One study (Katbamna et al., 1999) used the EHF age-appropriate thresholds as described by Osterhammel and Osterhammel (1979). One study (Geyer et al., 2015) used the classification system of the International Bureau for Audiophonology (BIAP). Only one study (Al-Malky et al., 2015) used an ototoxicity grading scale i.e. the Brock Paediatric ototoxicity grading scale (Brock et al., 1991), in which they observed that 73% of the children that they tested in their study, received a low grade of 0 or 1, indicating that the pure-tone thresholds of the participants were lower than 40 dB at all frequencies or that the thresholds were 40 dB or higher at 8 kHz, respectively.

Identification and monitoring test battery

Eleven studies (Finitzo-Hieber et al., 1985; Zorowka et al., 1993; Hotz et al., 1994; Stavroulaki et al., 1999, 2002; Mulheran et al., 2001, 2006; Riga et al., 2007; Naeimi et al., 2009; Al-Malky et al., 2011, 2015) mentioned that they first determined if the study participants were eligible to participate in the study. They made use of the following procedures to determine eligibility: a case history or review of the medical files of the participants (n=8); an otoscopic examination (n=3); tympanometry (n=2); acoustic reflexes (n=1); PTA (n=1); diagnostic TEOAE-testing (n=1); TEOAE screening (n=1) and/or a risk catalogue from the American Academy of Paediatrics (n=1).

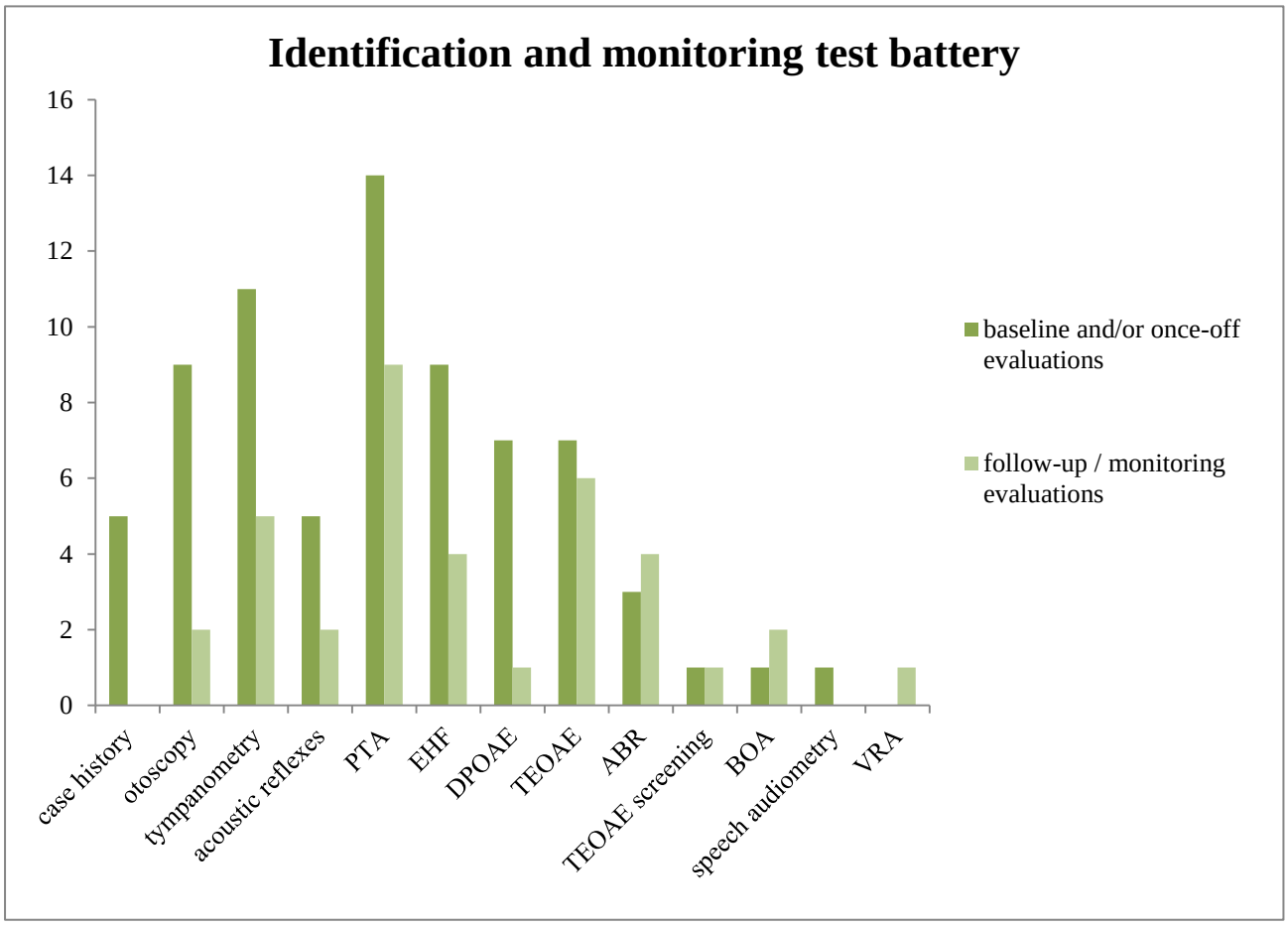
Procedures used for baseline assessment and/or hearing evaluation of once-off measurements

During the baseline assessment and/or hearing evaluation of studies performing a once-off measurement, conventional PTA was the preferred test for detecting cochleotoxicity in 14 studies (Warady et al. 1993; Hotz et al. 1994; Wood et al. 1996; Katbamna et al. 1999; Stavroulaki et al. 1999, 2002; Mulheran et al. 2001, 2006; Scheenstra et al. 2010; Al-Malky et al. 2011, 2015; Chen et al. 2013; Sagwa et al. 2015; Geyer et al. 2015) and the only test used in one study (Sagwa et al. 2015). EHF testing was the second most commonly used test

in nine studies (Wood et al. 1996; Katbamna et al. 1999; Stavroulaki et al. 1999; Mulheran et al. 2001, 2006; Scheenstra et al. 2010; Al-Malky et al. 2011, 2015; Geyer et al. 2015). Seven studies (Katbamna et al. 1999; Stavroulaki et al. 2002; Riga et al. 2007; Al-Malky et al. 2011, 2015; Chen et al. 2013; Geyer et al. 2015) used DPOAE-testing to detect cochleotoxicity. Diagnostic TEOAE-testing was used in seven studies (Zorowka et al., 1993; Hotz et al., 1994; Stavroulaki et al., 1999, 2002; Naeimi et al., 2009; Chen et al., 2013; Canet et al., 2018), while TEOAE screening was performed in one study (El-Barbary et al., 2015). Three studies (Finitzo-Hieber et al., 1985; Warady et al., 1993; Stavroulaki et al., 1999) used ABR. An overview of the procedures used for baseline and/or once-off hearing evaluations is depicted in Figure 2.

Figure 2

Test battery of procedures used for baseline and follow-up/monitoring



As shown in appendix E only 9/21 studies (Warady et al., 1993; Katbamna et al., 1999; Stavroulaki et al., 1999, 2002; Mulheran 2001, 2006; Al-Malky et al., 2011; Chen et al., 2013; Geyer et al., 2015) used a comprehensive test battery comprising of a variety of objective and subjective procedures during baseline/follow-up hearing evaluation.

Procedures used for follow-up/monitoring

In the studies which included follow-up evaluations/monitoring, conventional PTA was again the preferred test for cochleotoxicity monitoring in nine studies (Finitzo-Hieber et al., 1979; Warady et al., 1993; Hotz et al., 1994; Wood et al., 1996; Stavroulaki et al., 1999, 2002; Mulheran et al. 2006; Scheenstra et al. 2010; Sagwa et al. 2015), with one study (Sagwa et al. 2015) only using conventional PTA. TEOAE-testing was the second most commonly used test in six studies (Zorowka et al. 1993; Hotz et al. 1994; Stavroulaki et al. 1999, 2002; Naeimi et al. 2009; Canet et al. 2018). Three studies (Zorowka et al. 1993; Naeimi et al. 2009; Canet et al. 2018) only used TEOAE-testing for cochleotoxicity monitoring, while a single study (El-Barbary et al. 2015) used TEOAE screening. In four studies (Wood et al. 1996; Stavroulaki et al. 1999; Mulheran et al. 2006; Scheenstra et al. 2010) EHF-testing was used for monitoring purposes with another four studies (Finitzo-Hieber et al. 1985; Warady et al. 1993; Stavroulaki et al. 1999; El-Barbary et al. 2015) using diagnostic ABR. In one study (Finitzo-Hieber et al. 1985) only ABR was used as a monitoring procedure. A single study (Stavroulaki et al. 2002) used DPOAE-testing for monitoring purposes. Neither DPOAE screening nor speech audiometry was used in any of the studies included in this systematic review, for monitoring cochleotoxicity.

In six studies (Finitzo-Hieber et al. 1979, 1985; Warady et al. 1993; Zorowka et al. 1993; Stavroulaki et al. 1999; Mulheran et al. 2006) a comprehensive audiometric test battery was used comprising of a variety of objective and subjective procedures for follow-up assessments or monitoring purposes, as can be seen in appendix F.

Themes identified in each of the included studies

Three studies were performed to evaluate cochlear functioning after the administration of AG such as gentamicin, kanamycin, amikacin and/or netilmicin, using visual response audiometry (VRA), behavioural observation audiometry (BOA) and conditioned play audiometry (Finitzo-Hieber et al., 1979); ABR and BOA (Finitzo-Hieber et al., 1985) and

PTA, EHF audiometry and DPOAE-testing (Geyer et al., 2015). The study by Finitzo-Hieber et al. (1979) found no significant ($P > 0.05$) changes in hearing levels between the participants treated with gentamicin or kanamycin compared to the untreated controls. In the study by Finitzo-Hieber et al. (1985) a significant difference in wave V latency values was found between the participants of the control group and the participants included in the study group both at baseline and the first post-treatment follow-up ($P < 0.001$), with no significant differences at six weeks, six-, 12 and 18 months ($P > 0.1$). Geyer et al. (2015) found significantly higher PTTs and EHF mean values ($p = 0.016$; $p = 0.005$) respectively in the participants with cystic fibrosis treated with AGs, compared to the control group and significantly lower DPOAE amplitudes at 1 kHz, 1.4 kHz and 6 kHz.

The prevalence of AG induced cochleotoxicity was determined in seven studies by using PTA (Sagwa et al., 2015); PTA and ABR (Warady et al., 1993); PTA and EHF audiometry (Mulheran et al., 2001; Scheenstra et al., 2010); PTA, EHF audiometry and DPOAE-testing (Al-Malky et al., 2011) and TEOAE-testing (Zorowka et al., 1993; Canet et al., 2018). In the study by Sagwa et al. (2015), 206 / 353 (58%) of the participants included in the study developed hearing loss during treatment. Participants treated with amikacin had a greater incidence of hearing loss compared to the participants treated with kanamycin (78% vs 56%). In the study by Al-Malky et al. (2011), 8/39 (21%) of participants had clear signs of ototoxicity, with the thresholds at 8 to12.5 kHz significantly elevated in the high exposure groups ($p = 0.047$) compared to the low exposure groups ($p = 0.046$). In the abovementioned study, no significant difference was found in the mean DPOAE amplitudes between the two participant groups at the f2 frequencies of 0.8 to 1.6 kHz and 8 kHz. However, a significant difference was found in the mean DPOAE amplitudes at the f2 frequencies of 3.2 kHz to 6.3 kHz. In the study by Warady et al. (1993), four out of 14 participants (28%) developed hearing loss, with the study group showing significantly poorer PTA results at 6 kHz and 8 kHz at baseline and the one-year follow-up, compared to the control group ($P < 0.05$). No significant differences in ABR results were found between the two groups at baseline and at follow-up. Twelve of the 70 participants (17%) treated with gentamicin in the study by Mulheran et al. (2001) showed elevated PTT/s and EHF audiometry thresholds, with the range of loss using standard PTA varying from 20 to 85 dB HL. The abovementioned findings are in contrast to the study by Scheenstra et al. (2010) who found no significant difference in mean PTTs at 1 kHz, 2 kHz, 4 kHz and 8 kHz ($p = 0.69$), as well as 10 kHz and 12.5 kHz ($p = 0.42$) between the baseline and follow-up assessments. Interestingly, in the

study of Zorowka et al. (1993), 71/76 (93%) of the participants treated with the AG netilmicin, had equal or an increased amplitude and TEOAE-reproducibility responses at the time of the second follow-up assessment, with the authors suggesting that AG/s, administered in low doses to low-risk infants, are unlikely to cause ototoxicity (Zorowka et al., 1993). These findings are in agreement with the results of the study by Canet et al. (2018), in which 86/92 (93.5%) of the participants presented with normal TEOAE results after gentamicin treatment.

Two studies evaluated the effect of AG/s on OAE/s through TEOAE test results (Hotz et al., 1994) and DPOAE test results (Katbamna et al., 1999). In the study by Hotz et al. (1994) no significant changes in amplitudes were observed to click (P = .6) and tone burst stimuli (P = .3) in the participants treated with amikacin for nine to 12 days, compared to the participants treated for 17 to 33 days who showed a significant decrease in the amplitudes of click (P = .05) and tone burst (P = .006) responses. The group of participants who were treated for 17 to 33 days were again evaluated three to six days after the end of their treatment and in contrast to what is expected, an increase in the click-evoked TEOAE was observed in seven ears, a decrease observed in two ears and no change in one ear. Similarly, a partial recovery was observed in the tone-burst-evoked TEOAE in six ears and a further decrease in response levels in three ears. The increase in the TEOAE response level was only significant for the click-evoked TEOAE (P = .015). The authors of the abovementioned study (Hotz et al., 1994) suggest that during treatment with amikacin for a period of longer than 13 days, a decrease of TEOAE amplitude and reproducibility was observed to be a common occurrence. However, the authors also observed a significant recovery of click-evoked TEOAE/s after longer-term treatment, which was not found when tone-burst-evoked TEOAE/s were used (Hotz et al., 1994). The study by Katbamna et al. (1999) was performed to determine the sensitivity of DPOAE amplitudes, latencies (time interval of the wave measured in ms) and input/output (I/O) growth functions in participants with CF, treated with tobramycin, compared to the healthy participants. Although this is a different way of reporting and comparing DPOAE results, this study may have been one of the first and only studies done on participants with CF, treated with the AG tobramycin, which indicated changes in the DPOAE latencies without any changes to the cochlear function, as measured by DP-grams. The DP-grams of all the participants with CF, treated with AGs, were identical to the healthy controls, however, significant changes were found in the DPOAE latencies and I/O growth functions. DPOAE latency prolongations were found in the seven to 14-year age

group treated with low to moderate (<1250 mg/kg) cumulative doses of AG/s compared to the healthy group showing the shortest latencies at most frequencies. Prolonged DPOAE latencies were also found in the 15 to 23-year age group treated with low (<285 mg/kg) cumulative doses of AGs compared to the control group. In contrast, the group treated with moderate (1000 – 2000 mg/kg) cumulative doses of AG/s showed significant reductions in latencies compared to the low doses and healthy controls, in the 2 to 6 kHz region. Lastly, significant elevations were found in the I/O detection thresholds at the high frequencies, in all the participants with CF treated with AG/s, regardless of drug dosages, compared to the control groups. The authors (Katbamna et al., 1999) suggest that DPOAE latency prolongations could occur in the absence of threshold elevations or reductions in DPOAE amplitudes, in the CF group treated with tobramycin and could reflect the early effects of the build-up of AG/s. According to Katbamna et al. (1999), AG-induced cochleotoxicity may be more effectively monitored through assessing the DPOAE latencies and I/O detection thresholds, as DPOAE amplitudes might not reflect the earliest changes due to chronic AG treatment.

The potential of using OAE/s for the early identification of AG induced cochleotoxicity was evaluated in three studies with two studies (Stavroulaki et al., 1999; Naeimi et al., 2009) using TEOAE-testing and one study (Stavroulaki et al., 2002) using both DPOAE-testing and TEOAE-testing and comparing the results to the PTA test results. In both of these studies (Stavroulaki et al., 1999; Naeimi et al., 2009) the authors found that TEOAE/s were sensitive enough and able to measure the slightest changes due to early AG-induced cochleotoxicity. In the study by Stavroulaki et al. (2002) OAEs, especially DPOAE/s were more sensitive in detecting the slightest changes in auditory function after treatment with gentamicin, compared to PTA, as the PTA thresholds were within normal limits and remained unchanged throughout the exposure to gentamicin. With regards to DPOAE-testing compared to TEOAE-testing, Stavroulaki et al. (2002) found that DPOAE-testing was able to detect minor cochlear changes as they are more frequency sensitive.

Two studies were performed to determine the best audiological procedure/s for accurate AG induced cochleotoxicity monitoring by using PTA, EHF audiometry and DPOAE-testing (Al-Malky et al., 2015) and PTA, ABR and TEOAE-testing (Stavroulaki et al., 1999). In the study by Stavroulaki et al. (1999), no significant differences were found in the hearing levels between the two groups of participants with ABR and/or PTA. However, a significant difference was found in the group treated for longer periods with regard to the

mean response levels (P = 0.017) and a significant decrease in reproducibility of the 1 kHz spectral bands of the TEOAE/s in the participant group treated for a longer period (p <0.05). In this study (Al Malky et al., 2015) EHF audiometry detected two more participants who presented with early signs of cochleotoxicity compared to conventional PTA. There was a clear correlation between DPOAE/s at the 4 to 8 kHz range and EHF results at the 8 to 20 kHz range, suggesting that decreased hearing sensitivity in the EHF region could cause reduced DPOAE/s at the 4 to 8 kHz frequency range (Fabijańska et al., 2012).

A study by Chen et al. (2013) used PTA, DPOAE-testing, TEOAE-testing and speech audiometry to identify a group of child participants with cancer, treated with AG/s, who might have been at risk of developing AG induced hearing loss. Three of the 23 participants (13%) developed a significant (p < 0.01) hearing loss. In a study performed by Riga et al., 2007, the aim was to determine if a specific treatment protocol consisting of the Berlin-Frankfurt-Munster-95 (BFM-95) chemotherapeutic protocol combined with gentamicin had any long-term side effects on the medial olivocochlear bundle (MOCB). In this abovementioned study, there was a dysfunction of the olivocochlear reflex to some extent during the first two years after therapy, with a slow recovery seen in DPOAE/s three years after therapy.

Three studies evaluated the efficacy and toxic potential of different dosing regimens with two studies using PTA and EHF audiometry (Wood et al., 1996; Mulheran et al., 2006) and one study (El-Barbary et al., 2015) using TEOAE screening. Seven out of 18 (39%) participants in this study (Wood et al., 1996) receiving tobramycin at an eight-hourly dose displayed signs of cochleotoxicity compared to no cases of cochleotoxicity in the group receiving 12-hourly tobramycin dosing. In the study by Mulheran et al. (2006), no differences were found in the PTA and/or EHF audiometry thresholds in participants treated with a once versus three times daily tobramycin dosage at baseline, after 14 days and/or six to eight weeks after treatment. Although not statistically significant, participants treated with gentamicin for more than five days in the study of El-Barbary et al., 2015 showed higher percentages of TEOAE screening failures compared to the participants treated for less than five days. However, the authors suggest that factors other than gentamicin use in the neonatal intensive care unit could contribute to hearing loss (El-Barbary et al., 2015).

In summary, conventional PTA was the preferred test for detecting cochleotoxicity in the majority of the included studies, for both baseline and monitoring purposes. In the studies

which performed once-off evaluations, EHF audiometry was the second most preferred test compared to diagnostic TEOAE-testing in the studies with performed monitoring evaluations. The ASHA 1994 criteria for grading an ototoxic shift was the most used criteria in the included studies, although still underutilised. There was a wide variety in the reported prevalence of AG-induced cochleotoxicity, as was evident in the results reported above, which might be due to a variety of factors including the test procedures used (PTA / EHF / DPOAE / TEOAE), the dosing regimen and/or the type of AG used. EHF audiometry seemed to be more effective in identifying early signs of cochleotoxicity compared to conventional PTA as it was able to detect hearing loss early in the EHF/s before it reached the conventional frequencies.

Discussion and conclusion

This study aimed to examine the current available peer-reviewed evidence in order to gain insight into the most effective practices and/or procedures used for the early identification and monitoring of aminoglycoside-induced cochleotoxicity and to suggest a protocol based on these findings. The results reported in the previous section will be discussed in this chapter with regard to the objectives of the current study.

The ototoxic side effects of drugs - hearing loss and/or changes in the vestibular system- were already indicated in 1944, after a significant number of patients treated with streptomycin for TB developed cochlear and vestibular problems (Maru & Al-Malky, 2018). The global impact of ototoxicity in humans is unknown and its exact incidence varies across literature due to various reasons, such as different dosing regimens; the use of different types of drugs which might have had the potential to cause ototoxicity; individual patient characteristics including age, gender and diagnoses; a lack of referrals; diverse criteria to define ototoxicity, as well as diverse audiological protocols for evaluations (Schmuziger, Probst & Smurzynski, 2005; Ganesan et al., 2018). It was estimated that the incidence of ototoxicity ranges between 21% and 83% in humans treated with AG/s (Al-Malky et al., 2011, 2015; Handelsman et al., 2017; Zettner & Gleser, 2018), while cisplatin ototoxicity occurs in as many as 50% to 80% of adults (Frisina et al., 2016; Skalleberg et al., 2017) and 60% to 90% of children (Bass et al., 2014; van As, van den Berg & van Dalen, 2016). It is estimated that the incidence of ototoxicity caused by loop diuretics, such as furosemide, is 6% to 7% (Rybak, 1993). Given the high number of cases mentioned above, it is evident that AGs and platinum-based chemotherapeutic drugs such as cisplatin seem to be the drugs with the greatest potential to cause inner ear damage and hearing loss (Laurell, 2019). This emphasizes the importance of the role that audiologists, performing cochleotoxicity monitoring, have in providing the best possible patient care from a holistic health perspective.

Cochleotoxicity monitoring entails so much more than just a routine session performed to establish hearing thresholds, but is rather a long-term engagement with various goals such as identifying changes in hearing thresholds as early as possible; communication with the patient, family members and treating physician(s); prevention of residual hearing loss; planning of rehabilitation services, as well as monitoring of drug safety and efficacy (King & Brewer, 2018). Effective cochleotoxicity monitoring is only possible with an interdisciplinary

team of healthcare practitioners such as the audiologist, physician, pharmacist, nurse, psychologist, patient and family members working towards a common goal in the best interests of the patient.

According to the review of the literature done in this study, it is recommended that cochleotoxicity monitoring be performed before (baseline), during and after the treatment with AG/s to identify cochleotoxicity as early as possible and to prevent further deterioration of the auditory system (Wood et al., 1996; Naeimi et al., 2009; Scheenstra et al., 2010). The importance of regular, accurate and appropriate cochleotoxicity monitoring was emphasised in the studies included in this review (Hotz et al., 1994; Stavroulaki et al., 1999, 2002; Al-Malky et al., 2011, 2015; Sagwa et al., 2015) to identify AG-induced cochleotoxicity at an early stage and prevent permanent damage to the auditory system. Although the focus of the study by Bertolini et al. (2004) was on ototoxicity monitoring of children treated with platinum compounds and not AGs, worsening or progression of hearing loss was still found in patients two years after the completion of treatment. In the current systematic review, some studies reported either an improvement or a regression in hearing levels as observed during post-treatment evaluations at one year (Warady et al., 1993), three years (Riga et al., 2007) and six to 18 months (Sagwa et al., 2015) post-treatment, with the last mentioned study reporting on a participant who presented with normal hearing bilaterally 126 days after the initiation of treatment which regressed to a bilateral severe SNHL 250 days after treatment and finally a bilateral profound SNHL 606 days after treatment (Sagwa et al., 2015). In contrast to the findings in the abovementioned studies, the studies of Finitzo-Hieber et al., 1979, 1985; and Mulheran et al., 2006, found no significant changes at six, 12 and 18 months, as well as one, two, three and four years post-treatment, respectively. A possible reason for the difference in findings of the abovementioned studies could be attributed to the fact that different test procedures were used (e.g. ABR / DPOAE/s / TEOAE/s / EHF/s) which evaluated different frequencies and areas and, as the literature suggests, the risk and severity of AG-induced cochleotoxicity are influenced by various factors such as age, gender, noise exposure, previous and concomitant exposure to AG/s and/or ototoxic medication, renal failure, as well as the type, dosage and duration of AG treatment (Schmuziger et al., 2005; Ganesan et al., 2018) since certain AG/s tend to be more cochleotoxic or vestibulotoxic in nature (Al-Malky et al., 2011; Jiang et al., 2017). All of the above-mentioned studies reiterate the importance of post-treatment evaluations to identify and document the delayed onset of hearing loss and/or any hearing recovery Konrad-Martin et al. (2005).

It is well known that the first damage caused by AG/s is to the OHC/s at the basal turn of the cochlea, affecting the high frequencies first, followed by damage to the IHC/s at the apical region causing a low frequency hearing loss (Rizzi & Hirose, 2007; Bisht & Bist, 2011). With the OHC/s being most susceptible to ototoxic damage which could result in a high frequency SNHL, the importance of using audiometric procedures such as EHF audiometry and OAE-testing, which can evaluate the damage to these hair cells, is of great importance.

For the detection of AG-induced cochleotoxicity, the majority of the studies included in this systematic review used conventional PTA (for both baseline and monitoring purposes), thereby determining the thresholds of the frequencies between 125 Hz to 8 kHz. Depending on the criteria used, a cochleotoxic hearing loss is indicated by *a 20 dB decrease at any one test frequency; a 10 dB decrease at any two adjacent test frequencies; or no response at three consecutive frequencies where a response was previously reported* (ASHA, 1994:6). Although research has indicated that conventional PTA is not the most effective measure for detecting cochleotoxicity (AAA, 2009), a possible reason for conventional PTA being the most preferred method could be because of the majority of the included studies aimed to determine the prevalence of AG-induced cochleotoxicity. Basic audiological equipment, readily available at most audiological practices can be used for this and the fact that the conventional PTA is seen as the "gold standard" and used to diagnose a cochleotoxic threshold shift in the majority of the classification systems (Ganesan et al., 2018), as previously described may furthermore be the reason why standard PTA is used in the majority of studies.

Extended high frequency audiometry was the second most preferred method to detect cochleotoxicity in studies that performed once-off evaluations. EHF audiometry is one of the most important procedures to be included in a cochleotoxicity monitoring protocol as it can detect hearing loss early in the EHF/s before it reaches the conventional frequencies (Jacob et al., 2006; Knight et al., 2007; Klagenberg et al., 2011; Chauhan, Saxena & Varshey, 2011; Abujamra et al., 2013), although it is still underutilised due to the lack of normality criteria (Klagenberg et al., 2011), as well as its absence in patients with hearing thresholds of more than 60 dB HL and/or in patients with NIHL (AAA, 2009). In a study by Al-Malky et al. (2015) two additional test participants were identified to present with cochleotoxicity when using EHF audiometry compared to conventional PTT/s. This was also the case in a study by Geyer et al. (2015) where EHF audiometry identified a high prevalence of hearing loss which

was not detected by conventional PTA. A study by Blankenship et al. (2020) showed similar findings, where 47% of the participants had hearing loss in the EHF region compared to 38% in the region of the conventional frequencies, emphasising the importance of including EHF audiometry in a cochleotoxicity monitoring protocol (Weigert et al., 2013).

Otoacoustic emissions testing has gained popularity for cochleotoxicity monitoring purposes due to the sensitivity and specificity of the method (Lonsbury-Martin & Martin, 2001); the fact that the procedure is non-invasive and objective requiring no active participation of the patients (Beattie, Kenworthy & Luna, 2003; Mulheran et al., 2006), as well as their ability to detect the earliest changes in OHC-functioning (Zorowka et al., 1993; Hotz et al., 1994; Stavroulaki et al., 1999; Konrad-Martin et al., 2016). TEOAE-testing was the second most preferred method used in the studies which performed monitoring evaluations with only one study using DPOAE-testing, even though research suggests that DPOAE/s are particularly more effective for the early identification of ototoxicity as they are more frequency sensitive (Stavroulaki et al., 2002) and can be measured at higher frequencies and over a broader frequency range. This enables DPOAEs to detect "warning signs" of ototoxicity earlier than TEOAE/s (Lonsbury-Martin & Martin, 2001; Konrad-Martin et al., 2016). It is important to note however that OAE results may be affected by various internal and external factors. The internal factors include hearing loss and middle ear pathologies such as impacted cerumen, otitis media, otosclerosis and negative middle ear pressure (Hall, 2000:165), emphasising the importance of including an otoscopic examination and tympanometry testing as part of the monitoring protocol (AAA, 2009). The external factors which may affect the OAE results are the probe fitting and the most common factor being noise, which could either be equipment-related, ambient (environmental) and/or physiological (from the patient) (Hall, 2000:196).

The latest research suggests including SIN tests such as the Bamford-Kowal-Bench Speech-in-noise (BKB-SIN) and Digits-in-noise (DIN) test in the test battery for the early detection of high frequency hearing loss typically associated with AG-induced cochleotoxicity. In a study by Blankenship et al. (2020) in which the researchers used the BKB-SIN test, an abnormal SNR-Loss was identified in 64% of the study group with CF treated with AGs compared to 4% of the control group. The BKB-SIN test is an age- and language-appropriate measure to evaluate speech-in-noise and is therefore recommended for AG-induced cochleotoxicity monitoring (Blankenship et al., 2020), although more research is still required regarding the clinical value of the test. According to Yeend, Beach and Sharma

(2019) there is a significant correlation between poorer EHF audiometry thresholds and poorer SIN understanding. Zadeh et al. (2019:23753) found that a hearing loss in the high frequencies could be detected by utilising the DIN test *"by low-pass filtering the broadband masking noise."*

The ASHA (1994) criteria were recommended and preferred to indicate a cochleotoxic threshold shift in six studies included in this review (Warady et al., 1993; Wood et al., 1996; Mulheran et al., 2001, 2006; Stavroulaki et al., 2002; Al-Malky et al., 2011). The fact that four of the studies did not mention which criteria they used and/or did not use any criteria to determine a cochleotoxic threshold shift and another two studies mentioning the ASHA (1994) hearing loss classification and not the criteria for identifying a cochleotoxic threshold shift, is a reason for concern, as there is a variety of standardised criteria to grade a cochleotoxic shift easily available for use. Another area of concern, is that in five of the included studies a cochleotoxic threshold shift could not be indicated as there are currently no accepted criteria available to define a cochleotoxic threshold shift when using objective measures such as DPOAE/s, TEOAE/s and/or ABR/s (Beattie et al., 2003; Leigh-Paffenroth et al., 2005; Konrad-Martin et al. 2005; Mulheran et al., 2006). The lack of a description of norms to indicate the development of a cochleotoxic hearing loss is yet another area in need for research. It should be noted that a grading scale for adverse events (hearing loss), such as the Brock Paediatric ototoxicity grading scale, was only used in one study performed on children included in this review (Al-Malky et al., 2015). This reiterates the importance to create awareness regarding the use of grading scales and its implementation.

Strengths and limitations of the study

A variety of strengths and limitations were present in this systematic review. Firstly, the strengths include the adherence to the PRISMA-P statement and guidelines for conducting a systematic review. Secondly, the present study included literature subjected to several specific inclusion and exclusion criteria to include the most relevant studies and exclude studies with participants presenting with alternative causes and/or risks of hearing loss, to focus on the most effective procedures used to identify AG-induced hearing loss. The limitations to this systematic review include the fact that only studies published in English were used, which poses the possibility of missing valuable information due to a language

difference and possibly causing bias. Additionally, several studies' abstracts and/or full-texts were not available, again possibly resulting in missing valuable information.

Clinical implications

This systematic review may assist audiologists and clinicians involved in cochleotoxicity monitoring programmes to make informed decisions regarding the most effective procedures to be used. Earlier identification of a cochleotoxic hearing loss, followed by appropriate intervention may reduce the negative effects that a hearing loss may have on an individual's life (ASHA, 2006). Thus, using effective and efficient procedures to identify participants at risk of developing a cochleotoxic hearing loss may ensure appropriate prevention and intervention if needed.

Recommendations for future research

The findings of this systematic review emphasise the need for uniformity in the protocol used to identify and monitor AG-induced cochleotoxicity, with reference to the test-battery of procedures used and the criteria used to grade a cochleotoxic threshold shift. In addition, research is required to develop specifications for grading cochleotoxicity when including objective measures such as OAE/s (DPOAE and TEOAE) and ABR in the monitoring of cochleotoxic hearing loss. Finally, more research is needed to determine the use of SIN measures such as the DIN test, to be included in the AG-induced cochleotoxicity monitoring protocol.

Conclusion

The cochleotoxic potential of various drugs is well known and cochleotoxicity should be viewed as an urgent health concern with the potential of having far-reaching effects if an effective monitoring protocol is not implemented. There is a considerable need for educational programmes aimed towards physicians, nurses, pharmacists, patients and their family members/caregivers, as well as other medical professionals about the potential cochleotoxic effects of drugs, as well as the monitoring of the effects thereof in the individual. Audiologists should also be encouraged and made aware of the important role that they have in improving the quality of life of patients treated with cochleotoxic drugs.

In conclusion, the results of the studies presented in this review encourage the use of a standard protocol that consists of monitoring before, during and after the treatment with AG/s. Furthermore, it is recommended that a standard diagnostic grading system be used to define the diagnosis of a cochleotoxic threshold shift. Lastly, for the identification and monitoring of AG-induced cochleotoxicity, a combination of subjective and objective measures to establish hearing thresholds should be used, with special consideration of the OHCs by means of EHF audiometry and DPOAE-testing and possibly speech-in-noise tests such as the DIN and/or SPIN tests.

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Zorowka, P., Schmitt, H. J., Eckel, H. E., Lippert, K. L., Schonberger, W., & Merz, E. (1993). Serial measurements of transient evoked otoacoustic emissions (TEOAEs) in healthy newborns and in newborns with perinatal infection. *International Journal of Pediatric Otorhinolaryngology, 27*(3), 245–254. https://doi.org/10.1016/0165-5876(93)90230-z

Appendix A: Adapted PRISMA-P checklist used in this systematic review

Section / topic	#	Checklist item	Reported in the dissertation
ADMINISTRATIVE INFORMATION			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	Cover page
Update	1a	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	Chapter 2: Methodology. 2.2 Study design
Authors			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Refer to article
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Refer to article
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor / funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Chapter 1: Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Chapter 1: Introduction
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	Chapter 2: Methodology 2.3.2 Inclusion & exclusion criteria
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Chapter 2: Methodology 2.3.1 Search strategy

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Chapter 2: Methodology 2.3.1 Search strategy
STUDY RECORDS			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Chapter 2: Methodology 2.3.4 Data management and data items
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Chapter 2: Methodology 2.3.3 Study selection
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Chapter 2: Methodology 2.3.4 Data management and data items
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Chapter 2: Methodology 2.3.4 Data management and data items
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Chapter 2: Methodology 2.3.4 Data management and data items
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Chapter 2: Methodology 2.3.5 Study quality appraisal
DATA			
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Chapter 2: Methodology 2.3.6 Data analysis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Chapter 2: Methodology 2.3.6 Data analysis
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Chapter 2: Methodology 2.4.4 Risk of bias
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Chapter 2: Methodology 2.3.5 Study quality appraisal

Appendix B: Revised Critical Review form for quantitative studies

The revised critical review form for quantitative studies (Law et al., 1998).

<table>
<tr><td>STUDY PURPOSE:
Was the purpose stated clearly?
___Yes
___No</td><td>Outline the purpose of the study (i.e., study objective or aim):</td></tr>
<tr><td>LITERATURE:
Was relevant background literature reviewed?
___Yes
___ No</td><td>Describe the justification of the need for this study (3-4 key points)
⇒</td></tr>
<tr><td rowspan="3">DESIGN:
____randomized
____cohort (population -based)
____ before and after
____ case-control
____cross-sectional
(1+ group at 1 point in time)
____single case design
____case study</td><td>Describe the study design:</td></tr>
<tr><td>Can the author answer the study question with the study design?</td></tr>
<tr><td>Were the design and/or method used introducing biases. If so describe:</td></tr>
<tr><td rowspan="4">SAMPLE SIZE:
N =
Was sample size justified?
___Yes
___No
___N/A

Was Power Discussed?
___Yes
___No
___N/A</td><td>Sample Description (e.g., age, gender, diagnosis, other characteristics)</td></tr>
<tr><td>How was sample identified? Was it a representative sample?</td></tr>
<tr><td>If there were more than one group, was there similarity and differences between the groups? Describe:</td></tr>
<tr><td>Was informed consent and assent obtained?</td></tr>
<tr><td colspan="2">OUTCOMES:
Specify the frequency of outcome measurement (i.e., pre, post, follow-up):

<table>
<tr><td>Outcome areas
(e.g., self care, productivity)

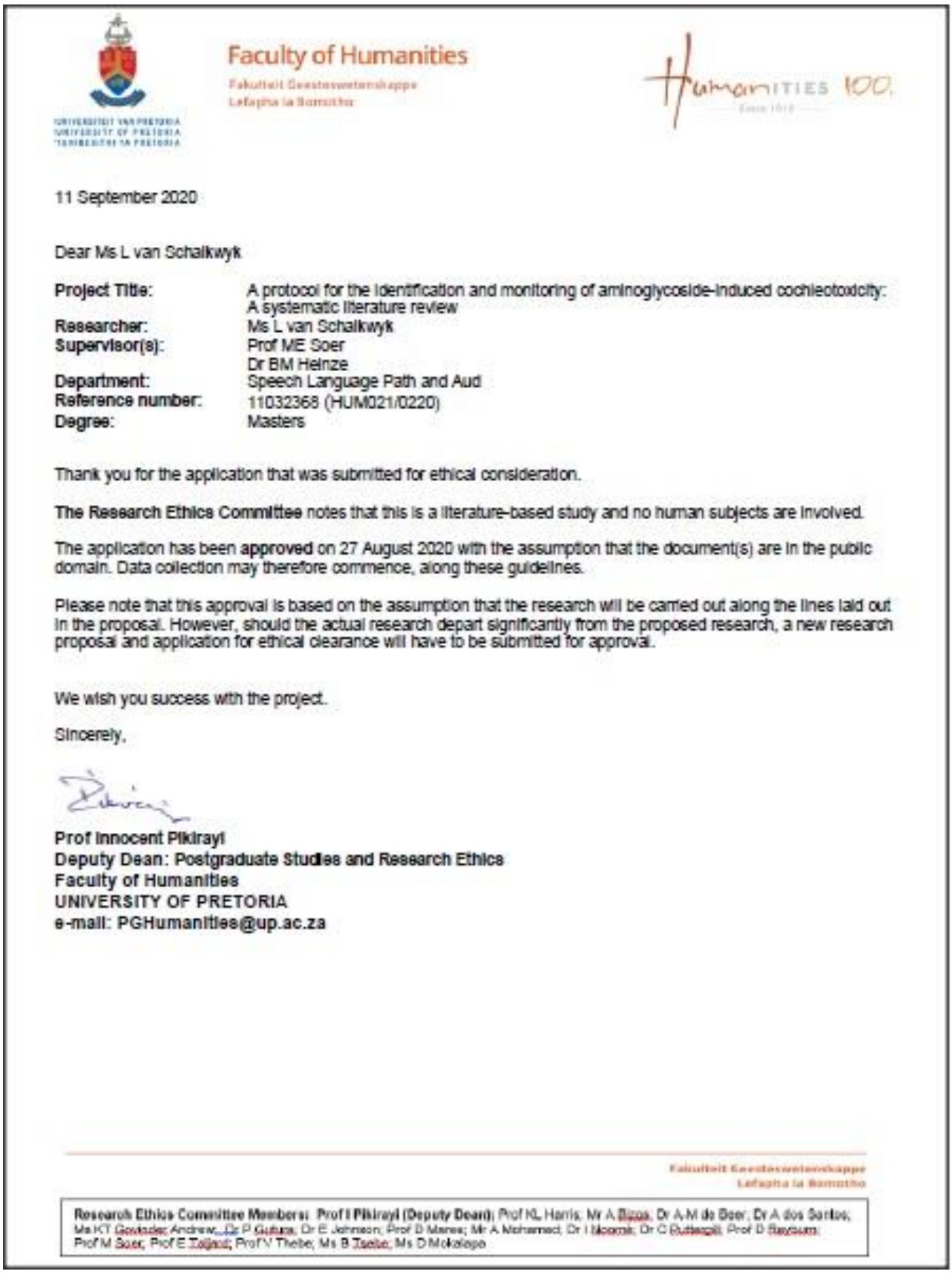
⇒</td><td>List measures used
(e.g., Sensory Profile, VMI)

⇒</td><td>Reliable and Valid?

⇒</td></tr>
</table>
</td></tr>
<tr><td>INTERVENTION:
Intervention was described in</td><td>Provide a short description of the intervention including type of intervention, who delivered it, how often and in what setting.</td></tr>
</table>

detail? ____Yes ____No ____Not addressed Contamination was avoided? ____Yes ____No ____Not addressed	
RESULTS: Results were reported in terms of statistical significance? ____Yes ____No ____NA ____Not addressed	What were the results? Outcomes ⇒ Results ⇒ Statistical Significance ⇒
Was the analysis, that is the type of statistically tests used, appropriate for the type of outcome measures and the methodology? ____Yes ____No ____Not addressed	Explain: If not statistically significant (i.e., $p < 0.05$ or 0.01), was study big enough to show an important difference if it should occur (power and sample size)?
Clinical importance was reported? ____Yes ____No ____Not addressed	What is the clinical importance of the results (that is even if the results were statistically significant were the differences large enough to be clinically meaningful?
Drop-outs were reported? ____Yes ____No	If yes, why did they drop out? How were drop-out participants included in the statistical analysis?
CONCLUSIONS AND CLINICAL IMPLECATIONS: The conclusions made by the authors were appropriate given study methods and results. ____Yes ____No	What did the author concluded? What were the main limitations of the study as stated by the author(s) and from your point of view? What are the implications of these results for your practice?

Appendix C: Ethical clearance certificate



Faculty of Humanities
Fakulteit Geesteswetenskappe
Lefapha la Bomotho

Humanities 100

11 September 2020

Dear Ms L van Schalkwyk

Project Title:	A protocol for the identification and monitoring of aminoglycoside-induced cochleotoxicity: A systematic literature review
Researcher:	Ms L van Schalkwyk
Supervisor(s):	Prof ME Soer Dr BM Heinze
Department:	Speech Language Path and Aud
Reference number:	11032368 (HUM021/0220)
Degree:	Masters

Thank you for the application that was submitted for ethical consideration.

The Research Ethics Committee notes that this is a literature-based study and no human subjects are involved.

The application has been **approved** on 27 August 2020 with the assumption that the document(s) are in the public domain. Data collection may therefore commence, along these guidelines.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. However, should the actual research depart significantly from the proposed research, a new research proposal and application for ethical clearance will have to be submitted for approval.

We wish you success with the project.

Sincerely,

Prof Innocent Pikirayi
Deputy Dean: Postgraduate Studies and Research Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: PGHumanities@up.ac.za

Fakulteit Geesteswetenskappe
Lefapha la Bomotho

Research Ethics Committee Members: **Prof I Pikirayi (Deputy Dean)**; Prof KL Harris; Mr A Biggs; Dr AM de Boer; Dr A dos Santos; Ms KT Govender-Andrew; Dr P Gutura; Dr E Johnson; Prof D Maree; Mr A Mohamed; Dr I Nkomo; Dr C Ruttenglit; Prof D Seyffert; Prof M Soer; Prof E Taljard; Prof V Thebe; Ms B Tsebe; Ms D Mokalapa

Appendix D: The Cochrane Collaboration's tool for assessing risk of bias

An adapted version of The Cochrane Collaboration's tool for assessing risk of bias (Higgins & Green, 2011)

Reviewer's initials: Study ID: Date:

Domain	Description	Risk of bias	Consensus (circle)
Random sequence generation		Was the allocation sequence adequately generated? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Allocation concealment		Was allocation adequately concealed? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Blinding of participants and personnel	Subjective outcomes	Was knowledge of the allocated intervention adequately prevented during the study? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes		
Blinding of outcome assessment	Subjective outcomes	Was knowledge of the allocated intervention adequately prevented during the study? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes		
Incomplete outcome data	Subjective outcomes	Were incomplete outcome data adequately addressed? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes		
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome reporting? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Other sources of bias		Was the study apparently free of other problems that could put it at a high risk of bias? LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
Overall risk of bias	Subjective outcomes	LOW / HIGH / UNCLEAR	LOW HIGH UNCLEAR
	Objective outcomes	LOW / HIGH / UNCLEAR	

Appendix E: Baseline procedures and/or once-off hearing measures

Author (year)	case history	otoscopy	tympanometry	reflexes	**PTA**	**EHF**	**DP-OAE**	**TE-OAE**	**ABR**	**DP-OAE screening**	**TE-OAE screening**	BOA	VRA	speech audiometry	other
Finitzo-Hieber et al. 1979	x											x			
Finitzo-Hieber et al. 1985									**x**						
Warady et al. 1993	x		x		**x**				**x**						
Zorowka et al. 1993		x	x					**x**							
Hotz et al. 1994		x			**x**			**x**							
Wood et al. 1996					**x**	**x**									
Katbamna et al. 1999			x		**x**	**x**	**x**								
Stavroulaki et al. 1999		x	x	x	**x**	**x**		**x**	**x**						
Mulheran et al. 2001		x	x		**x**	**x**									
Stavroulaki et al. 2002		x	x	x	**x**		**x**	**x**							
Mulheran et al. 2006		x	x		**x**	**x**									
Riga et al. 2007		x	x				**x**								
Naeimi et al. 2009								**x**							
Scheenstra et al. 2010					**x**	**x**									
Al-Malky et al. 2011		x	x	x	**x**	**x**	**x**								
Chen et al. 2013	x		x	x	**x**		**x**	**x**						x	
Sagwa et al. 2015					**x**										

Author (year)	case history	otoscopy	tympanometry	reflexes	**PTA**	**EHF**	**DP-OAE**	**TE-OAE**	**ABR**	**DP-OAE screening**	**TE-OAE screening**	BOA	VRA	speech audiometry	other
El-Barbary et al. 2015	x	x									**x**				
Geyer et al. 2015	x		x	x	**x**	**x**	**x**								ENT ax
Al-Malky et al. 2015					**x**	**x**	**x**								
Canet et al. 2018								**x**							
Total	5	9	11	5	**14**	**9**	**7**	**7**	**3**	**0**	**1**	1		1	1

Appendix F: Follow-up assessment and/or monitoring procedures

Author (year)	otoscopy	tympanometry	reflexes	**PTA**	**EHF**	**DP-OAE**	**TE-OAE**	**ABR**	**DPOAE screening**	**TEOAE screening**	BOA	VRA	speech audiometry
Finitzo-Hieber et al. 1979		x	x	x							x	x	
Finitzo-Hieber et al. 1985		x	x					x			x		
Warady et al. 1993		x		x				x					
Zorowka et al. 1993	x	x					x						
Hotz et al. 1994				x			x						
Wood et al. 1996				x	x								
Stavroulaki et al. 1999				x	x		x	x					
Stavroulaki et al. 2002				x		x	x						
Mulheran et al. 2006	x	x		x	x								
Naeimi et al. 2009							x						
Scheenstra et al. 2010				x	x								
Sagwa et al. 2015				x									
El-Barbary et al. 2015								x		x			
Canet et al. 2018							**x**						
Total = 14	2	5	2	**9**	**4**	**1**	**6**	**4**	**0**	**1**	2	1	0

Appendix G Recording parameters of objective measures used in the included studies

Author (Year)	Parameter
	DPOAE studies
Katbamna et al. (1999)	Mimosa Acoustics CUBeDIS system (v5.21); f2/f1 ratio: 1.2; L1= 65 dB SPL, L2= 50 dB SPL); 8 to 1.6 kHz at 3 points/ octave intervals; present if amplitudes are ≥ 6dB above the NF.
Al-Malky et al. (2011)	ILO292 DP-Echoport (Otodynamics); f1/f2 ratio: 1.22; f1= 65 dB SPL, f2= 55 dB SPL; 1/3-octave frequency intervals
Al-Malky et al. (2015)	ILO292 system (Otodynamics); f1/f2 ratio: 1.22; f1= 65 dB SPL, f2= 55 dB SPL; 1/3-octave frequency intervals; DPOAE response valid if SNR > 6dB SPL (SNR cut-off of > 3 dB SPL also measured)
Geyer et al. (2015)	ILO292 system (Otodynamics); f2/f1 ratio: 1.22; f1= 65 dB, f2= 55 dB; frequencies: 1, 1.5, 2, 3, 4 & 6 kHz; present if amplitudes are ≥ 3 dB SPL above the NF
	TEOAE studies
Hotz et al. (1994)	ILO88 & ILO92; non-linear Stimuli: clicks & 4-kHz tone-burst (5 cycles, 2.5 msec) 256 responses Click intensity: 85 dB SPL (± 2.5 dB); tone-burst intensity: 75 dB SPL (± 1.4 dB)
Naeimi et al. (2009)	ERO-SCAN TEOAE test system; click stimulus; frequency range: 0.7 – 4 kHz; intensity: 83 dB SPL (±3dB)
Canet et al. (2018)	Screening done and not diagnostic..

Author (Year)	Parameter
	ABR studies
Warady et al. (1993)	Intensity: 80 dB nHL
	TEOAE & ABR studies
Stavroulaki et al. (1999)	**TEOAE:** ILO88 system (v3.92, Otodynamics); non-linear; stimuli: rectangular clicks; duration: 80s; click rate: 50/s; intensity: 82 dB SPL (± 2 dB); 260 responses; band-pass filter: 0.5–6 kHz; noise rejection level: 45 dB SPL **ABR:** Biologic Traveller express; clicks with a rate of 31.1/s; average of 2048 responses;
	DPOAE & TEOAE studies
Stavroulaki et al. (2002)	**DPOAE:** ILO92 (v1.2, Otodynamics); f2/f1 ratio: 1.22; L1=L2= 70 dB SPL; 3 points / octave; f2 frequency range: 1001 - 6348 Hz; stimulus: 30-70 dB SPL in 5-dB steps **TEOAE:** ILO88 system (v4.2, Otodynamics); 0.8 – 4 kHz in 800-Hz bands

Appendix H Procedures used, timing, criteria and conclusions

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Finitzo-Hieber et al. (1979)	**First year exam:** questionnaire filled by parents re child's hearing gross auditory abilities ax by taped filtered environm sounds (70-90dB SPL) BOA **Second year exam:** tympanometry acoustic reflexes @ 500 – 4000 Hz BOA (behavioural observation audiometry) VRA (visual response audiometry) **Third year:** tympanometry acoustic reflexes (500 – 4000 Hz) PTTs using conditioned play audiometry **Fourth year:** PTA if the child failed the 3rd year exam	1, 2, 3 and 4 years after treatment with AGs	not mentioned	not mentioned		Gentamicin and kanamycin during the new-born period could not be implicated as a cause of SNHL	3

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Finitzo-Hieber et al. (1985)	**Eligibility ax:** case history **Baseline ax:** ABR within 48 hours of starting AG therapy **6 weeks, 6, 12 & 18 months follow-up ax:** ABR immittance measurements Behavioural response protocol	Baseline, 6 weeks, 6, 12 and 18 months post treatment	not mentioned	not mentioned	Significant difference in wave V latency values between the control group and 2 groups given AGs (P<0.001)	The risk of developing significant HL from a 3-7 day course of amikacin or netilmicin is small. ABR is useful to identify infants receiving AG therapy who require follow-up audiological evaluation and management	3
Warady et al. (1993)	**Baseline ax:** reviewed medical records tympanometry conventional PTA click-evoked ABR (ce-ABR) **Follow-up ax:** tympanometry PTA Click-evoked ABR (ce-ABR) **Follow-up ax:** tympanometry PTA Click-evoked ABR (ce-ABR) **1 year follow up ax:** tympanometry PTA ce-ABR	Baseline ax within 48 hours of initiating therapy, follow-up ax within 48 hours of completing therapy, follow-up ax 4-6 weeks later post therapy and a follow-up ax 1 year later.	ASHA, 1994	not mentioned	No significant correlation between the presence or severity of the HL and either the plasma AG levels or total dosage of AGs	PTA might be more effective to indicate abnormal hearing in children receiving peritoneal dialysis compared to ce-ABR	3

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Zorowka et al. (1993)	**Eligibility ax:** Risk catalogue of the American Academy of Pediatrics **Baseline ax:** otoscopy tympanometry TEOAEs **Follow-up ax:** otoscopy tympanometry TEOAEs	Baseline ax within first 4 days of life and follow-up ax within 24 hours of the last dose of AG , usually 8-10 days after the first test	not mentioned	not mentioned		TEOAE is quick to perform, non-invasive, objective and reflects the earliest changes to the cochlear OHCs, making it useful for new-born hearing screening	1
Hotz et al. (1994)	**Eligibility ax:** otoscopy PTA TEOAEs **Baseline ax:** otoscopy PTA TEOAEs **Follow-up ax: < 10 days therapy:** PTA & TEOAE **Follow-up ax: > 10 days therapy:** PTA & TEOAE	Baseline ax before the start of therapy with a follow-up ax on the last day of tx if tx < 10 days OR a follow-up ax at 3-day intervals after 10th day of therapy and until 3-6 days after the end of therapy	not mentioned	not mentioned	No correlation found between dosage, duration of therapy and amount of change in TEOAEs	AG induced cochleotoxicity might be better indicated by changes in TEOAE level and reproducibility by frequency, compared to PTA	4

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Wood et al. (1996)	**Baseline ax:** PTA EHF audiometry **Follow-up ax:** PTA EHF audiometry	Baseline ax before the start of treatment and a follow-up ax at the end of treatment	ASHA, 1994	not mentioned	Significant association between ototoxicity and AG dosing schedule	AG dosage administered 12 hourly might be less toxic and equally effective as 8 hourly dosages	1
Katbamna et al. (1999)	tympanometry PTA EHF audiometry DPOAEs	once off testing	Age-appropriate thresholds in the EHF range as described by Osterhammel and Osterhammel (1979)	not mentioned		Toxic effects of chronic tobramycin initially observed in DPOAE latencies and detection thresholds. DPOAE amplitudes might not reflect the earliest changes by AGs but rather latencies and detection thresholds.	1

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Stavroulaki et al. (1999)	**Eligibility ax:** case history **Baseline ax:** otoscopy immittance PTA EHF until 12 KHz TEOAEs ABR (for younger / uncooperative children) **Follow-up ax / monitoring:** PTA EHF until 12 KHz TEOAEs ABR (for younger / uncooperative children)	Within 48 hours after initiation of therapy (baseline) and within 24 hours after last AG dose	not mentioned	not mentioned		TEOAEs are sensitive enough to detect the early, subtle cochlear damage before standard PTA or ABR and probably at a stage that they are still reversible	3
Mulheran et al. (2001)	**Eligibility ax:** case history **Hearing Ax:** otoscopy tympanometry PTA EHF (until 16 kHz)	once off testing	ASHA, 1994	not mentioned	Nonlinear relationship between the courses of AGs received and the incidence of hearing loss	Relatively low risk of cochleotoxicity with <10 courses of AGs. Possibility that CF significantly reduces the progression of AG cochleotoxicity, possibly due to the rapid renal elimination of drugs, including AGs.	3

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Stavroulaki et al. (2002)	**Eligibility ax:** case history **Baseline ax:** otoscopy tympanometry acoustic reflexes PTA DPOAEs & TEOAEs **Follow-up ax:** PTA DPOAEs & TEOAEs	Baseline & follow-up ax within 24h after the last AG dose	ASHA, 1994	not mentioned	Significant association between history of AG exposure on total emission level as well as DP-gram amplitude (only at highest Hz tested) (P<.05). No significant association between history of exposure and reproducibility at each Hz.	OAEs (especially DPOAEs) are more sensitive than PTA in detecting the minor changes in auditory function after gentamicin treatment. DPOAEs are preferable to TEOAEs for OM due to their range being more extensive and frequency specific.	3

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Riga et al. (2007)	**Eligibility ax:** case history tympanometry **Hearing measurement:** otoscopy tympanometry DPOAEs with and without contralateral white noise @ 60dBHL	Once off measurements with different groups at different stages ≤4 months after tx: low dose AG < 13 days; 2 years after tx: medium dose AG >13, less than 23 days; ±3 years after tx: low AGs doses and high AG doses, > 23 days	not mentioned	N/A		Olivocochlear reflex dysfunction during the first 2 years after AG treatment, then recovers slowly.	4
Naeimi et al. (2009)	**Eligibility ax:** case history otoscopy TEOAEs **Baseline ax:** TEOAEs **Follow-up ax:** TEOAEs	Baseline within 24 hours of onset of therapy; follow-up ax within 24 hours after the last AG dose	not mentioned	N/A		TEOAE is a valid, reliable, sensitive and efficient method for identification and monitoring of possible gentamicin-induced cochleotoxicity. Might be more sensitive than PTA.	4

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Scheenstra et al. (2010)	**Baseline ax:** PTA EHF audiometry (9-16 kHz) **Follow-up ax:** PTA EHF audiometry (9-16 kHz)	Baseline ax before first tobramycin treatment and follow-up ax ±3 weeks later	not mentioned	not mentioned	No correlation between cumulative tobramycin exposure and either cumulative hearing loss or increase in hearing thresholds	No significant hearing loss found in patients with CF after treatment with tobramycin for 3 weeks. Lower than expected prevalence of hearing loss in patients with CF treated with tobramycin.	3
Al-Mallky et al. (2011)	**Eligibility ax:** case history **Hearing ax:** otoscopy tympanometry acoustic reflexes PTA EHF audiometry (9-20kHz) Play audiometry for younger children DPOAEs	once off testing	ASHA 1994	not mentioned	Significant correlation between hearing loss and high AG exposure	EHF and DPOAEs significantly discriminated between normal and abnormal hearing compared to standard PTA frequencies and are both considered to be more sensitive and reliable clinical tools for monitoring for ototoxicity than standard audiometry	1

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Chen et al. (2013)	Case history / parent questionnaire tympanometry acoustic reflexes (500 – 4000 Hz) PTA speech audiometry DPOAE & TEOAE	once-off testing, 5 months after last AG dose	ASHA 1994	not mentioned	Correlation between hearing loss and increased AG exposure ($P < 0.05$)	Patients with cancer treated with AGs, without platinum exposure or cranial radiation, are still at risk of developing severe hearing loss.	4
Sagwa et al. (2015)	**Baseline ax:** PTA **Follow-up ax in intensive phase:** PTA **Follow-up ax in continuation phase:** PTA	Baseline Follow-up ax in 6-8 month intensive therapy phase Follow-up ax in 12-18 month continuation phase	ASHAs hearing loss classification	not mentioned		Amikacin treatment in the long term causes more severe HL compared to kanamycin treatment.	3

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
El-Barbary et al. (2015)	**Baseline ax:** case history (medical, perinatal & family) otoscopy TEOAE screening **Follow-up ax:** TEOAE screening If a subject had a failed or partial pass response in one or both ears for the second time, a referral were made for diagnostic ABR after 3 months. If a subject had elevated thresholds, low probe tone tympanometry were done and a re-test ABR when tympanometry revealed a type A or C tympanogram.	Baseline immediately after birth and a follow-up test before hospital discharge	TEOAEs: Rhode Island criteria	N/A		The administration of gentamicin at extended interval doses does not seem to increase the incidence of hearing loss.	3
Geyer et al. (2015)	Evaluation by ENT case history – patients medical record tympanometry contralateral acoustic reflexes PTA EHF audiometry (9-16 kHz) DPOAEs	Once off measurement	International Bureau for Audiophonology (BIAP) classification	not mentioned	Significant correlation between alterations in EHF audiometry and number of courses of AGs (p=0.005)	EHF audiometry is more effective to detect hl compared to PTA.	3

Author (year)	Procedures used	Timing of evaluations	Criteria used to identify a cochleotoxic threshold shift	Grading criteria used	Correlations between results of CG and SG	Conclusions	Level of evidence
Al-Malky et al. (2015)	**Eligibility ax:** otoscopic examination tympanometry acoustic reflexes **Hearing measurements:** PTA EHF (9-16 kHz) DPOAEs	Once off measurement	ASHA criteria for hearing loss British Society of Audiology (BSA) criteria for severity of hearing loss	Brock et al. 1991	Mildly significant correlation between the number of amikacin courses taken and EHF pure-tone average ($p<0.05$), however no correlation with the same analysis for tobramycin ($p=0.730$) or gentamicin ($p=0.373$)	EHF audiometry detected ototoxicity earlier and showed a significant drop in hearing thresholds (25 – 85 dB) compared to standard PTA	1
Canet et al. (2018)	**Baseline:** TEOAEs **Follow-up:** TEOAEs	Baseline before the start of treatment; follow-up ax before discharge	N/A	N/A		Gentamicin in the standard dose used for a short term did not cause ototoxicity. EOAE is a valid, reliable and efficient method for identification and monitoring of possible gentamicin-induced cochleotoxicity.	3