EXTENDED HIGH-FREQUENCY AUDIOMETRY FOR OTOTOXICITY MONITORING: A LONGITUDINAL EVALUATION OF DRUG-RESISTANCE TUBERCULOSIS TREATMENT

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Journal: American Journal of Audiology

Abstract

Purpose: To describe extended high-frequency (EHF) pure tone audiometry monitoring of ototoxicity in a longitudinal treatment program for drug-resistant tuberculosis (DRTB).

Method: This was a retrospective record review of longitudinal conventional (0.25–8 kHz) and EHF (9–16 kHz) audiometry for ototoxicity monitoring of DRTB patients undergoing treatment at community-based clinics between 2013 and 2017. Data from 69 patients with an average age of 37.9 years (SD = 11.2; range = 16.0 to 63.8 years) were included. Patients were assessed by primary health care (PHC) audiologists (87%) or community health care workers (CHWs) (13%) using portable audiological equipment. The average length of time between initial and exit assessments was 84.6 days (SD = 74.2; range = 2 to 335 days).

Results: EHF ototoxicity of a mild or greater degree of hearing loss (> 25 dB HL in one or both ears across frequencies) was evident in 85.5% of patients' post-treatment, compared to 47.8% of patients across conventional frequencies. EHF audiometry demonstrated an ototoxic shift (ASHA criteria) in 56.5% of cases compared to 31.9%

when only conventional audiometry was considered. Mean hearing deterioration for patients was significant across EHFs (9–16 kHz) bilaterally ($p < 0.05$). Absent EHF thresholds at the initial assessment, owing to maximum output limits, was a limitation that occurred most frequently at 16 kHz (17.4%; 24/138).

Conclusion: EHF audiometry is most sensitive for the early detection of ototoxicity and should be included in monitoring programs. Clinical ototoxicity monitoring protocols should consider shortened assessment approaches that target frequencies most sensitive to ototoxicity, including EHF.

Introduction

A plethora of drugs are known to cause ototoxicity (Lanvers-Kaminsky et al., 2017; Watts, 2019), resulting in damage to the cochlear or vestibular system of the inner ear, or both (Rizk et al., 2020), depending on their dosage, duration and route of administration (Lanvers-Kaminsky et al., 2017; Steyger, 2011). Cochleotoxicity typically results in tinnitus and/or hearing loss, while vestibulotoxicity causes impairment of coordination, such as dizziness, balance and vertigo (Rizk et al., 2020). The drug classes commonly associated with ototoxicity include aminoglycoside antibiotics, typically used in the treatment of bacterial and mycobacterial infections (Kros & Steyger, 2019; Lanvers-Kaminsky et al., 2017; Steyger, 2021a), and platinum-based chemotherapies, used in the treatment of cancers (Campbell & Le Prell, 2018; Lanvers-Kaminsky et al., 2017).

Ototoxic medications can cause vestibular and cochlear damage via several mechanisms (Rizk et al., 2020). Damage caused to the cochlea (Meiyan et al., 2017; Steyger, 2021a), resulting in permanent ototoxic hearing loss, typically progresses from the high to low frequency ranges of hearing sensitivity (Blankenship et al., 2021; Ganesan et al., 2018; Ghafari et al., 2020; Steyger, 2021a). Both platinum-based chemotherapeutic agents and aminoglycosides initially affect outer hair cells at the basal, high frequency region of the cochlea, resulting in high frequency hearing loss (Campbell & Le Prell, 2018; Ganesan et al., 2018; Meiyan et al., 2017; Rizk et al., 2020; Steyger, 2021a). Outer hair cell damage progresses to the lower frequencies of the apical region of the cochlea with continued ototoxic drug exposure, eventually leading to inner hair cell death (Campbell & Le Prell, 2018; Ganesan et al., 2018; Meiyan et al., 2017; Rizk et al., 2020; Steyger, 2021a).

Monitoring the hearing of patients undergoing ototoxic treatment is a necessary precaution to preserve hearing and to mitigate the negative impact of hearing loss (Campbell & Le Prell, 2018; Ganesan et al., 2018; Prendergast et al., 2020; Watts, 2019). Serial ototoxicity monitoring detects changes in hearing for the purpose of early identification, prevention and treatment of hearing loss (American Academy of Audiology [AAA], 2009; American Speech-Language-Hearing Association [ASHA], 1994; Health Professions Council of South Africa [HPCSA], 2018). The detection of ototoxic shifts in hearing allows clinicians to adjust treatment regimens, or substitute treatment with an all-oral regimen, which is less toxic and more effective (Khoza-Shangase & Prodromos, 2021; Lange, Aarnoutse, et al., 2019; Lange, Dheda, et al., 2019; Lanvers-Kaminsky et al., 2017; Van Deun et al., 2020; Watts, 2019). The basic test battery for detecting ototoxic hearing loss includes the use of conventional behavioural pure tone audiometry where air conduction hearing thresholds of the frequencies 0.25–8 kHz are assessed (Campbell & Le Prell, 2018; Ganesan et al., 2018).

Extended high-frequency (EHF) pure tone audiometry, assessing hearing above 8 kHz, is a sensitive behavioural method for detecting early cochlear outer hair cell damage (Campbell & Le Prell, 2018; Ganesan et al., 2018; Harris, Peer, et al., 2012). EHF audiometry has been recommended for ototoxicity monitoring in patients receiving potentially ototoxic drugs, such as aminoglycosides and platinum-based chemotherapy, for the treatment of illnesses such as tuberculosis, cancer and cystic fibrosis (AAA, 2009; ASHA, 1994; Caumo et al., 2017; HPCSA, 2018). Despite recommendations for using EHF audiometry, it is still not routinely employed for ototoxicity monitoring (Blankenship et al., 2021; Ganesan et al., 2018). The lack of routine EHF audiometry use has been attributed to, amongst others, time constraints and limited audiological equipment resources (Blankenship et al., 2021; Campbell & Le Prell, 2018). A key limitation of EHF audiometry is that it may be impractical because of the additional time needed for an assessment (Ganesan et al., 2018). Patients in need of ototoxic medications are often ill and fatigued, and completing valid behavioural testing may be challenging and time consuming for them (Rieke et al., 2017). In addition, the possibility of absent hearing thresholds in the EHF range of hearing, equipment output limitations, and the choice of which EHFs to assess are

challenges faced by testers when using EHF audiometry in clinical settings (Prendergast et al., 2020; Wang et al., 2021).

Drug-resistant tuberculosis (DRTB), which occurs when tuberculosis-causing bacteria become resistant to the drugs used to treat tuberculosis, is a widespread condition with ototoxic treatment regimens (Centres for Disease Control and Prevention (CDC) [CDC], 2016). Half a million people developed DRTB globally in 2019, with the incidence remaining stable in 2021 (World Health Organisation [WHO], 2020b, 2021a). China, India and the Russian Federation account for approximately half the global burden of DRTB (WHO, 2020b). Up to 2018, before the release of the updated DRTB treatment regimen guidelines (Department Health Republic of South Africa [DOH], 2018; WHO, 2020c), the treatment regimen for DRTB patients included the use of aminoglycosides (DOH, 2018). The latest WHO DRTB treatment guidelines (WHO, 2020c) have now recommended the use of less toxic, more efficient all-oral DRTB treatment regimens. Access to these newer drugs is, however, very limited in some countries (Lange, Aarnoutse, et al., 2019). Almost half (46%; 17/37) of the high-burden TB countries recently surveyed reported still using injectable aminoglycosides in the treatment of DRTB (MSF, 2020b), resulting in the continued risk of ototoxicity and the need for ototoxicity monitoring for these patients.

Limited studies have reported using EHF audiometry for DRTB ototoxicity monitoring (Appana et al., 2016; Ghafari et al., 2020; Hong et al., 2020a). In instances where ototoxicity monitoring of DRTB patients employed EHF audiometry, a high prevalence of ototoxic hearing loss (74 to 100%) was reported (Appana et al., 2016; Ghafari et al., 2020; Hong et al., 2020a). Owing to the limited use of EHF audiometry and the application of various criteria to define ototoxicity, the prevalence of aminoglycoside-induced EHF hearing loss, and the subsequent value of EHF audiometry to identify early changes in hearing remains unclear (Ganesan et al., 2018; Steyger, 2021a). Additional insights into cochleotoxicity can be garnered from widespread ototoxicity monitoring with improved, data-driven measures of hearing loss, including EHF audiometry (Steyger, 2021a, 2021b). This study therefore aimed to describe longitudinal monitoring of ototoxicity with EHF audiometry in patients receiving aminoglycoside treatment for DRTB.

Method

This retrospective record review aimed to describe EHF audiometry monitoring of ototoxicity for DRTB treatment with EHF audiometry, and the prevalence of ototoxic hearing loss observed in this population. The study was part of a larger longitudinal, retrospective descriptive study of a decentralised community-based ototoxicity monitoring program (OMP) for patients with DRTB, using conventional and EHF audiometry facilitated by community health workers (CHWs) and primary health care (PHC) audiologists between 2013 and 2017 (Stevenson et al., 2021). The objective of the larger study was to compare the OMP service delivery practices with the international (AAA, 2009; ASHA, 1994) and national (HPCSA, 2018) recommended guidelines for ototoxicity monitoring to improve services and to guide future OMP implementations. Quantitative data was collected at community-based community health centres and primary health care (PHC) clinics in two sub-districts of the City of Cape Town, South Africa, namely the Mitchells Plain/Klipfontein and the Western/Southern sub-districts and made available to the authors of this study only.

The study was approved by the Institutional Review Board (or Ethics Committee) of the University of Pretoria (GW20161128HS; 63/2017), the City of Cape Town (7788) and the Western Cape Department of Health (WC_2017RP22_896).

Participants

This study included patients from the larger study who met the following selection criteria: 1) tested using both conventional (0.25, 0.5, 1, 2, 4, 6 and 8 kHz) and EHF (9, 11.2, 12.5, 14, and 16 kHz) behavioural pure tone audiometry; 2) had an initial assessment conducted, and one or more follow-up monitoring assessments conducted thereafter; 3) EHF audiometry was used for both the initial and exit assessments. Non-probability purposive sampling was used to select all patients with DRTB, regardless of age, gender or hearing status. Of the 831 patients included in the parent study, 69 patients met the selection criteria and were eligible for inclusion in this study (Figure 1). The patient interviews and ototoxicity monitoring assessments were conducted by six CHWs and two PHC audiologists who were the testers at 19 PHC clinics and community health centres. In 2012, the Western Cape Department of Health initiated a pilot project where 30 CHWs underwent upskill training to become members of the PHC team (Gamiet & Rowe, 2019). The CHWs were trained for

community-based rehabilitation to support people with disabilities in two underserved communities of the Western Cape (DOH, 2018; Gamiet & Rowe, 2019). These CHWs were also trained to facilitate ototoxicity monitoring for DRTB in community-based settings.

Data Collection Procedures

The data collection procedure for this study was the same as that of the larger study (Stevenson et al., 2021) from which the patient sample was obtained. At the time of data collection, patients receiving the standardised DRTB treatment regimen stipulated by the South African Department of Health would have been administered second-line drugs, including injectable aminoglycosides (DOH, 2013). Patients undergoing DRTB treatment visited a PHC clinic or community health centre daily for the first six months of treatment to receive their medication from a nurse. After the initial six-month treatment period, medication was continued for 18 months with patients visiting a clinic/centre weekly to obtain their medication, and monthly to consult with their managing doctor. All patients who received ototoxic medication for treatment of DRTB were referred by their managing doctor and included in the OMP as part of the package of care.

At the time of data collection OMP developers relied on the international guidelines of the American Speech-Language-Hearing Association (ASHA) (ASHA, 1994) and the American Academy of Audiology (AAA) (AAA, 2009) when developing the OMP procedure protocol. An unpublished draft of the Health Professions Council of South Africa's (HPCSA) national ototoxicity monitoring guideline was, however, available to the OMP developers. OMP developers made adaptions to the recommendations of the international and national guidelines for the timing and frequency of ototoxicity monitoring assessments, to suit the context and resources available to the OMP.

Testers travelled with portable audiological equipment to the clinics/centres in each sub-district to conduct ototoxicity monitoring assessments. PHC audiologists and CHWs were testers in the Michell's Plain/Klipfontein sub-district whereas only PHC audiologists were testers in the Western/Southern sub-district. The protocol followed by the OMP for audiological ototoxicity monitoring assessments at the time of data collection was as follows: At the time of a patient's initial assessment a case history

intake interview was conducted by the CHW or PHC audiologist who manually recorded patient information on a paper-based data collection form. During the interview, information was obtained from the patient's medical records in a clinic file and/or verbally reported by the patient to the CHW or PHC audiologist. Identifying information including the patient's name, date of birth and gender was recorded on the data collection form. CHWs and PHC audiologists also completed a checklist on the data collection form indicating patients' HIV status, DRTB medication/s and risk factors for ototoxic hearing loss, such as exposure to excessive noise and pre-existing hearing loss. Excessive noise exposure was defined by the OMP as exposure to noise with an intensity of ≥ 85 dBA (A-weighted decibels) for a duration of eight hours or longer (DOH, 2001). Initial and monitoring assessments included bilateral otoscopy, conventional behavioural pure tone audiometry and EHF audiometry (0.25, 0.5, 1, 2, 4, 6, 8, 9, 11.2, 12.5, 14 and 16 kHz). If pathology was suspected following otoscopy, the patient was referred to the managing doctor or nurse for appropriate treatment, and referred for audiometry, according to the OMP protocol. Initial assessments were conducted prior to, on the same day, or within two weeks of the DRTB treatment initiation, while monitoring assessments were conducted once a month during the initial six-month treatment regimen, and then at three, six, and 18 month intervals thereafter. The presence of an ototoxic shift was determined according to the three criteria developed by ASHA (1994), the most widely used and validated criteria (AAA, 2009), where a change in hearing thresholds was determined relative to the hearing thresholds obtained during the initial assessment. The criteria to indicate hearing decrease for ototoxicity monitoring were defined as: ≥ 20 dB HL pure tone threshold decrease at any one test frequency; ≥ 10 dB HL pure tone threshold decrease at any two adjacent test frequencies; no response at three consecutive test frequencies where pure tone threshold responses were previously obtained. Changes were confirmed by repeat testing. Where an ototoxic shift meeting the criteria (ASHA, 1994) was evident, the managing doctor was informed, and monitoring assessments were then conducted every two weeks until no change in hearing thresholds was detected. Assessments were conducted in a quiet environment using the KUDUwave audiometer (eMoyo, Johannesburg, South Africa) employing insert earphones covered by noise-reducing circumaural earcups. Typically, automated testing would have been done applying the Hughson-Westlake procedure (ISO 8253-1), automatic standard ascending and shortened and standard bracketing; however, a manual mode

of threshold determination, using the modified method of limits test paradigm (Stach & Ramachandran, 2017), may also have been selected by PHC audiologists in some instances. The maximum audiometer output limits across EHFs were 90 dB at 6 kHz; 80 dB at 8, 9 and 12.5 kHz; 75 dB at 11.2 kHz; 65 dB at 14 kHz and 45 dB at 16 kHz.

Each patient's descriptive (gender, audiological symptoms, treatment regimen), audiological data and risk factors for ototoxicity (history of exposure to excessive noise, pre-existing hearing loss and DRTB and HIV coinfection) were recorded manually by the testers on data collection forms and stored in the patient's clinic file. A copy of each patient's data collection form was kept with the tester and regularly made available to the managing PHC audiologist responsible for each sub-district for review. Upon completion of a patient's DRTB treatment and ototoxicity monitoring, the data collection form was stored permanently with the PHC audiologist responsible for each sub-district. The researchers requested the hardcopies of the patients' data collection forms from the managing PHC audiologists in each sub-district for anonymised data capturing and analysis.

Data analysis

This study aimed to describe longitudinal monitoring of ototoxicity with EHF audiometry in patients receiving aminoglycosides for DRTB treatment by determining the sensitivity of EHF audiometry for the early detection of ototoxicity. Therefore, a statistical analysis plan was defined prior to data analysis describing which variables, outcomes and statistical analysis methods would be included in the study to achieve the aim (Yuan et al., 2019) and how missing data would be handled. Statistical analysis models used a within subject comparison of longitudinal hearing deterioration (dependant variables) when considering conventional and EHFs (independent variables). Data were imported from Excel into Statistical Package for Social Sciences (SPSS) software (version 27) after which descriptive statistics such as frequency distributions, measures of central tendency, and measures of variability were used to present and interpret the data in a meaningful way. Since all the continuous scale data differed significantly from normal distribution (Shapiro-Wilk p-values < 0.05), nonparametric tests were used (Field, 2018). The Wilcoxon signed-rank (Z) test was used to determine whether there were significant differences between dependent groups (initial and exit audiometric assessment and left and right ears).

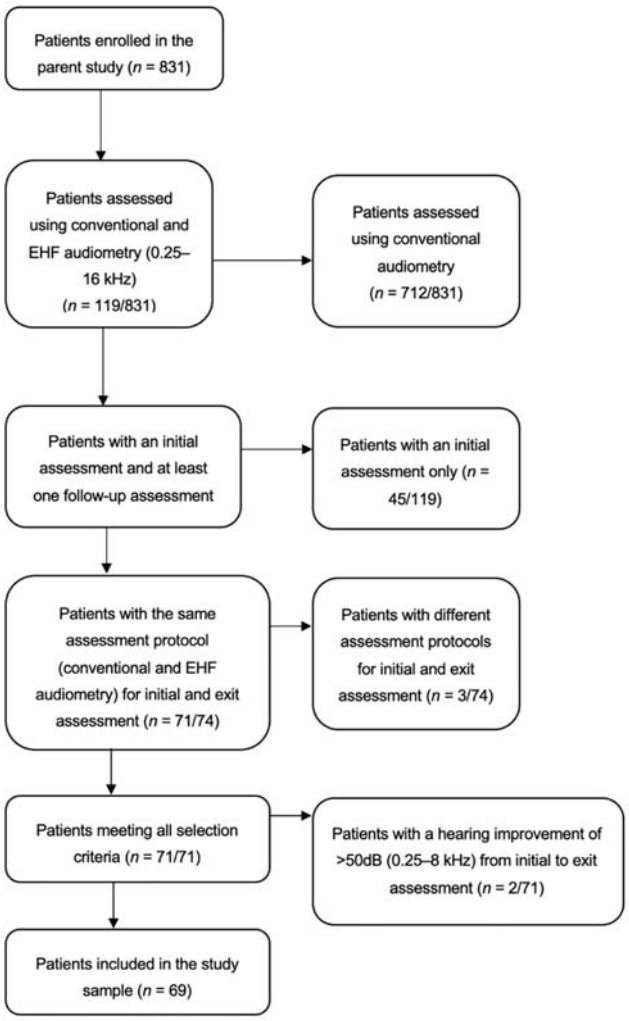
Some hearing thresholds could not be obtained for initial and exit assessments owing to the maximum equipment output limits being reached. In these cases, analysis included only instances where thresholds were present at initial assessment. Where exit assessment thresholds were unobtainable because of the maximum output limits being reached, corrections were made by replacing absent values with the maximum output limit plus one intensity increment (viz. 5 dB).

Some descriptive data (gender and medication type) were missing as this was not recorded on the data collection forms by the CHWs and PHC audiologists and was therefore unavailable to the researchers for inclusion in this retrospective study. For some patients, hearing thresholds were not measured by the CHWs and PHC audiologists, most frequently occurring at the low frequencies (0.25 and 0.5 kHz) of the exit assessments. The pairwise deletion method for handling missing data was used instead of the listwise deletion method because the latter leads to a smaller sample size and lower statistical power, as the entire record is excluded from analysis if a single value is missing (Raaijmakers, 1999).

Results

Participants

Of the 831 patients included in the parent study, 71 met the selection criteria and were eligible for inclusion. Two patients with results indicating technical or procedural issues related to their initial assessments were excluded. The final analytic sample included 69 patients (Figure 1) with a mean age of 37.9 years (SD = 11.2; range = 16.0 to 63.8 years) (Table 1).



EHF, extended high-frequency; kHz, kilohertz

Figure 1 *The ototoxicity monitoring program's application of EHF audiometry and the study patient selection procedure*

Table 1 *Patient description at the time of the initial assessment (n = 69)*

	%	*n*
Gender		
Not recorded	27.5	19
Male	43.5	30
Female	29.0	20
Risk factor for ototoxicity		
DRTB and HIV coinfection	17.4	12
Noise exposure	10.1	7
Audiological self-reported symptoms		
Tinnitus	13.0	9
Otalgia	2.9	2
Hearing loss	5.8	4
Tester		
CHW	13.0	9
PHC audiologist	87.0	60

DRTB, drug-resistant tuberculosis; HIV, human immunodeficiency; CHW, community health worker; PHC, primary health care.

At the time of the initial assessment, 17.4% (12/69) of patients reported DRTB and HIV co-infection, 10.1% (7/69) reported a history of excessive noise exposure, and 13.0% (9/69) reported experiencing tinnitus. Gender (27.5%; 19/69) and medication type (47.8%; 33/69) administered were not recorded on the data collection forms by some testers. Of the 36 patients with a medication type recorded on their data collection form, 100%were administered kanamycin. Of the 36/69 patients who had a medication type recorded, 30/36 also had a treatment initiation date and initial assessment date recorded, allowing the determination of treatment duration at the time of the initial assessment. Initial assessments were conducted on average 40.3 days (SD = 70.9; range = 0 to 301 days) after treatment initiation, with just one patient having an initial assessment conducted on the same day as treatment initiation. The average length of time between initial and exit assessments was 84.6 days (SD = 74.2; range = 2 to 335 days).

Ototoxicity characteristics

In the current study, hearing loss was defined as one or more hearing threshold > 25 dB HL in one or both ears across conventional frequencies (0.25–8 kHz) and EHFs (0.25–16 kHz) (ASHA, 2022; Stach & Ramachandran, 2017). At the initial assessment, 36.2% (25/69) of patients presented with a hearing loss in one or more frequency in the conventional range (0.25–8 kHz) compared to 65.2% (45/69) of patients when also considering EHF thresholds (0.25–16 kHz). Hearing loss in patients at the time of the exit assessment increased to 47.8% (33/69) considering only conventional frequencies compared to 85.5% (59/69) when EHFs were also considered. Some hearing thresholds could not be determined for initial and exit assessments because of the maximum equipment output limits reached (Table 2).

Table 2 *Absent hearing thresholds for pure tone audiometry owing to maximum audiometer output limits across frequencies (left and right ears combined; n = 138)*

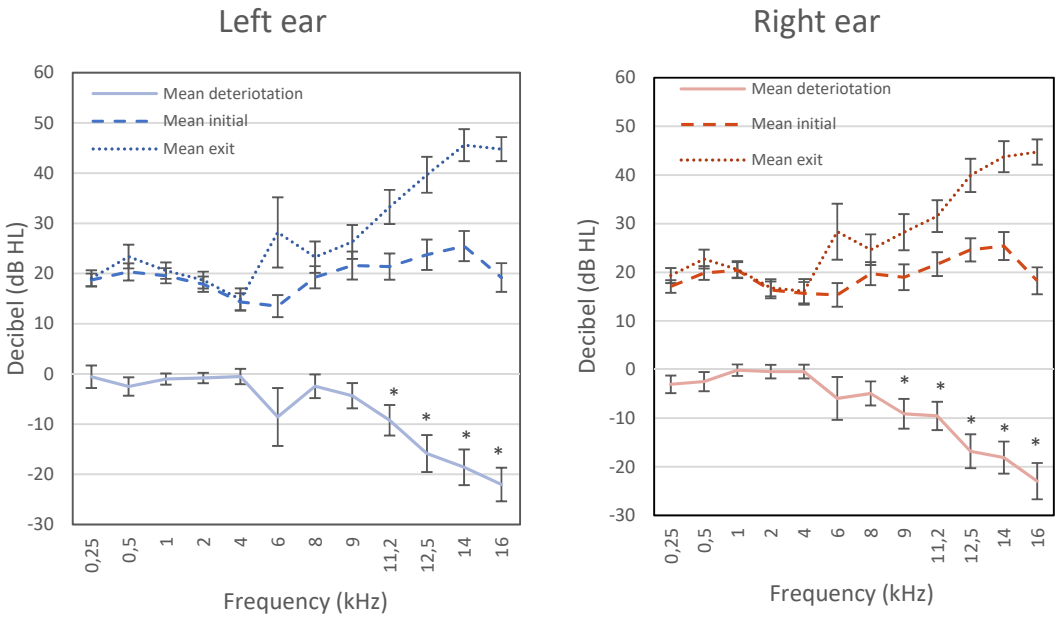
Frequency kHz* and maximum output (dB)	**6 (90)**	**8 (80)**	**9 (80)**	**11.2 (75)**	**12.5 (80)**	**14 (65)**	**16 (45)**
Initial test % (n)	0.7 (1)	1.4 (2)	0.7 (1)	2.2 (3)	3.6 (5)	3.6 (5)	17.4 (24)
Exit test % (n)	0.7 (1)	1.4 (2)	7.2 (10)	3.6 (5)	7.2 (10)	10.1 (14)	23.2 (32)

**Absent thresholds owing to the maximum output limits only recorded for frequencies above 4 kHz.*

kHz, Kilohertz; dB, decibel.

The distribution of initial and exit assessment hearing thresholds and longitudinal changes in hearing for the patients are presented in Figure 2 (Table 5.5 of supplementary material). On average, a decline in hearing thresholds from the initial to exit assessment was evident across all frequencies in both ears, with the deterioration most pronounced in the EHF range (Figure 2). The mean deterioration was statistically significant at EHF thresholds of the left (11.2, 12.5, 14 and 16; p = 0.000 to 0.005; Z = -4.947 to -2.801) and the right ears (9, 11.2, 12.5, 14 and 16 kHz; p = 0.000 to 0.007; Z = -4.705 to -2.711). Patients' mean hearing thresholds at the initial assessment were compared to the mean hearing thresholds at the exit assessment according to various pure tone averages (PTA) (Table 3). Hearing deterioration was evident across all PTA groups in both ears; however, deterioration was most pronounced in the EHF PTA group in both ears (Table 3 and Figure 3).

Results indicated significant deterioration in the mean EHF PTA for the left (p = 0.000; Z = -4.160) and right (p = 0.000; Z = -4.546) ears.



** statistical significance of p < 0.05*

Figure 2 *Mean hearing thresholds and deterioration (error bars = standard error) of the left (panel A) and right (panel B) ears from initial to exit assessment (n = 69)*

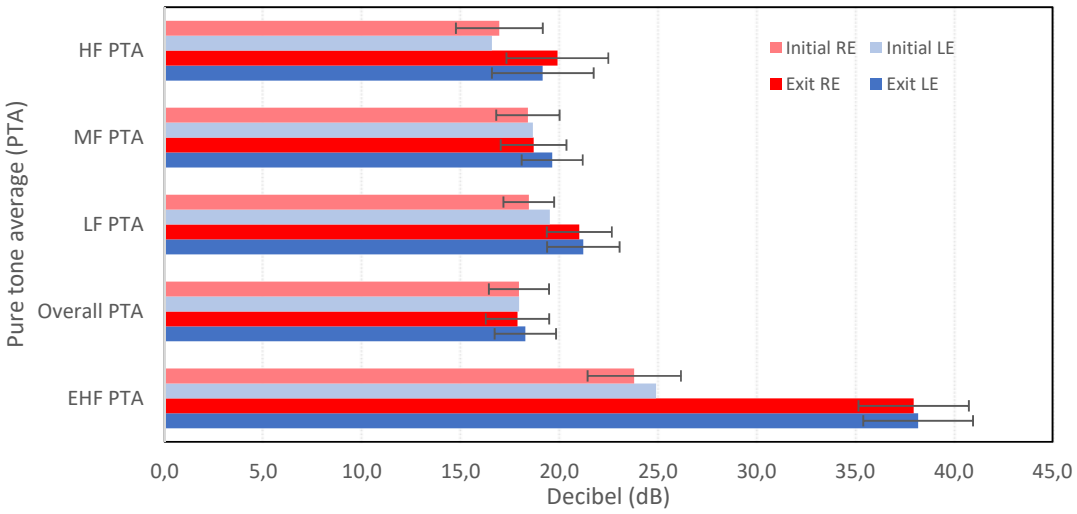
There was no significant deterioration in hearing thresholds for frequencies below 9 kHz in the right ear (p = 0.153 to 0.913; Z = -0.077 to -1.54), or for frequencies below 11.2 kHz in the left ear (p = 0.124 to 0.939; Z = -1.918 to -0.049). In addition, there was no significant deterioration in the mean PTA of the overall low frequency, mid frequency, or high frequency PTA groups for the left (p = 0.305 to 0.832; Z = -0.212 to -1.025) or right ears (p = 0.120 to 0.623; Z = -0.491 to -1.556). No statistically significant difference in the mean hearing threshold deterioration (p = 0.055 to 0.961; Z = -1.918 to -0.049) or mean PTA deterioration (p = 0.209 to 0.534; Z = -1.256 to 0.622) was found between the left and right ears.

Table 3 *Mean pure tone averages and hearing deterioration across ears (n = 69)*

Frequency (kHz)	Overall PTA (0.5 – 4)	LF PTA (0.25 – 0.5)	MF PTA (1 – 2)	HF PTA (3 – 8)	EHF PTA (9 – 16)
Left ear					
Mean initial dB (SD)	18.0 (11.6)	19.5 (11.0)	18.7 (12.0)	16.6 (15.5)	24.9 (21.7)
n	69	62	69	69	68
Mean exit dB (SD)	18.3 (12.9)	21.2 (11.2)	19.6 (12.9)	19.2 (21.4)	38.2 (23.1)
n	69	37	69	69	69
Mean deterioration dB (SD)	-0.7 (7.9)	-1.5 (11.7)	-1.0 (8.1)	-1.6 (15.0)	-11.9 (22.9) *
n	69	36	69	69	67
Right ear					
Mean initial dB (SD)	18.0 (12.7)	18.5 (10.2)	18.4 (13.3)	17.0 (18.3)	23.8 (19.7)
n	69	63	69	69	69
Mean exit dB (SD)	17.9 (13.4)	21.0 (10.0)	18.7 (13.8)	19.9 (21.4)	38.0 (23.3)
n	69	37	69	69	69
Mean deterioration dB (SD)	-0.3 (9.2)	-2.8 (10.4)	-0.3 (10.1)	-2.6 (14.7)	-13.0 (23.0) *
n	69	36	69	69	69

kHz, kilohertz; PTA, pure tone average; LF PTA, low frequency pure tone average; MF PTA, mid frequency pure tone average; HF PTA, high frequency pure tone average; EHF PTA, extended high-frequency pure tone average; dB, decibel; SD, standard deviation.

** statistical significance of p < 0.05*



HF, high frequency; MF, mid frequency; LF, low frequency; EHF, extended high-frequency; LE, left ear; RE, right ear.

Figure 2 *Mean initial and exit assessment pure tone averages of the left and right ears (n = 69) (error bars = standard error)*

The presence of an ototoxic shift was determined according to the three criteria developed by ASHA (1994), as indicated in Table 4. Including EHF thresholds resulted in more than half the patients (56.5%; 39/69) presenting with a significant ototoxic shift meeting one or more of the ASHA criteria, compared to 31.9% (22/69) if EHFs were not considered (Table 4). There was no significant difference in ototoxic shifts (meeting one or more of the ASHA criteria) between the left and right ears (conventional audiometry: $p = 0.237$, $Z = -1.182$; EHF audiometry: $p = 0.785$, $Z = -0.272$).

Table 4 *Distribution of patients presenting with an ototoxic shift according to ASHA criteria when considering conventional and EHF pure tone audiometry at the exit assessment (ASHA, 1994) (n = 69)*

ASHA ototoxic shift criteria	No ototoxic shift evident	ASHA Group 1	ASHA Group 2	ASHA Group 3
Conventional audiometry (0.25–8 kHz) *				
Patients % (n/69)	68.1 (47)	29.0 (20)	21.7 (15)	0.0 (0)
Left ear % (*n*/69)	75.4 (52)	23.2 (16)	18.8 (13)	1.4 (1)
Right ear % (*n*/69)	78.3 (54)	20.3 (14)	14.5 (10)	0.0 (0)
Bilateral (Left and right) % (*n*/69)	84.1 (58)	14.5 (10)	11.6 (8)	0.0 (0)
EHF audiometry (0.25–16 kHz) **				
Patients % (n/69)	43.5 (30)	52.2 (36)	52.2 (36)	15.9 (11)
Left ear % (*n*/69)	47.8 (33)	47.8 (33)	47.8 (33)	11.6 (8)
Right ear % (*n*/69)	50.7 (35)	49.3 (34)	49.3 (34)	5.8 (4)
Bilateral (Left and right) % (*n*/69)	55.1 (38)	44.9 (31)	44.9 (31)	1.4 (1)

ASHA, American Speech-Language-Hearing Association; ASHA Group 1, shift of ≥20 dB at a single frequency; ASHA Group 2, shift of ≥10 dB at two adjacent frequencies; ASHA Group 3, shift to 'no response' at three consecutive frequencies; kHz, kilohertz; EHF, extended high-frequency.

** 22/69 (31.9%) patients presented with an ototoxic shift which may have met one or more ASHA criteria: 11.6% (8) met one ASHA criterion, 20.3% (14) met two ASHA criteria and 0.0% (0) met three ASHA criteria.*

*** 39/69 (56.5%) patients presented with an ototoxic shift which may have met one or more ASHA criteria: 5.8% (4) met one ASHA criterion, 37.7% (26) met two ASHA criteria and 13.0% (9) met three ASHA criteria.*

Discussion

When EHFs were included in data analysis in the present study, the prevalence of patients (56.5%) presenting with an ototoxic shift meeting one or more of the ASHA criteria was almost twice as high as when EHF were not considered (31.9%). The mean hearing threshold deterioration from initial to exit assessment in the present study was significant only at EHFs from 9-16 kHz for the right and 11.2-16 kHz for the left ears. Furthermore, following treatment, mean PTA deterioration was significant only in the EHF PTA range (9-16 kHz) for the right and left ears. This suggests that EHF audiometry may be more sensitive for early detection of aminoglycoside induced deterioration than conventional audiometry. The early detection of ototoxic hearing loss through the use of EHF audiometry may offer medical professionals the opportunity to adjust treatment regimens, or to substitute ototoxic drugs with non-ototoxic drugs where suitable, before hearing loss becomes disabling to the patient (Konrad-Martin et al., 2018). In cases where alteration of treatment regimens is not possible, early detection of ototoxic hearing loss using EHFs allows proactive counselling of patients on the expected impact of progressive hearing loss on activities of daily living, and timeous referral for aural rehabilitation (Konrad-Martin et al., 2018).

In this study, the occurrence of ototoxic shifts according to ASHA criteria (56.5%) after aminoglycoside treatment was lower than that of previous reports, where 82.4 to 100% (Appana et al., 2016; Ghafari et al., 2020) of DRTB patients assessed using EHF audiometry developed an ototoxic shift according to ASHA criteria following kanamycin treatment. A possible reason for the higher occurrence of ototoxic shifts reported by Appana et al. (2016) and Ghafari et al. (2020) is that 94% and 63.7% of their patients presented with DRTB and HIV co-infection respectively, compared to the 17.4% of patients in the current study. DRTB with HIV co-infection is an additive risk factor for the development of an aminoglycoside-induced hearing loss for patients with DRTB (Harris, De Jong, et al., 2012; Hong et al., 2018; Stevenson et al., 2021).

There was a high prevalence of pre-existing hearing loss (one or more hearing threshold > 25 dB in one or both ears across all frequencies [0.25-16 kHz]) in this study with more than half (65.2%) of patients presenting with a pre-existing hearing loss at the time of the initial assessment. These results are consistent with previous findings (Hong et al., 2020b; Stevenson et al., 2021) indicating some degree of pre-

existing hearing loss prior to treatment in DRTB patients in South Africa. The pre-existing hearing loss prevalence in the current study may also have been exacerbated by the timing of initial assessments, where patients were assessed for the first time on average 40.3 days after treatment initiation, which was a limitation of the study. This is contrary to the ototoxicity monitoring guidelines recommending that initial assessments should be conducted prior to, or within three days of treatment initiation (AAA, 2009; ASHA, 1994; HPCSA, 2018). Kanamycin-induced hearing deterioration can occur as soon as one week after treatment initiation (Sogebi et al., 2021) and some patients who are more susceptible to ototoxicity can present with ototoxic damage after a single aminoglycoside injection (Huth et al., 2011). Therefore, it is possible that ototoxic shifts meeting one or more of the ASHA criteria may well have been present in more than 56.5% of patients reported in the current study, had initial assessments been completed at or prior to treatment initiation.

Recommendations (AAA, 2009; ASHA, 1994; HPCSA, 2018) for the inclusion of EHFs in ototoxicity monitoring are supported by the study findings but important considerations must be taken in to account. The limitation of test intensity ranges for EHF audiometry can restrict its usefulness in ototoxicity monitoring (Prendergast et al., 2020). When assessing individuals above the age of 30 to 40 years, the likelihood of observing no measurable hearing at 16 kHz and above increases dramatically and so the value of EHF audiometry to monitor hearing becomes reduced (Prendergast et al., 2020; Wang et al., 2021). In addition, any history of pre-existing hearing loss may limit the value of EHF audiometry (AAA, 2009). In the current study, where patients had an average age of 37.9 years and the prevalence of possible pre-existing hearing loss was high (65.2%), absent EHF thresholds owing to maximum intensity constraints were most pertinent at 16 kHz, with 17.4% of patient thresholds absent at the time of the initial assessment. However, missing data points were much less prevalent (0.7 to 3.6%) in frequencies below 16 kHz. The use of EHF audiometry will also significantly increase the time required to conduct an assessment, which may be impractical for patients who are likely to be ill and who are easily fatigued (Konrad-Martin et al., 2005). One way to reduce test time when EHF audiometry is included is to consider an optimized approach by testing only a selected group of frequencies that are most likely to be sensitive to ototoxicity (Rieke et al., 2017). Results of the current study indicate that hearing deterioration was most prevalent at 6, 8, 9, 11.2, 12.5, 14 and 16 kHz,

which suggests that these frequencies may be most sensitive to identifying deterioration. Since 16 kHz had the highest prevalence of absent thresholds at initial assessment, this frequency may need to be excluded from an optimised protocol. A shortened method of assessing EHF hearing, such as the sensitive range for ototoxicity (Fausti et al., 1992, 1999; Ganesan et al., 2018), or the fixed-level frequency threshold method by Rieke et al. (2017) should also be evaluated for their potential efficiency and efficacy (Prendergast et al., 2020; Rieke et al., 2017). Distortion product otoacoustic emission testing could be considered as an ototoxicity monitoring assessment tool, as it offers a quick, reliable, cost-effective method to detect initial cochlear ototoxic changes before they are able to be detected by conventional audiometry (Ganesan et al., 2018).

There have been significant advances in point-of-care testing and mobile health technologies in hearing assessment (Garinis et al., 2021), which could also serve to improve the accessibility and efficiency of EHF ototoxicity monitoring. The use of mobile smartphone-based EHF audiometry with calibrated headphones has recently been demonstrated to be a reliable method for accurate measurement of EHF hearing thresholds (Bornman et al., 2019). In addition, decentralised community-based DRTB ototoxicity monitoring, using portable technology facilitated by nonprofessional hearing health care providers (e.g. CHWs) has been demonstrated to be a promising service model at infectious disease clinics and PHC settings (Brittz et al., 2019; Stevenson et al., 2021).

Limitations of this study included a limited number of patients from the larger study cohort and the absence of measured noise levels in the test environments to confirm the reliability of testing. Ototoxicity monitoring outside a soundproof booth requires attenuation and monitoring of ambient noise levels to ensure the accurate measurement of hearing thresholds (Swanepoel et al., 2013). An additional limitation of this study was the timing of initial assessments after medication initiation. Timing of initial assessments exceeded recommended guidelines (AAA, 2009; ASHA, 1994; HPCSA, 2018) and may have contributed to the prevalence of pre-existing hearing loss, the mean hearing threshold deterioration values and ototoxic shifts meeting ASHA (1994) criteria which were reported in this study. Future research utilising a prospective study design would address these limitations.

Conclusion

Findings of this study suggest that EHF audiometry may be more sensitive for early detection of aminoglycoside induced hearing deterioration than conventional audiometry. In cases of ototoxicity monitoring, such as in DRTB treatment, assessment of EHFs should be considered to ensure the best sensitivity to early changes in hearing. Clinical ototoxicity monitoring protocols must consider shortened assessment approaches that target frequencies most sensitive to ototoxicity, including EHF, to optimise time-efficiency in patient groups who are often sick.

Acknowledgements

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article. The authors received no financial support for the research, authorship, and/or publication of this article. The data that support the findings of this study are available on request from the corresponding author [L.J.S.] for ethical reasons. The data are not publicly available as they contain information that could compromise the privacy of research participants.

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Supplementary material

Table 5 *Mean hearing thresholds for initial and exit assessment with hearing deterioration across ears (n = 69)*

Frequency (kHz)	0.25	0.5	1	2	4	6	8	9	11.2	12.5	14	16
Left ear												
Mean initial dB (SD)	18.7 (10.1)	20.3 (13.4)	19.6 (12.6)	17.9 (12.6)	14.4 (14.3)	13.5 (16.6)	19.3 (18.1)	21.6 (22.2)	21.4 (21.1)	23.8 (23.5)	25.5 (24.0)	19.2 (21.6)
n	62	62	69	68	69	57	67	63	65	60	64	57
Mean exit dB (SD)	19.1 (9.7)	23.4 (14.4)	20.6 (13.6)	18.7 (14.0)	14.9 (18.1)	28.2 (32.8)	23.3 (26.0)	26.3 (26.6)	33.3 (28.3)	39.7 (28.0)	45.6 (26.5)	44.8 (19.9)
n	37	37	69	69	69	22	69	62	69	61	69	69
Mean deterioration dB (SD)	-0.6 (13.5)	-2.5 (11.0)	-1.0 (9.3)	-0.8 (8.5)	-0.5 (12.7)	-8.6 (26.4)	-2.5 (19.3)	-4.3 (19.5)	-9.2 (24.6) *	-15.9 (28 0) *	-18.6 (28.4) *	-22.0 (25.3) *
Right ear												
Mean initial dB (SD)	17.1 (10.3)	19.8 (11.3)	20.4 (13.6)	16.4 (14.4)	15.7 (19.4)	15.3 (18.7)	19.7 (19.7)	19.0 (21.0)	21.7 (20.4)	24.6 (18.6)	25.4 (23.0)	18.2 (20.4)
n	63	63	69	69	69	59	69	63	69	61	64	54
Mean exit dB (SD)	19.3 (9.4)	22.7 (11.8)	20.6 (14.1)	16.8 (14.6)	16.1 (20.8)	28.3 (26.4)	24.6 (26.2)	28.2 (29.0)	31.5 (27.0)	39.9 (26.7)	43.8 (26.4)	44.7 (21.6)
n	37	37	69	69	69	21	69	61	68	61	69	69
Mean deterioration dB (SD)	-3.1 (10.9)	-2.5 (11.8)	-0.1 (9.8)	-0.4 (11.6)	-0.4 (11.7)	-6.0 (20.2)	-4.9 (20.6)	-9.1 (23.7) *	-9.6 (24.0) *	-16.8 (26.6) *	-18.1 (26.4) *	-23.0 (27.4) *

kHz, kilohertz; dB, decibel; SD, standard deviation

** significant hearing deterioration (p < 0.05)*