Health Professions Council of South Africa

PROFESSIONAL BOARD FOR SPEECH, LANGUAGE AND HEARING PROFESSIONS

AUDIOLOGICAL MANAGEMENT OF PATIENTS ON TREATMENT THAT INCLUDES OTOTOXIC MEDICATIONS

GUIDELINES

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Preamble

The South African health system has to address challenges posed by the quadruple burden of disease, which includes communicable diseases, non-communicable diseases, perinatal and maternal disorders, as well as injury-related disorders (Mayosi, Flisher, Lalloo, Sitas, Tollman & Bradshaw, 2009). The quadruple burden of disease has led to an increase in the proportion of individuals with acquired hearing impairment as a consequence of treatments that are ototoxic. More specifically, medications used to treat some communicable diseases [such as drug-resistant tuberculosis (DR-TB) and some non-communicable diseases (such as cancer and hypertension)] have been shown to be ototoxic in nature (Harris, Peer, & Fagan, 2012; Whitehorn, Sibanda, Lacerda, Spracklen, Ramma, Dalvie et al, 2014).

The Health Professions Council of South Africa (HPCSA) and its' professional boards have to ensure sound professional and ethical practices are maintained for the delivery of health care services to the South African public. There are currently no national guidelines for practitioners on the standards, competence, care and conduct for the management of patients who are at risk of ototoxic effects. It is with the aim of protecting the public and guiding the professions that the Professional Board for Speech, Language and Hearing Professions of the HPCSA sets out this clinical guideline on audiologic management of individuals receiving ototoxic medication.

These guidelines are based on several existing protocols [such as the American Speech-Language Hearing Association (ASHA, 1994) and the American Academy of Audiology (AAA, 2009)]. Guidelines, such as ASHA (1994) have been validated by clinical research and served as benchmarks in the development of the South African guidelines. The current guidelines have been formulated specifically for the South African context and include the following areas: Auditory pharmacology, protocols for ototoxicity monitoring (taking into account levels of service delivery), roles and responsibilities of individuals involved in ototoxicity monitoring, management of patients with ototoxicity-induced hearing loss, as well as curriculum and training issues.

Rationale

Hearing impairment is a highly prevalent societal problem and it is one of the biggest contributors to the burden of disabilities in the world. In 2015, hearing impairment affected more than 10% of the world population (Voss, 2016), and the second leading impairment by a number of individuals affected was hearing loss when chronic diseases were ranked globally (Voss, 2016). Within the South African context, some of the major health problems (communicable and non-communicable) require treatment that includes ototoxic medications (Harris et al, 2012; Whitehorn et al, 2012). This exposure to ototoxic medications has the potential to increase the overall number of individuals with acquired hearing impairment in the country. It is therefore important that ototoxicity management becomes an integral component of the treatment of these patients.

Ototoxicity management as envisioned in these guidelines is recommended for all patients who are being treated with medication that may have an ototoxic effect, to ensure:

1. Early detection of changes in hearing thresholds so that alterations in the treatment regimen may be considered by the medical doctor.
2. Appropriate audiologic intervention is provided where a disabling hearing impairment is diagnosed (AAA, 2009).

The evidence suggests a variable relationship between medication administration parameters such as dose, treatment duration, and blood serum concentration and the likelihood of developing ototoxic effects (Fausti, Frey, Henry, Olson & Schaffer, 1993; Whitehorn et al, 2014). It is therefore difficult for the attending medical doctor to rely solely on medication administration factors to predict the risk of ototoxicity (ASHA, 1994). Consequently, prospective assessments of hearing status for all individuals on treatment that includes ototoxic medications remain the only reliable method for early detection of change in hearing thresholds prior to the presentation of symptomatic hearing loss (Konrad-Martin, Gordon, Reavis, Wilmington, Helt & Fauti, 2005; ASHA, 1994).

Ototoxicity management is grounded on the twin principles of early identification and early intervention to decrease the burden of disease and maintain quality of life.

Position Statement

It is the position of the Professional Board for Speech, Language and Hearing Professions of the Health Professions Council of South Africa that hearing loss caused by ototoxic medications must be prevented. Therefore, the Professional Board of Speech Language and Hearing Professions recommend prospective monitoring of hearing thresholds of all patients receiving ototoxic therapy/treatment. The professional board also acknowledges that there will be some instances where ototoxic hearing loss cannot be prevented. In such cases, rational clinical-risk evaluations must be undertaken (Cianfrone, Pentangelo, Cianfrone, Mazzei, Turchetta, & Orlando, 2011) to weigh the need for continuing with prescribed treatment against the risk of permanent hearing loss and the implications of such disability (Petersen & Rogers, 2015).

While all individuals being treated with ototoxic medications are potentially at risk of developing hearing loss as a result of their treatment, children (≤ 5 years old) and elderly patients have been shown to be especially vulnerable to ototoxic effects of their treatment (Li, Worner & Silner, 2004). Furthermore, impact of ototoxic hearing loss has far reaching negative consequences in children when compared to other patient groups because it can impact negatively on their speech - language development, social-emotional achievements and academic achievements (McKay, Gravel & Tharpe, 2008). Therefore, children ≤ 5 years must be prioritized for ototoxicity management.

These guidelines advocate for patient-centred services that are responsive to the preferences, needs and values of patients and their families. Furthermore, those using these guidelines should be mindful of the following dimensions which form the core of patient-centred care; respect, emotional support, physical comfort, information and communication, continuity and transition, care coordination, involvement of family and carers and access to care (Gerteis, Edgman-Levitan Daley & Delbanco, 1993). It is also hoped that practitioners using these guidelines will embrace a culture of evidence-based health care i.e. lifelong, self-directed learning in which caring for the health of the public inspires the need for the latest important information (using the best available research evidence) about clinical and other health issues, (Centre for Evidence-based Health Care, 2015).

Finally, ototoxic management as envisioned in these guidelines should adopt a programmatic approach grounded in core principles of inter-professional collaboration and practice (Bridges, Davidson, Odegard, Maki & Tomkowiak, 2011). These professional board guidelines therefore recognise that the lack of collaboration between different professionals when working with patients predisposed to ototoxic hearing loss could undermine the quality of care they receive.

Audiologists by virtue of their professional training will be expected to design, implement and manage ototoxicity management programmes as well as implement appropriate aural rehabilitation interventions for patients who end up with hearing loss. Where appropriate the audiologists must

train other health care workers to conduct/assist in ototoxicity monitoring as well as provide regular health education activities for both patients and other health care workers to motivate them to take ototoxicity management seriously.

Background

Ototoxicity can be defined as the functional impairment and cellular degeneration of the tissues of the inner ear caused by therapeutic agents, resulting in loss of hearing and/or vestibular function (Rybak & Ramkumar, 2007). It can be a result of an exposure to occupational and/or environmental ototoxins, however, the bulk of ototoxicity cases are due to drug therapy (WHO, 1994). Regardless of the source/cause of ototoxicity, damage to cochlear and vestibular end organs is usually permanent (and or irreversible) except in the case of non-steroidal anti-inflammatory drugs and loop diuretics (Schacht, 2007). It is therefore important that this information is communicated to all patients who are being treated with ototoxic drugs as part of patient counselling before and during treatment.

Over 200 medications commonly prescribed can have adverse ototoxic effects on the inner ear mechanism (cochlea). Common symptoms of ototoxicity due to anti-neoplastic agents (platinum compounds) and aminoglycosides are; tinnitus and high frequency sensorineural hearing impairment ranging from mild to profound hearing impairment that progresses towards the lower frequencies (Rybak & Ramkumar, 2007). The hearing impairment is usually bilateral and often symmetrical. It is also permanent and usually irreversible (Rybak & Ramkumar, 2007).

For salicylates, NSAIDs, Loop diuretics and quinine, clinical manifestation of ototoxicity has been shown to be predominantly bilateral SNHL, mostly transient, starting in the high frequencies (could also be flat) and high frequency tinnitus (salicylates). The most distinctive characteristic of ototoxic effects from these classes of drugs is that the hearing loss is usually reversible when the drug clears from the blood with the exception of patients with compromised renal function or patients who received high doses of the drug. Loop diuretics have also been shown to potentiate (i.e. increase the risk) the ototoxic effect of other drugs (Rybak, 1992).

Ototoxicity can occur after a single dose of ototoxic medication (Vasques & Mattucci, 2003) and may occur within hours or within days of treatment (Rybak & Ramkumar, 2007.; Fausti, Henry, Schaffer, Olson, Frey & McDonald, 1992). Vasques and Mattucci (2003) report that agents that are toxic to the cochlea have a distinct pattern of damage; whereby the outer hair cells in the basal turn of the cochlea are destroyed, which causes a high-frequency sensorineural hearing loss and may affect speech

comprehension (Duggal & Sarkar, 2007). The pattern of damage progresses through the cochlea and later a flat sensorineural hearing loss occurs (Vasques & Mattucci, 2003).

These agents do not only damage cochlea hair cells but also vestibular hair cells, with damage continuing for weeks after discontinuation of treatment (Vasques & Mattucci, 2003). In some patients decrease in hearing sensitivity may continue beyond the end of treatment, including patients who did not exhibit a hearing loss at the end of treatment (Kolinsky, Hayashi, Karzon, Mao & Hayashi, 2010). This phenomenon was referred to by Kolinsky et al. (2010) as a late onset hearing loss, which refers to a significant change in hearing thresholds, six months after the end of treatment. Taking the above into account, it is recommended that long term follow up of patients who are being treated with platinum derivative drugs and aminoglycosides be considered, since patients being treated with these chemotherapeutic agents could end up with undiagnosed hearing loss and the accompanying psychosocial and other consequences (Al-Khatib, Cohen, Carret & Daniel, 2010).

1. CATEGORIES OF OTOTOXIC DRUGS

There are a range of drugs that are ototoxic in nature. The table below provides information reflecting current known ototoxic drugs according to category and class. Audiologists must stay abreast of developments in the pharmacologic management field. The impact of ototoxic drugs (reversible vs irreversible) is dependent on presenting risk factors of each patient.

Table 1: Table of Ototoxic Medications

Category of Drug	Class of Drug	Subclass of Drug	Examples of Drug(s)	Ototoxic Side effects of drugs			
				Hearing Impairment		Tinnitus	Vertigo/Dizziness
				Reversible	Irreversible		
Anti-Infective	**Antibiotics**	**Aminoglycosides**	Amikacin		**X**	**x**	**X**
			Gentamicin		**X**		**X**
			Netilmicin		**X**	**X**	**X**
			Neomycin		**X**		
			Tobramycin		**X**	**X**	**X**
		Glycopeptides	Vancomycin		**X**	**X**	
		Macrolides	Erithromycin	**X**			**X**
			Azithromycin	**X**		**X**	**X**
			Clarithromycin	**X**		**X**	**X**
		Quinolones	Ciprofloxacin			**X**	**X**
			Levofloxacin				**X**
			Ofloxacin			**X**	**X**
			Norfloxacin			**X**	**X**
		Penicilins	Amoxicillin				**X**
			Piperacillin				**X**
		Cephalosporins	Cefpodoxime			**X**	**X**
			Cefadroxil				**X**
			Ceftazidime				**X**
			Cefixime				**X**
			Cefalexin				**X**
			Cefaclor				**X**
			Cefazolin				**X**
			Ceftriaxone				**X**
			Cephradine				**X**
		Other	Tetracyclines			**X**	**X**
			Teicoplanin			**X**	**X**
			Colistin				
			Co-trimoxazole			**X**	**X**
			Linezolid			**X**	**X**
			Metronidazole				**X**
			Tinidazole				**X**
			Clindamycin				**X**

			Pentamidine				**X**
	Antivirals		Ganciclovir			**X**	**X**
			Zalcitabine			**X**	**X**
			Ribavirin + interferon				
			Acyclovir				**X**
			Zidovudine				**X**
			Amantadine				**X**
			Ritonavir				**X**
			Lopinavir				**X**
			Indinavir				**X**
	Antifungals		Amphotericin B			**X**	
			Flucytosine				**X**
			Fluconazole				**X**
			Itraconazole				**X**
			Terbinafine,				**X**
			Griseofulvin				**X**
	Antimalarials		Chloroquine	**X**			
			Mefloquine	**X**		**X**	**X**
			Quinine	**X**		**X**	**X**
			Artemether and Lumefantrine				
	Anti-tuberculosis		Capreomycin		**X**	**X**	
			Isoniazid				**X**
			Rifampicin				**X**
			Cycloserine				**X**
	Anthelminthic		Piperazine				**X**
Chemotherapeutic Agents	**Cytotoxics**	**Platinum compounds**	Cisplatin		**X**	**X**	**X**
			Carboplatin		**X**	**X**	
			Oxaloplatin		**X**		
		Vinca alcaloids	Vincristine		**X**		**X**
			Vinblastine		**X**		
		Antimetabolites	Capecitabine				**X**
			Methotrexate				**X**
			Cytarabine				**X**
		Others	Etoposide				**X**

			Hydroxyurea				X
			Procarbazine				X
			Docetaxel				X
Analgesics	**NSAIDs**		Aspirin	X		X	X
			Indomethacin	X		X	X
			Ibuprofen	X		X	X
			Diclofenac	X		X	X
			Sulindac	X		X	X
			Naproxen	X		X	X
			Celecoxib	X		X	X
			Mefenamic acid	X			X
Cardiac Drugs	**Diuretics**	**Loop Diuretics**	Furosemide	X		X	X
			Bumentanide	X			X
			Torasemide	X		X	X
		Carbonic anhydrase inhibitor	Acetazolamide	X		X	X
			Dorzolamide				X
		Potassium sparing diuretic	Amiloride			X	X
			Spironolactone				X
		Thiazides	Indapamide				X
	Beta blockers	**Beta-Blockers Cardio selective**	Metoprolol	X		X	X
			Atenolol	X			X
			Bisopralol	X			
		Non-Selective	Timolol			X	X
			Propranalol				X
			Sotalol				X
		Alpha and Beta-Blocking Agents	Labetolol				X
			Carvedilol				X
	ACE inhibitor		Enalapril			X	
			Captopril				X
			Perindopril				X
			Lisinopril				X
	AT-II receptor antagonist		Irbesartan			X	
			Losartan				X
			Candesartan				X
			Valsartan				X

	Antiarrhythmic agents	**Class 1a**	Disopyramide			**X**	**X**
			Quinidine			**X**	**X**
		Class 1c	Flecainide			**X**	**X**
			Digoxin				**X**
		Class III	Amiodarone				**X**
		Other cardiac preparations	Adenosine				**X**
	Calcium channel blockers	**Dihydropyridine**	Nimodipine			**X**	
			Nicardipine			**X**	
			Amlodipine				**X**
			Nifedipine				**X**
		Non-dihydropyridine	Verapamil				**X**
			Diltiazem				**X**
	Organic Nitrates		Isosorbide mononitrate				**X**
			Glyceryl trinitrate				**X**
Neurologic drugs	**Anticonvulsant**		Sodium valproate				**X**
			Carbamazepine			**X**	**X**
			Phenytoin				**X**
			Gabapentin				**X**
			Lamotrigine				**X**
			Ethosuximide				**X**
	AntiParkinsonian Agents	**COMT-inhibitor**	Entacapone				**X**
		MOA type B-inhibitor	Selegiline				**X**
		Anticholinergic Agents	Biperiden				**X**
		Dopamine Agonists	Bromocriptine				**X**
			Pramipexole				**X**
	Antidepressants	**Tricyclic agents**	Imipramine			**X**	**X**
			Amitriptyline			**X**	**X**
		SSRIs	Citalopram			**X**	**X**
			Fluoxetine				**X**
			Sertraline				**X**
		MAO type A inhibitors	Moclobemide				**X**

	Antimigraine Preparations	**5HT-1_B/1_D antagonist**	Almotriptan			**X**	**X**
			Sumatriptan				**X**
	Hypnotics	**Benzodiazepine**	Clonazepam				**X**
			Lorazepam				**X**
			Diazepam				**X**
			Midazolam				**X**
			Alprazolam				**X**
		Other hypnotics	Zopiclone				**X**
			Zolpidem				**X**
	Antipsychotics	**Atypical**	Quetiapine				**X**
			Olanzapine				**X**
			Clozapine				**X**
		Phenothiazines with Aliphatic Side-Chain	Chlorpromazine				**X**
		Butyrophenone Derivative	Haloperidol				**X**
	Drugs for dementia		Memantine				**X**
			Galantamine				**X**
			Donepezil				**X**
	Muscle Relaxant		Dantrolene				**X**
			Baclofen				**X**
Endocrine & Metabolic drugs	**Hypoglycaemic agents**		Glipizide				**X**
			Glimepiride				**X**
			Pioglitazone				**X**
			Insulin				**X**
	Corticosteroids	**Glucocorticoids**	Dexamethasone				**X**
		Mineralocorticoids	Fludrocortisone				**X**
	Bisphosphonates		Pamidronic acid				**X**
			Zoledronic acid				**X**
Gastro intestinal drugs	**Antiemetic agents**		Metoclopramide				**X**
			Ondansetron				**X**
	Antiulcer	**H2 antagonist**	Ranitidine				**X**
			Cimetidine				**X**
		Proton pump	Omeprazole				**X**
			Pantoprazole				**X**

Serum Lipid-Modifying Agents	**Lipid regulating**	**Fibrates**	Fenofibrate				**X**
		HMG-CoA Reductase Inhibitors	Simvastatin				**X**
Others	**Immunosuppressant**		Tacrolimus			**X**	**X**
			Azathioprine				**X**
	Anti-rheumatoid agents	**Disease Modifying Anti-Rheumatic Drugs (DMARDs)**	Hydroxychloroquine			**X**	
			Leflunomide				**X**
			Etanercept				**X**
	Local anaesthetics		Ropivacaine				**X**
			Lignocaine			**X**	**X**
	Anti-gout	**Preparation inhibiting uric acid production**	Allopurinol				**X**
	Antihistamines	**Sedating**	Chlorpheniramine			**X**	**X**
			Cyclizine				**X**
			Promethazine				**X**
		Non-Sedating	Cetirizine				**X**
			Fexofenadine				**X**
	Antimuscarinic agents		Atropine				**X**
			Hyoscine butylbromide				**X**
			Dicycloverine				**X**
	β_2 Receptor agonist		Salbutamol				**X**
			Salmeterol				**X**
	Leukotriene receptor antagonist		Montelukast				**X**

2. SIGNS AND SYMPTOMS OF OTOTOXICITY

Audiologists need to be aware of the signs and symptoms of ototoxicity to educate patients during pre-treatment counselling. Signs and symptoms include:

- Tinnitus
- Hearing loss
- Distorted hearing
- Hyperacusis and loudness recruitment
- Aural fullness
- Difficulty understanding speech in noise
- Vertigo/Dizziness
- Nausea and/or vomiting

• PREDISPOSING FACTORS

Audiologists should take cognisance that within the South African context, socio-demographic conditions exacerbate the following known risk factors. All patients on ototoxic medication presenting with these risk factors must be monitored.

- Type of drug
- Drug interactions (with other toxins)
- High cumulative dose
- Mode/method of administration i.e. rapid intravenous bolus injections
- Length/duration of treatment
- Concurrent use of other ototoxic medications
- Age extremes i.e. very young and advanced age
- Renal dysfunction and/or Hepatic dysfunction
- Noise exposure
- Pre-existing hearing loss
- Anaemia
- Hypo-albuminemia
- Prior cranial irradiation
- Predisposing genetic factors
- Sex i.e. females are at higher risk

- ## ROLE OF THE AUDIOLOGIST

Audiologists design and implement ototoxicity management programs within the International Classification of Function and Disability as well as the Primary Healthcare frameworks. Successful implementation and sustainability of such programs requires good collaboration between the patient and their family with the inter-professional team. This team includes the medical doctor, nurse, pharmacist, clinical psychologist, occupational therapist, physiotherapist, social worker, and speech therapist.

Audiologists must:

1. Conduct an analysis to determine the need for an ototoxicity management program at the health facility
2. Design, implement and quality assure ototoxicity management programs
3. Establish a protocol comprising of referral criteria and referral pathways
4. Ensure that ototoxic monitoring resources are in place including appropriate infrastructure, equipment and consumables, educational materials, and personnel.
5. Educate, train (see training programme) and oversee personnel who conduct ototoxicity monitoring.
6. Upon early detection of ototoxic signs, implement an intervention program to prevent exacerbation.
7. Assess and manage individuals presenting with ototoxic symptoms
8. Implement appropriate management (rehabilitation) for patients who end up with disabling ototoxic hearing loss.
9. Record a minimum data set and establish a data base for monitoring and service development

Table 2: Inter-professional team collaboration to Ototoxicity Management

Healthcare Worker	Collaboration
DOCTOR	• Assess patients for co-morbidities and request for baseline assessments • Initiate treatment regime for patients • Review treatment of patient in response to the identification of ototoxicity
NURSING STAFF	• Monitor ototoxic signs and symptoms and refer when appropriate
PHARMACIST	• Raise awareness of potential for ototoxicity of drugs prescribed • Make recommendations for otoprotective treatments as well as less ototoxic drug options
CLINICAL PSYCHOLOGIST	• Manage patients' psychological well-being when dealing with ototoxic impairment
OCCUPATIONAL THERAPIST	• Manage return to education and work
PHYSIOTHERAPIST	• Provide inter-professional vestibular rehabilitation
SOCIAL WORKER	• Assist with linking to available resources in the community
SPEECH THERAPIST	• Communication intervention

- ## PRINCIPLES

The following key principles of an ototoxicity management programme should be underpinned by the PHC and the ICF frameworks.

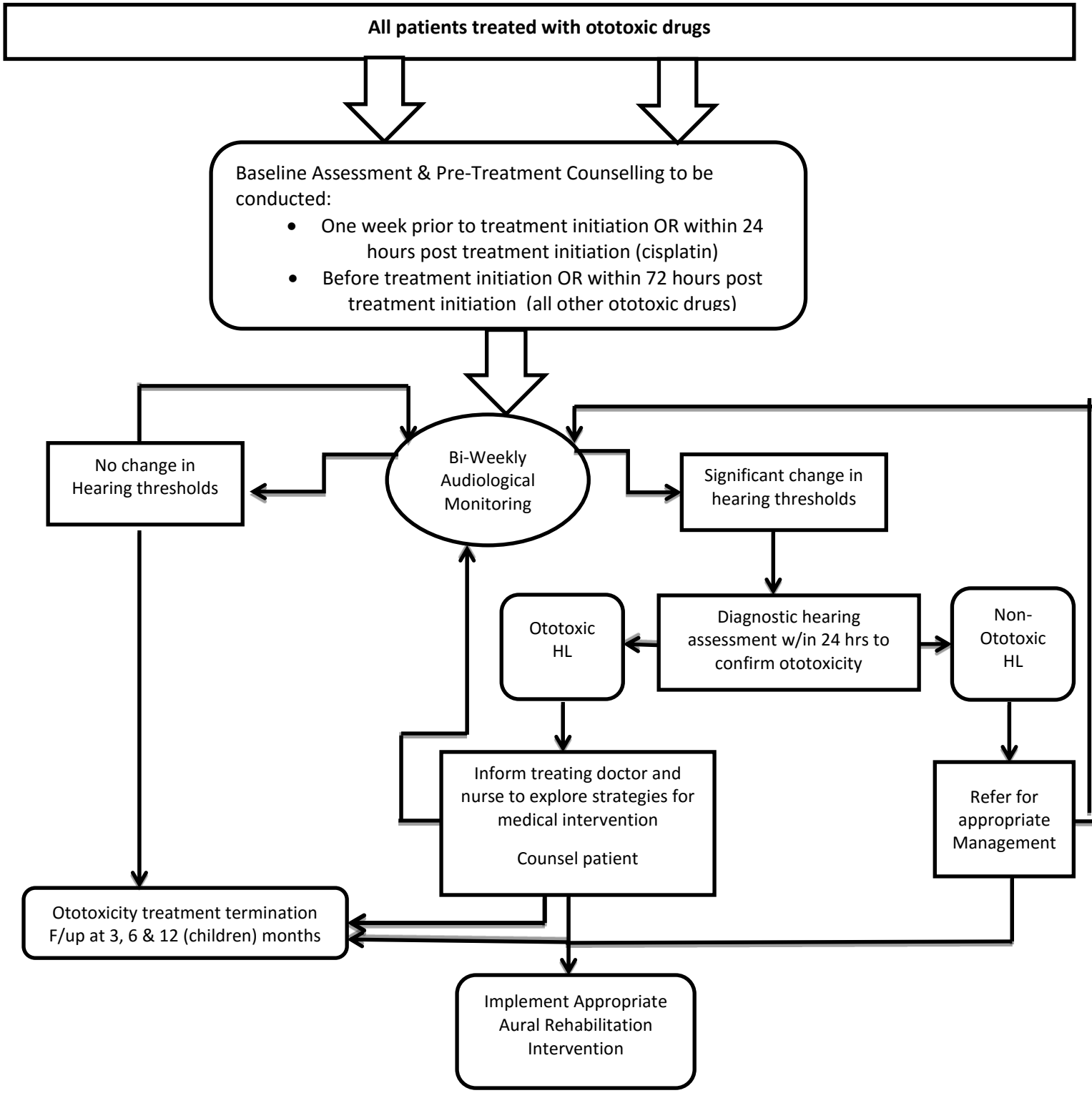
All patients on ototoxic medications:

- Are afforded access to early detection and intervention to prevent hearing loss and vestibular signs.
- Are afforded access to an effective referral system. The referral system is efficient and prompt to medical and audiologic evaluations to confirm the presence of ototoxicity and to prevent exacerbation of ototoxic signs and symptoms
- Are provided with access to aural rehabilitation which should include issuing of assistive devices
- Are empowered to identify and monitor symptoms of ototoxicity for early detection
- Are provided with intervention that is family centred and asset-based, built on informed choice and recognition of and respect for cultural beliefs and traditions of families.
- Must be afforded access to services which are based on current evidence, adhere to appropriate infection control standards, and are guided by human rights and ethical principles.
- Are managed within a collaborative inter-professional seamless system of care
- Assessed using clinical protocols and equipment that are sensitive to changes in the basal (high frequency) region for earliest detection of ototoxic damage. Monitoring tests must be sensitive to ototoxic damage (high hit rate), specific (low false positive rate) and reliable (low test retest variability) across measurements.
- Must have the first audiological assessment before the administration of ototoxic medications.
- Should be monitored at intervals which are drug specific to allow for earliest detection
- Must be provided with post-treatment audiologic evaluation follow-up for at least 6 months (12 months in the case of children ≤5 years old)

THE OTOTOXICITY MANAGEMENT PROGRAMME

The ototoxicity management programme is based on the principles mentioned above. The programme outlined (see Figure 1) can be implemented at all levels of service delivery (unless otherwise specified).

Figure 1: Ototoxicity monitoring and management



Essential Components of an Audiological Ototoxicity management programme

The following components are basic elements of an ototoxicity monitoring programme (ASHA, 1994):

1. ***Pre-treatment counselling regarding risk of ototoxic effects from the treatment***

   Once identified, all patients whose treatment includes (or will include) ototoxic medications should be counselled regarding the ototoxic effects of those drugs prior to initiation of treatment. At the pre-treatment counselling the patient should be educated to monitor for signs and symptoms, predisposing factors and referral pathways.

2. ***Timely identification of patients at risk of developing ototoxicity***

All patients whose treatment includes therapeutic drugs known or suspected to have ototoxic effects must be identified and baseline results obtained.

Baseline Measures

A baseline audiogram needs to be comprehensive and must show evidence of a thorough assessment because it serves as a pre-treatment record to which monitoring thresholds (during and post treatment) will be compared, in order to determine whether changes in hearing sensitivity have occurred. The time for obtaining a baseline varies for different medications (refer to Figure 1).

A baseline audiogram must (at the minimum) include:

- Case history,
- Otoscopic examination,
- Pure-tone audiometry (air conduction including frequencies; 250-8000Hz plus 9000 - 12500 Hz). For some groups of patients (e.g. children <5 years old and non-responsive patients), behavioural audiometry may not be feasible therefore distortion product otoacoustic emissions (DPOAE) should be used instead of pure tone audiometry.
- Diagnostic DPOAEs should be obtained at high frequencies i.e. ≥ 4kHz, include a minimum of 4 frequencies, and yield at least 2 replicable measurements with test-retest differences not exceeding ±7 dB (Beattie, Caldwell & Kenworthy, 2005) in one seating. An indication of an emission is an amplitude ≥ 6 dB above the noise floor. All testing procedures should be carried out bilaterally.

Patients who show abnormal audiometric (pure tone/DPOAE results must immediately be referred for a comprehensive diagnostic audiologic evaluation.

Adaptations of testing procedures: Testing procedures need to be adapted for patients who are unable to cope with a complete assessment due to various reasons such as illness, physical condition and age. Therefore, in these cases, the most crucial information from the assessment procedure should be obtained for baseline audiogram purposes. Efficient objective tests such as distortion product otoacostic emission (DPOAEs) and immittance testing as well as a reduced number of pure tone and high frequency thresholds selected for assessment (e.g. assess only frequencies 4,6,8,10, 12.5 kHz), can be prioritised in such instances. Upon improvement in the patient's condition and/or compliance with the testing procedure, more comprehensive assessment can be undertaken.

3. Monitoring Evaluations

Bi-weekly audiological monitoring should comprise:

- bilateral otoscopic examination
- bilateral pure tone air conduction testing, including frequencies 250-12500 Hz and 4000-12500 Hz (done on alternate visits).
- Bilateral DPOAEs

If hearing thresholds are worse relative to baseline audiogram results, a comprehensive audiological assessment should be carried out within 24 hours or before the next administration of ototoxic medication for the purpose of confirming hearing loss due to ototoxicity. A comprehensive assessment must include (at the minimum) the following test procedures:

- Adults: Case history, otoscopic examination, immittance testing, pure-tone audiometry (air conduction and bone conduction; and include 250-8000Hz plus 9000 - 12500 Hz).
- ≥ 20 dB pure tone threshold shift at a single frequency, ≥ 10 dB shift at 2 consecutive frequencies or threshold response shifting to "no response" at three consecutive frequencies confirmed with a retest on the same day. (ASHA, 1994)

- Children <5 years old and non-responsive patients: DPOAEs should be done.
- A reduction in DPOAE amplitude ≥ 6 dB in at least 3 frequencies should be considered to indicate a significant change in patient auditory status.
- If DPOAEs are absent, other measures that can give an indication of hearing sensitivity such as Auditory Brainstem Response (ABR) and Auditory Steady State Response (ASSR) should be used.

Detection of hearing threshold shift: As soon as there are indications that the patients' hearing thresholds are deteriorating following treatment, the Audiologist must inform the prescribing medical doctor immediately and different options for modifications of patients' treatment must be explored. Possible treatment modification includes:

- reducing the dose of the drug administered, and if feasible,
- changing the dosage schedule or,
- switch to a less ototoxic regimen

  (Vasques & Mattucci, 2003; Konrad-Martin et al, 2005).

4. ***Criteria for Determining the Presence of an Ototoxic Shift and Grading Adverse Effects on Hearing Due to Ototoxicity***

Criteria for determining a shift: Criteria for determining changes in the patient's hearing due to treatment must be decided beforehand. Such criteria must at the minimum convey the following; a standard way of documenting a shift in patient's hearing thresholds and recommendation for audiologic intervention. The ASHA (1994) criteria for a threshold shift is recommended in these guidelines. This criteria (and must be confirmed via a re-test during the same day) states the following: *≥ 20 dB pure tone threshold shift at a single frequency, ≥ 10 dB shift at 2 consecutive frequencies or threshold response shifting to "no response" at three consecutive frequencies.*

Grading of severity: Once the presence of an ototoxic shift is identified as described above, the adverse effect on hearing ability needs to be graded in accordance with an adverse event scale, specific to hearing. There are several grading criteria that can be used for this purpose e.g. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4, the ASHA (1994) criteria, etc.

For the current guidelines, we recommend using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (NCI, 2006). The NCI CTCAE ototoxicity grades for children (adult guidelines are stipulated in parentheses) include:

- **GRADE 1:** Threshold shift or loss of 15- 25dB relative to baseline, averaged at two or more contiguous frequencies in at least one ear *(same for adults).* In the case where baseline evaluation has not been carried out a paediatric patient, it is assumed that baseline thresholds are <5dBHL.

- **GRADE 2:** Threshold shift or loss of >25 – 90dB, averaged at two contiguous test frequencies in a least one ear *(same for adults)*

- **GRADE 3:** Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g. >20dB bilateral hearing loss in the speech frequencies; 30dB unilateral hearing loss; and requiring additional speech language related services). *(Adults: >25 – 90dB, averaged at three contiguous test frequencies in at least one ear).*

- **GRADE 4:** Indication for cochlear implant and requiring additional speech-language related services *(Adults: profound bilateral hearing loss >90dBHL)*

The criteria for identifying ototoxic shift as well as grading adverse effects on hearing can be applied to conventional as well as high frequency audiometry (HFA), as this allows for earlier identification of sensitivity to ototoxicity (AAA Position Statement, 2009).

5. ***Follow-up evaluations***

Upon completion of an ototoxic treatment schedule, a complete pure tone air conduction and high frequency threshold audiogram should be obtained. If a change in hearing thresholds is noticed, audiological monitoring should be repeated once a month until hearing thresholds stabilize and no further change in hearing threshold is observed.
Audiological re-evaluation should then take place at approximately three and six months post ototoxic treatment. These evaluations provide information relating to the progression of hearing loss or recovery thereof, post ototoxic treatment.

In the case of a child (≤ 5 years old) follow-up audiological testing after the completion of an ototoxic treatment regime should occur at the point of completion of treatment, at three months, six months as well as at one-year post treatment.

VESTIBULAR TOXICITY MONITORING PROGRAMME

Vestibular deficits could result from treatment with ototoxic medications (Day, Lue, Yang, & Young, 2007) and patients should be managed accordingly. There are no widely accepted guidelines in use for monitoring vestibular deficits on patients who are being treated with ototoxic medications (AAA, 2009).

Available methods used to evaluate vestibulotoxicity are not always sensitive enough to show subtle changes (Halmagyi, Fattore, Curthoys & Wade, 1994). Vestibular assessment is generally challenging

in most ill patients (Edson & Terrell, 1999) and therefore makes it difficult to monitor patients at regular intervals.

The following references are recommended for clinicians involved in monitoring for ototoxicity-induced vestibular deficits in patients; Handelsman (2007) and Black and Pesznecker (2007). Vestibular toxicity monitoring includes:

- A baseline assessment prior to initiation of treatment and that must include (at the minimum) the following 'bedside' tests; head-thrust and dynamic visual acuity (Black & Pesznecker, 2007)
- Monitoring using dynamic visual acuity test at least once during treatment or as soon as the patient reports vestibular symptoms (whatever comes first)
- Assessment using head-thrust and dynamic visual acuity after termination of treatment (see Table 3)
- All patients whose vestibular assessment results from these two tests suggest ototoxicity must be referred for a comprehensive vestibular assessment.at the appropriate level of care.

Table 3: Criteria for determining the presence of a vestibulotoxic deficit (Black and Pesznecker, 2007; Rogers and Petersen, 2011).

Test	Aim of the evaluation	Results if vestibulotoxic	Notes
Head thrust test	Establish if VOR input is present and normal	Will have saccades in both directions	Need appropriate training; sensitivity of 84-100% if vestibular hypofunction
Dynamic Visual Acuity Test	Establish if patient has early oscillopsia	Will have decline in vision when head is moving	Snell chart/similar required

VOR = Vestibular-ocular-reflex

MEDICAL AND AUDIOLOGICAL INTERVENTION AND MANAGEMENT – AURAL REHABILITATION

Medical management

As far as medical intervention is concerned, audiologists, physicians, and pharmaceutical companies should intensify their efforts toward development of nonototoxic therapeutic agents with systematic trials to ensure that enough evidence is gathered for proper benefit/risk evaluations. Moreover,

increased efforts should also be placed on the development of and the increasing of the evidence-base for otoprotective agents which can serve as a preventative measure where ototoxic medication cannot be avoided. Otoprotective agents in the form of compounds such as angiotensin-converting enzyme magnesium, D-methionine (sulfur-containing compound), and L-N-acetylcysteine should be investigated. Furthermore, restorative care which involves regeneration of hair cells damaged by ototoxic drugs through the use of neurotrophins also requires careful consideration. These strategies are especially important in developing country contexts for strategic long-term financial savings which will be made by eliminating potential litigation costs, amplification devices costs, rehabilitation costs, as well as social grants linked costs because of the economic impact associated with the consequent unemployment of the affected individual. (Khoza-Shangase, 2017)

Audiological Management

Audiological Intervention for patients with cochlear/vestibular deficit following treatment with ototoxic medications:

Hearing aid fitting

Hearing aid selection should provide suitable amplification in accordance to hearing thresholds and hearing aid fittings should be verified and validated wherever possible and adjusted in accordance to a change in hearing thresholds when applicable.

Tinnitus

Tinnitus retrainers or maskers should be explored and tinnitus therapy provided. Referrals to other medical professionals (such as psychologists) are necessary if further assistance is required for the management of tinnitus.

Cochlear Implantation

The suitability for a cochlear implant needs to be discussed with relevant cochlear implant team, patient and families.

Communication strategies training and speech reading

It is essential that patients diagnosed with hearing loss due to ototoxicity are educated on skills and techniques that can be employed both as a listener and as a speaker in any communication environment that may assist them to partake in conversation more comfortably and smoothly; regardless of whether or not the patient is making use of an assistive listening device.

Counselling

It is the responsibility of the treating audiologist to explain and validate information that pertains to audiological status of the patient as well as the aural rehabilitation thereof.

Vestibular Management

Vestibular rehabilitation consists of the following (Holmes and Rodriguez, 2009, as cited in Schow and Nerbonne*):*

- Multidisciplinary involvement (usually with a Physiotherapist)
- Thorough case history and detailed report concerning symptoms (onset, duration, frequency, severity)
- Physical assessment related to range of movement and strength
- Combined visual/motion assessments
- Use of the Dizziness Handicap Inventory (DHI) (**Caution:** DHI scores are poorly correlated to the quantitative testing, AAA, 2009)
- Implement a set of well-constructed exercises that improve balance and gait through muscle strength and retraining

A comprehensive discussion of general principles and clinical methods in balance assessment and rehabilitation are provided by Jacobson and Shepherd: Balance Function Assessment and Management (2008).

Strategies to Minimize Ototoxic Effects

Certain ototoxic risk factors are linked with genetic predisposition and age, and therefore ototoxic side effects cannot always be prevented, however some indicators which could contribute to minimising ototoxic side effects include:

- Patients should be made aware of the early warning signs of ototoxicity (e.g. dizziness, tinnitus, aural fullness, fluctuating hearing loss) and doctors to be informed of these symptoms immediately.
- Patients should inform doctors of any existing hearing or balance issues prior to commencement of ototoxic treatment regime.
- Dosage instructions to be followed strictly as prescribed.
- Patients are to be kept hydrated during the course of ototoxic treatment.
- Patients are to avoid taking multiple ototoxic drugs simultaneously, if possible.
- Noisy environments are to be avoided for at least 6 months after completing ototoxic treatment regime.

- Frequent follow-up with an audiologist for hearing threshold monitoring purposes should be embraced.

QUALITY INDICATORS

Monitoring and evaluation of the effectiveness and quality of the ototoxicity monitoring services is essential. The following are indicators of quality and effectiveness of an ototoxicity monitoring programme which must be recorded as minimum data sets:

- Timely assessment and monitoring (e.g. Aminoglycoside treatment within 72 hrs of treatment)
- Timely establishment of a rehabilitation plan (inter-professional team) within 1 month of diagnosis of disabling hearing loss
- Documentation of number/percentage of patients on ototoxic medication who have been assessed for the purpose of ototoxicity monitoring within a given time period
- Documentation of the number/percentage of patients monitored for ototoxicity who develop a hearing loss
- Documentation of potential disabling hearing losses (percentage) prevented through different medical interventions/strategies
- Documentation of Rehabilitation services provided (quantity + nature of rehabilitation) to patients who ended up with hearing loss (percentage) following treatment with ototoxic medications

Considerations for variability in context

All audiological evaluations should be conducted in a sound-treated booth. In cases where patients are unable to move from the ward, bedside audiological assessment using portable audiometers, in a quiet environment (Vasques & Mattucci, 2003). Ambient noise within the ward may affect the testing reliability of low frequency thresholds; however, higher frequencies appear to be less influenced. There are no documented standard permissible ambient noise levels in which audiometric testing can be conducted, however, sound-level measurements in such cases may be helpful when comparing monitoring assessments to the baseline audiogram, as ambient noise levels may vary within the ward between each assessment. Noise-attenuation headphones must be used when assessing patients outside of an audiometric booth and the assessment must also include the highest frequency that could be measured with the available equipment.

There are also diagnostic audiometers that do not require audiometric booths and utility of such equipment must be explored in ototoxicity monitoring.

REFERENCE LIST

1. Al-Khatib, T., Cohen, N., Carret, A., & Daniel, S. (2010). Cisplatin ototoxicity in children, long-term follow-up. International Journal of Paediatric Otorhinolaryngology, 74, 913-919. doi 10.1016/j.ijporl.2010.05.011

2. American Academy of Audiology (2009). Position statement and clinical practice guidelines: Ototoxicity monitoring. Available from: www.audiology.org/resources/documentlibrary/Documents/OtoMonPositionGuideline.pdf

3. American Speech-Language-Hearing Association (1994). Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. ASHA,36 (Suppl.12)11–19.

4. Beattie, R.C., Caldwell, S., & Kenworthy, O.T. (2005). Variability in DPOAE Measurements and Its Relation to the Magnitude and Frequency of Occurrence of Peaks in the DPOAE-Gram. The Australian and New Zealand Journal of Audiology, 27 (2):113-130.

5. Bluestone C. D. (2003). Paediatric Otolaryngology (4th Ed.). United States of America: BC Decker Inc.

6. Bridges, D.R.; Davidson, R. A.; Odegard, P.S., Maki, I.V. & Tomkowiak, J. (2011). Inter-professional Collaboration: Three Best Practice Models of Inter-Professional Education. Medical Education Online 2011, 16: 6035 - Doi: 10.3402/meo.v16i0.6035

7. Centre for Evidence-based Health Care, (2015). Evidence-based Health Care (definition). Available at: http://www.cebhc.co.za/. Accessed January 2015.

8. Cianfrone, G., Pentangelo, D., Cianfrone, F., Mazzei, F., Turchetta, R. & Orlando M. P. (2011). Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. Eur Rev Med Pharmacol Sci.;15(6):601601)

9. Cummingham, R. F. (2011). Otoacoustic Emissions: Beyond Newborn Hearing Screening. Retrieved from www.audiologyonline.com on the 30th January 2013.

10. Day, A. S.; Lue, J. H.; Yang, T.; & Young Y. H. (2007). Effect of intratympanic application of aminoglycosides on click-evoked myogenic potentials in guinea pigs. Ear Hear 28:18-25.

11. Duggal, P. & Sarkar, M. (2007). Audiologic Monitoring of Multi-Drug Resistant Tuberculosis Patients on Aminoglycoside Treatment with Long Term Follow-up. BMC, Ear, Nose and Throat Disorders, 7 (5).

12. Edson, R. S. & Terrell, C. L. (1999). The aminoglycosides. Mayo Clin Proc.; 74:519–528.

13. Fausti, S. A.; Henry, J. A.; Schaffer, H. I.; Olson, D. J.; Frey, R. H.; &, McDonald, W. J. (1992). High-frequency audiometric monitoring for early detection of aminoglycoside ototoxicity.J Infect Dis. 165(6):1026-32.

14. Fausti, S. A.; Frey, R. H.; Henry, J. A.; Olson, D. J., & Schaffer, H. I. (1993). High-frequency testing techniques and instrumentation for early detection of ototoxicity. J Rehabil Res Dev 30:333-341.

15. Fausti, S. A.; Henry, J. A.; Helt, W. J.; Phillips, D. S.; Frey, R. H.; Noffsinger, D.; Larson, V. D.; & Fowler, C. G. (1999). An individualized, sensitive frequency range for early detection of ototoxicity. Ear Hear,20(6):497–505.

16. Gelfand, S. A. (2009). The Acoustic Reflex. In Katz, J., Medwetsky, L., Burkard, R., and Hood, L (Eds.). Handbook of Clinical Audiology (6th Ed.) (pp.189-221). New York: Lippincott Williams & Wilkins.

17. Gerteis, M., Edgman-Levitan, S., Daley, J., & Delbanco, T. (1993) Through the Patient's Eyes:Understanding and Promoting Patient-Centered Care. San Francisco: Jossey-Bass,

18. Halmagyi, G. M.; Fattore, C. M.; Curthoys, I. S.; & Wade, S. (1994). Gentamicin vestibulotoxicity. Otolaryngol Head Neck Surg. 111:571–574.

19. Handelsman, J. A. (2007) Audiologic findings in vestibular toxicity. In KCM Campbell (Ed.), Pharmacology and Ototoxicity for Audiologists. Clifton Park, NY: Thomson/Delmar Learning, pp272-286.

20. Harris, T.; Peer, S.; & Fagan, J. J. (2012) Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting. J Laryngol Otol 126:548-551.

21. Holmes, A. E.; & Rodriguez, G. P. (2009). 'Cochlear Implants and Vestibular/Tinnitus Rehabilitation'. In Introduction to Audiologic Rehabilitation. R.L.Schow & M. A. Nerbonne (Eds.). MA: Pearson Education Inc.

22. Khoza-Shangase, K. (2017). Risk vs Benefit: Who assesses this in the management of patients on ototoxic drugs? Journal of Pharmacy and BioAllied Sciences, 9(3), 171-177

23. Kolinsky, D. C.; Hayashi, S. S.; Karzon, R.; Mao, J.; & Hayashi, R. (2010). Late onset hearing loss: A significant complication of cancer survivors treated with cisplatin containing chemotherapy regimens. Journal of Peadiatric Hematology/Oncology, 32, 119-123. Retrieved from http://xa.yimg.com/kq/groups/18817297/2145742899/name/deniz+tuz.pdf

24. Konrad-Martin, D.; Gordon, J. S.; Reavis, K. M.; Wilmington, D. J.; Helt, W. J.; & Fausti, S. A. (2005) Audiological Monitoring of Patients Receiving Ototoxic Drugs Perspectives on Hearing and Hearing Disorders: Research and Diagnostics. Vol. 9, No. 1, pp. 17-22

25. Li, Y.; Worner, R. B.; & Silber, J. H. (2004). Predicting cisplatin ototoxicity in children: The effect of age and the cumulative dose. European Journal of Cancer, 40, 2445-2451. Doi

26. Mayosi, B.M., Flisher, A.J., Lalloo, U.G., Sitas, F., Tollman, S.M., & Bradshaw, D. (2009). The burden of non-communicable diseases in South Africa. The Lancet, 374, 934-947.doi 10.1016/S0140-6736(09)61087-4

27. McKay, S.; Gravel, J. S.; & Tharpe, A. M. (2008). Amplification considerations for children with minimal or mild bilateral hearing loss unilateral hearing loss. Trends in Amplification, 12, 43-55. doi 10.1177/1084713807313570

28. National Cancer Institute (2006). Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. Available at: http://ctep.cancer.gov.

Accessed February 2015

29. Petersen, L. & Rogers, C. (2015). Aminoglycoside-induced hearing deficits-a review of cochlear ototoxicity. South African Family Practice, 1-6, http://dx.doi.org/10.1080/20786190

30. Rybak, L. P & Ramkumar, V. (2007). Ototoxicity Kidney International (2007) 72, 931–935; doi:10.1038/sj.ki.5002434

31. Rybak L. P. (1992) “Hearing: The effects of chemicals.” Otolaryngology—Head & Neck Surgery, 106(6):677–686, Available at: http://vestibular.org/ototoxicity#sthash.BNZ6bkaT.dpuf.

Accessed November 2014.

32. Schacht J. (2007). Aminoglycoside antibiotics. In: Campbell KCM, editor. Pharmacology and ototoxicity for audiologists. New York, NY: Thomson Delmar Learning; p. 163.

33. Stach, B. (1998). Clinical Audiology: An Introduction. California: Singular Publishing Group.

34. Vasques, R.& Mattucci, K. F. (2003). A proposed protocol for monitoring ototoxicity in patients who take cochleo- or vestibulotoxic drugs. Ear Nose Throat Journal.;82 (3):181-4.

35. Vaughn, N. E.; Fausti, S. A.; Chelius, S.; Phillips, D.; Helt, W.; & Henry, J. A. (2002). An efficient test protocol for identification of a limited, sensitive frequency test range for early detection of ototoxicity. Journal of Rehabilitation Research Development. Vol 39. No. 5. September/October.

36. Whitehorn, H.; Sibanda, M.; Lacerda, M.; Spracklen, T.; Ramma, L.; Dalvie, S. & Ramesar, R. (2014). High prevalence of cisplatin-induced ototoxicity in Cape Town, South Africa. South African MedicalJournal.;104(4):288-91

37. Wilmington, D. J.; Konrad-Martin, D. L.; Helt, W. J.; Dille, M. F.; Gordon, J. S.; & Fausti, S. A. (2011). Ototoxicity Monitoring: Program Approaches and Considerations. Seminars in Hearing, 32 (3).

38. World Health Organization (1994). Report of an Informal Consultation on Strategies for Prevention of Hearing Loss from Ototoxic Drugs. Available at http://www.who.int/pbd/deafness/ototoxic_drugs.pdf. Accessed on January 2015

- **APPENDICES**

Appendix A

Procedures for Baseline testing

Case History

An in-depth case history proves essential for the holistic management of ototoxicity. According to Vasques and Mattucci (2003) any one of the following factors may indicate a patient's risk of ototoxicity during a case history interview; previous use of ototoxic medication, current use of ototoxic medication, treatment courses greater than 14 days, a pre-existing hearing loss prior to treatment and renal dysfunction. Factors that are crucial to probe during every subsequent audiogram after the baseline audiogram include whether the patient experiences tinnitus, otalgia, otorrhea, vertigo or dizziness and the sensation of blocked ear(s) (Vasques & Mattucci, 2003). These symptoms should be reviewed during every visit and the patient should immediately report any onset of change in these symptoms (Vasques & Mattucci, 2003). The case history indicates the possible cause or contributing factors to the hearing loss.

Children are at a potential greater risk for ototoxicity than adults therefore when assessing paediatric patients, case history should also include questions pertaining to:

- the child's history of speech and language development
- the child's history of motor development
- any noticeable changes in the child's overall demeanour during ototoxic treatment

Otoscopic examination

The visual inspection should include examination of the head and neck area and otoscopic inspection of the ear canal and tympanic membrane (Bluestone, 2003). Conditions that warrant additional testing or medical referral include:

- Developmental defects
- Ear canal occlusion
- Ear canal inflammation
- Otorrhea (drainage from the ear)
- Foreign bodies in the ear canal
- Tympanic membrane abnormalities (perforation / inflammation)
- Abnormal landmarks or colour of the tympanic membrane

Immittance Audiometry

According to Stach (1998), immittance audiometry, including both tympanometry and acoustic reflex testing, is one of the most powerful tools available for the evaluation of auditory disorder and is recommended by Vasques and Mattucci (2003) to be included in the test battery protocol for an ototoxicity assessment. It serves at least three functions in an audiological assessment. It is sensitive in detecting middle ear disorder, it can be useful in differentiating cochlear from retrocochlear disorder and it is helpful in estimating the degree of peripheral sensitivity and is often used as cross check to pure-tone audiometry (Stach, 1998).

Distortion Product Otoacoustic Emissions (DPOAE)

According to Wilmington et al. (2011) patients may become unable to give reliable behavioural results as their treatment progresses; therefore, an objective measure of auditory function may be necessary. Wilmington et al. (2011) suggests that either an OAE or an ABR can be used. The advantages of OAE testing include good reliability, time efficacy, and portability (Wilmington et al., 2011). Moreover, OAEs are sensitive to outer hair cell function and therefore can alert the audiologist to early signs of hearing loss, due to ototoxicity (Wilmington et al, 2011; Cummingham, 2011).

OAEs prove to be an efficient objective assessment tool and therefore, OAEs are recommended in the diagnostic hearing assessment of children. However, OAE testing results reliability is affected by the presence of middle ear pathology. Pre-existing hearing loss highlights further restrictions in the use of OAE assessment in terms of monitoring purposes as initial OAE assessment results may be absent or limited due to pre-existing cochlear damage of outer hair cells. Therefore, OAE testing should not be conducted in isolation, but rather form one of the components within the audiological test battery for ototoxicity. OAEs have been shown to decrease simultaneously with changes in HFA thresholds and before changes appear in the conventional audiometric frequencies (AAA Position Statement, 2009).

Pure Tone Audiometry

As Gelfand (2009) explains, test signals can be presented by air-conduction or bone-conduction. This is necessary because a comparison between the two sets of results enables us to distinguish between different kinds of hearing losses (Gelfand, 2009).

- **Air Conduction**

Gelfand (2009) states that air conduction testing usually involves presenting the test signals through standard audiometric earphones (e.g. supra-aural) or insert earphones (Gelfand, 2009). During baseline assessment for potential ototoxic hearing loss, conventional audiometric threshold testing should be conducted at specific frequencies including 125Hz, 250Hz and 500Hz, 1000Hz, 2000Hz, 3000Hz and 4000Hz as well as 6000Hz and 8000Hz; low, mid and high frequencies respectively. Threshold testing of low-frequency inter-octave frequencies as well as masking principles should be applied when indicated.

- **Bone Conduction**

Bone conduction threshold testing is carried out at 250Hz, 500Hz, 1000Hz, 2000Hz and 4000Hz in order to confirm type of hearing loss (i.e. sensori-neural hearing loss) as well as rule out the possibility of an existing middle ear pathology which may warrant further referral.

- **Speech Testing**

According to the AAA Position Statement (2009), speech testing (including speech reception thresholds as well as speech discrimination testing) is to be carried out during baseline assessment as a means of comparison for future audiological monitoring results as sensori-neural hearing loss may progress into conventional audiometry threshold frequencies (250Hz – 8000Hz), which would affect speech discrimination ability. Linguistically appropriate speech materials should be used.

- **High Frequency Audiometry (HFA)**

As indicated by the literature, the outer hair cells (OHCs) of the basal turn of the cochlear appear initially to be most vulnerable to ototoxic effects. Therefore, in accordance with the tonotopic organisation of the basal turn of the cochlea, HFA, using the principles of conventional air conduction audiometry, allows for the assessment of high frequency thresholds above 8000Hz. Threshold testing should be conducted at frequencies including 9000Hz, 10 000Hz, 11 000Hz, 12 000Hz 14 000Hz, 16 000Hz and if possible (dependant on audiometer) ranging up to 18 000Hz and 20 000Hz. HFA is not yet standardised, however, shows evidence of ototoxic loss prior to the realisation of threshold shift seen in conventional air conduction audiometry. Threshold testing of ultrahigh frequencies is necessary in the detection of the early processes of ototoxicity before the damage progresses and affects the speech frequencies (Vasques & Mattucci, 2003). Upon completion of air conduction

threshold testing and HFA, retesting of some frequencies should be performed (e.g. at 2000Hz, 8000Hz and 12 000Hz) to confirm reliability of results.

Shortened Monitoring Protocol: Sensitivity Range of Ototoxicity (SRO)

The initial phase of hearing loss caused by ototoxic medications appears to have certain associated characteristics (Vaughn, Fausti, Chelius, Phillips, Helt & Henry, 2002). Ototoxic hearing changes tend to become evident within a limited range of frequencies near the highest frequencies where high frequency hearing sensitivity is present and susceptible to ototoxic insult, at thresholds of 100dB SPL or less (Vaughn, et al, 2002). The SRO therefore is defined as the highest audible frequency at a threshold of 100dBSPL or less, followed by the next six lower adjacent frequencies in $1/6^{th}$ octave steps or the one octave range nearest to the highest audible frequency (AAA Position Statement, 2009).

Current testing procedures used for ototoxicity assessment and monitoring are time-consuming and therefore, patients are not always monitored effectively due to time constraints as well as other challenges such as staff availability in relation to patient case load. The use of a shortened monitoring protocol based on a patient's SRO may allow for quicker monitoring procedures aimed at early detection of ototoxicity, specific to each individual patient. The SRO will not be the same for each patient and instead, will be relative to each individual patient's hearing configuration (AAA Position Statement, 2009).

A patient's individual SRO is determined at baseline (assuming that HFA has been carried out). Thereafter, during monitoring procedures, only the SRO frequencies are assessed until a change in hearing is observed. At such time, a complete evaluation of hearing thresholds is then required. The use of SRO for monitoring procedures encourages a decrease in testing time without compromising the ability of early detection of ototoxicity.

Frequencies shown to be most sensitive for early detection of ototoxicity are generally at 8000Hz and above (Fausti, Frey, Henry, Olson & Schaffer, 1999). For patients with existing hearing loss at baseline assessment, SRO will primarily occur within the frequency range of 8000Hz and below. The effectiveness of monitoring SRO within the conventional frequency range has not been established for the purposes of early identification of ototoxicity.

It is recommended that the use of a shortened monitoring protocol, through the identification of individual SRO only be considered for standard practice once an ototoxicity monitoring programme can provide evidence of effective implementation, efficient assessment and positive outcomes in relation to reliability and accuracy of audiological findings.

Appendix B:

Infection Control

Tuberculosis (TB) is a contagious and potentially life-threatening infectious disease caused by an organism/bacterium called Mycobacterium Tuberculosis (M.Tuberculosis). These bacteria can attack any part of the body, but they most commonly attack the lungs, because it is an easier environment in which the bacteria can flourish. The transmission of TB is a recognised risk for both patients and healthcare workers.

Drug-susceptible (regular) TB and MDR (multi-drug resistant) TB are spread in the same manner. Transmission is most likely to occur from patients who have unrecognised TB or from patients who have received ineffective treatment. The TB bacteria are spread from person to person via air transmission. The TB droplet nuclei containing M.Tuberculosis are expelled into the air when a person with active TB disease; of the lungs or larynx (throat); coughs, sneezes, speaks, or sings. Tuberculosis droplet nuclei can remain suspended in the air for several hours, depending on the environment. People who breathe in the air containing the TB nuclei can become infected with the TB bacterium. Infection usually requires prolonged sharing of airspace with a person actively spreading TB bacteria into the area. The risk of the spread of TB escalates when greater numbers of infectious TB patients are treated at healthcare facilities which do not have adequate infection control measures in place. It is of vital importance to eliminate the transmission of tuberculosis within the health care sector, due to the emergence of multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB), which is posing a threat to healthcare workers and other patients. Effective infection control practices are therefore critical to prevent the transmission of TB and further spread of TB within healthcare settings as well as other congregate settings (e.g. prisons).

Infection Control Measures

The World Health Organisation (WHO) recommends the following set of infection control measures that should be implemented in healthcare facilities:

- Managerial measures and administrative measures
- Proper environmental and ventilation measures
- Respiratory protective equipment measures

[Refer to WHO Policy on Infection Control at Health Care Facilities (2009) available at http://apps.who.int/iris/bitstream/10665/44148/1/9789241598323_eng.pdf]

Most importantly, audiologists need to familiarize themselves with relevant/applicable OHS and infection control policies regarding prevention of transmission of TB and other diseases in their work environments.

Infection Control Consumables

The following consumables need to be available at all times and at all levels of service delivery within healthcare settings (especially when dealing with an infectious patient population):

- Liquid hand-soap (strict hand-washing measures to be implemented after each patient session)
- Alcohol based hand scrub (e.g. Dismed)
- Ultracide (for disinfectant purposes of nubs and speculae)
- Gloves of varying sizes
- N95 masks (to be worn by the clinician)
- Surgical masks (to be worn by the patient)
- Alcohol swabs
- Appropriate medical waste disposal facilities

Appendix C:

Occupational Health and Safety (OHS)

An audiologist has a vital role in the field of ototoxicity, and thus is required to be in direct contact with patients who are at risk for ototoxicity. These include patients with non-communicable diseases such as cancer, as well as patients with communicable diseases such as tuberculosis.

The importance of OHS when working with patients with TB cannot be emphasized enough. 'On account of higher exposure to TB than the general population, healthcare workers have a higher incidence of latent (dormant TB) and active TB (TB disease)' (RHRU, 2009). Due to the infectious nature of TB, audiologists need to be aware of the risk of contracting TB, and the procedures involved in preventing or minimizing occupational hazards. The following procedures for audiologists involved with TB, MDR-TB and XDR-TB patients are suggested:

Baseline and follow-up assessments

- Baseline chest x-ray and thereafter follow-up every 6months
- Basic blood testing
- HIV Test, due to the increased incidence of TB in patients with HIV.
- If TB/ HIV Status is positive on a follow-up test, or if TB/ HIV symptoms are experienced, the audiologist should report this immediately to their hospital/ clinic staff health/ wellness facility

Audiologist/healthcare worker health status

Audiologists with compromised immune systems (such as cancer, HIV/AIDS, degenerative diseases, diabetes mellitus, etc.) should not be in contact with TB-infected patients.

The following conditions can yield increased risk to the susceptibility to TB infection or re-infection:

- HIV/Aids
- Diagnosis of M.Tuberculosis within the previous two years
- Infants and children under the age of four years old
- Immuno-compromising conditions:
    - Silicosis
    - Diabetes mellitus
    - Chronic renal failure or end-stage renal disease
    - Certain hematologic disorders (leukaemia and lymphoma)
    - Other specific malignancies (e.g. carcinoma of the head, neck or lungs)

- Body weight (10% below ideal body weight/underweight)
- Prolonged corticosteroid use
- Other immuno-suppressive treatments (including treatment for tumours and necrosis factor-alpha antagonists)
- Organ transplant
- Intestinal bypass or gastrectomy
- History of untreated or inadequately treated TB disease

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