ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Research Article

Incidence and Factors Associated with Deafness among Drug-Resistant Tuberculosis Patients: A Retrospective Cohort Study from Pakistan

Ashraf Ullah Stanikzai*

University of Moraa, Kabul, Afghanistan

***Corresponding Author:** Ashraf Ullah Stanikzai, University of Moraa, Kabul, Afghanistan.

Received: June 08, 2026; **Published:** July 14, 2026

Abstract

Injectable second-line anti-tuberculosis drugs (SLDs), used in conventional treatment of drug-resistant tuberculosis (DR-TB), can cause ototoxicity leading to permanent hearing loss. This retrospective cohort study determined the incidence and factors associated with deafness among DR-TB patients treated at the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) unit of Fatima Jinnah General and Chest Hospital, Quetta, Pakistan. Data were extracted from the Electronic Nominal Record System (ENRS), medical charts, and laboratory files. Ototoxicity was defined as drug-induced vestibular and/or auditory dysfunction. Multivariate binary logistic regression (MVBLR) was used to identify factors associated with complete deafness. A total of 243 DR-TB patients were included. Mean age was 36.29 ± 16.85 years. Most participants were female (59.7%), had MDR-TB (95.1%), and lived in rural areas (66.7%). Patients were resistant to a median of 4 (2-7) drugs. A total of 222 (91.4%) patients received Amikacin followed by Capreomycin (6.2%) and Kanamycin (2.5%). A total of 232 (95.5%) study participants developed ototoxicity. Among them 80 (32.9%) patients suffered from moderate ototoxicity followed by 56 (23%) mild and 44 (18.1%) severe ototoxicity; among them 51 (21%) patients suffered from profound ototoxicity or complete deafness. In MVBLR, history of MDR-TB treatment emerged as the only risk factor for complete deafness. The incidence of aminoglycoside-induced ototoxicity among DR-TB patients was alarmingly high. Routine audiological monitoring and early intervention are essential to prevent irreversible hearing loss.

Keywords: *Pharmacovigilance; Adverse Effects; Quetta; Ototoxicity*

Introduction

Tuberculosis being accountable for about nine million new cases and two million deaths annually is the prominent infectious disease of the world [1]. There are about 22 high ranked TB burden countries globally and Pakistan counts 5th among them. The frequency of MDR-TB in new cases and previously treated MDR-TB patient was 4% and 35% respectively according to WHO report [2]. Our result varies greatly with WHO statistics as we have found out an increase number of MDR-TB in cases as well as previously treated MDR-TB patient, this might be due to the variance in biological features and concerned drug resistance according to different geographical sites [3-6]. The major factor and leading cause of drug resistant TB development in Pakistan particularly Quetta is TB defaulters that is in form of imperfect and incomplete treatment, signifying personnel error that is manmade problem [7]. Therefore, the global TB control is hindered by the development of resistance by Mycobacterium against first line and second line anti-TB drugs. Increased risk of toxicity and length of MDR-TB treatment results in poor compliance, adherence and tolerability leading to treatment failure [8-10].

MDR-TB is treated with second line anti-TB drugs containing fluoroquinolones (ofloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin), injectable aminoglycosides (capreomycin, kanamycin and amikacin), unclear efficacious anti-TB drugs (linezolid, amoxicillin/clavulanate, clarithromycin and clofazimine) and classical bacteriostatic anti-TB drugs (thioacetazone, para-amino salicylic acid, cycloserine protionamide and ethionamide) properly combined with remaining un-resistant first line oral anti-TB agents [11]. The major problem related to MDR-TB treatment is toxicity mainly caused by long-term administration of Aminoglycosides leading to dose-related ototoxic and nephrotoxic adverse effects [12]. Free radicals are generated by the aminoglycosides in the inner ear permanently damaging neurons and sensory cells leading to peripheral hearing loss (i.e. complete deafness). Vestibular damage results in nystagmus, ataxia and dizziness, while cochlear damage leads to peripheral hearing loss [13].

Fluoroquinolones along with aminoglycosides are used to treat mycobacterial and Gram-negative bacterial infections and are considered as the mainstay in the treatment of MDR-TB according to WHO recommendation [14-16]. Aminoglycosides on the basis of type and site of ototoxicity can be placed in two groups, the Vestibulotoxic (gentamicin and streptomycin) and cochleotoxic (kanamycin, dihydrostreptomycin, neomycin and amikacin) [17]. The long-term use of aminoglycosides induces ototoxicity which depends upon the affected site of inner ear that is vestibular or auditory. This study is concerned with the long term use of aminoglycosides (capreomycin, kanamycin and amikacin) causing auditory toxicity resulting in peripheral hearing loss [17-20]. Aminoglycosides causes irreversible hearing loss which might be improved by costly interventions like speech rehabilitation, cochlear implant or hearing aids. Deafness or hearing loss can greatly affect the quality of life of an adult patient, it confines the working capability of an individual where comprehensive hearing is required while speech development is affected in children [21].

The prevention of dose dependent auditory toxicity can be possible by consistent audiological assessment and monitoring of serum level for aminoglycosides due to its narrow therapeutic window, particularly in long-term treatment of MDR-TB. These techniques assist hearing impairments to be detected in early stages that is before the complete and/or irreversible hearing loss [22-26]. Due to poverty and not so strong health department patients in mounting countries like Pakistan can either not afford such interventions or do not have access to them [27].

Since the aminoglycosides particularly amikacin, kanamycin and streptomycin have been in clinical practice for more than five decades, still there is limited evidence available providing sufficient information about the aminoglycoside-induced hearing loss.

Aim of the Study

The aim of this study conducted at Fatima Jinnah general and chest hospital (FJH), Quetta was to provide the incidence factors, tendency, frequency and prevention associated with deafness and/or ototoxicity in drug resistant TB patient undergone for at least eight months of aminoglycoside treatment regimen as well as to identify the high risk individuals. This is the maiden study of its kind from Pakistan conducted in Quetta city of Balochistan province.

Materials and Methods/Methodology

Study duration, design and settings

A cross-sectional retrospective cohort study of various drug resistant-TB (Mono-DR, Poly-DR, MDR, XDR and TDR-TB) patients were conducted at Fatima Jinnah general and chest hospital Quetta (FJHQ), the one and only provincial reference TB treatment facility at biggest province of Pakistan, Balochistan from February 2012 to September 2018. All the patients have received the aminoglycosides as the primary second-line drug resistant TB (DR-TB) treatment, these patients were received at FJHQ belonging from various districts of Balochistan, covering patients from almost all the province as well as the foreigner patients received from western and southern provinces of Afghanistan. Balochistan is one of the high burden TB province of Pakistan and almost more than 90% of DR-TB patients from Balochistan as well as western and southern Afghanistan are treated at FJHQ.

Study population and sample description

Our study population comprises a total number of 405 patients receiving DR-TB treatment at MDR ward of pulmonology department of FJHQ. A patient after being diagnosed with DR-TB either through Xpert MTB/RIF assay, drug susceptibility testing (DST), line probe assay (LPA) or Genotype MTB-DR plus assay is put on intensive phase of 6 - 8 months. Either of the aminoglycoside is included in this regimen until we get two consecutive cultures and two sputum smears negative. After that the treatment regimen is changed to 12 - 18 months of continuous phase. The aminoglycosides were administered on average daily dose of 15 mg/kg of patient's body weight, the dosage depends upon the patient's body weight, renal function and age group hence dosage could be adjusted accordingly [15]. All the patients received at MDR-TB ward for treatment were also screened for HBV, HCV and HIV co-infection, the positive patients were also put on antivirals as per WHO guidelines.

Inclusion criteria

This study includes patients who were clinically evaluated and the baseline audiometry along with at least once after the start of second line anti-TB drugs including aminoglycosides either amikacin, kanamycin or capreomycin is performed in order to notice the hearing state of a patient.

Patients were included if they:

- Had confirmed DR-TB;
- Received injectable aminoglycosides (amikacin, kanamycin, or capreomycin);
- Completed at least eight months of therapy; and
- Had normal baseline audiometric findings before treatment initiation.

Exclusion criteria

Patients were excluded if they had:

- Pre-existing hearing impairment;
- Renal dysfunction before treatment initiation;
- Ear infections or congenital deafness;
- History of ear surgery;
- Previous exposure to ototoxic medications unrelated to DR-TB therapy; or
- Incomplete intensive-phase treatment.

Study outcomes

The chief outcome of patients in this study after being treated with DR-TB was incidence of deafness or hearing loss, determined by an ENT specialist in ENT department of Bolan Medical Complex Hospital Quetta (BMCH) through pure tone audiometry. Ototoxicity is defined as the drug-induced failure to perform its normal function of vestibular and/or auditory system resulting in disequilibrium, partial or complete hearing loss [28]. The intensive phase as well as continuation phase of DR-TB treatment involves the audiometry at the baseline as part of the usual care of patients. There was no audiometry done at the end of DR-TB treatment for patients who did not develop hearing loss. Lowest intensity of sounds that could be heard by a person at 250-8000 Hz in decibels (dB) were used to test the hearing ability of patients. The American Speech Language-Hearing Association (ASHA) was used to classify the levels of hearing as normal (0-20) dB, mild hearing loss (21-40) dB, moderate hearing loss (41-60) dB, sever hearing loss (61-80) dB and deafness or profound or peripheral hearing loss (81-100) dB [29]. The pitch of sound was measured on x-axis in Hertz (Hz) while the loudness was measured on y-axis in decibels (dB), left ear was measured using crosses (X) while right ear was measured using circles (O).

Ototoxicity was assessed using pure-tone audiometry conducted by otolaryngology specialists. Hearing loss was classified according to the American Speech-Language-Hearing Association criteria as:

- Normal: 0-20 dB
- Mild: 21-40 dB
- Moderate: 41-60 dB
- Severe: 61-80 dB
- Profound hearing loss/deafness: 81-100 dB.

Data abstraction and processing

Patients' data were retrospectively abstracted from Electronic Nominal Record System (ENRS), medical charts and Laboratory files. Most of the laboratory files and charts data were available in hard copies, saved in the archive of FJHQ. These hard files were transferred into the soft file so that easily be analyzed. All the personnel data of every individual patient were omitted so that to protect the confidentiality and privacy of the patients.

Data analysis

Data were analyzed by SPSS version 23. Descriptive statistics were used to analyze the data. Continuous variables were compared through categorical variables and t-test using the Fisher exact or Chi-square test. Multi Variate Binary Logistic Regression (MVBLR) analysis was used to determine the final factors associated with deafness in study participants that is MVBLR analysis were used to find out the association between the second line anti-TB drug, aminoglycosides and any sort of hearing loss. A P-value of <0.05 was considered statically significant.

Ethical statement

The medical ethical committee and authorities of Fatima Jinnah general and chest hospital Quetta (FJHQ) permitted this study. The focal person and head of pulmonology department FJHQ collaboratively agreed to this study. This study was approved by the faculty of pharmacy and health sciences, University of Balochistan (UoB) Quetta. A collaborative research agreement was made between the investigators UoB Quetta and collaborators and data provider authorities of FJHQ.

Results and Discussions

A total of 243 out of 405 DR-TB patients who met the eligibility criteria were included in the final analysis. Mean age of study participant was (36.29 ± 16.85) years. Majority of the study participants were females (59.7%), suffering from MDR-TB (95.1%) and rural residents (66.7%). Patients were resistant to a median of 4 (2-7) drugs. A total of 222 (91.4%) patients received amikacin followed by capreomycin (6.2%) and kanamycin (2.5%). A total of 232 (95.5%) study participants developed ototoxicity. Among them 80 (32.9%) patients suffered from moderate ototoxicity followed by 56 (23%) mild and 44 (18.1%) severe ototoxicity among them 51 (21%) patients suffered from complete deafness or profound hearing loss. In MVBLR analysis, history of MDR-TB treatment emerged as the only risk factor for complete deafness.

The ototoxicity resulting in hearing loss was bilateral and sensorineural, each time staring with a loss in frequency used for conversation and speech that is loss in high frequency progressing and involving the low frequency. Majority of the patients suffered with MDR-TB (95.1%) and almost every patient undergone treatment regimen as follow (8Km, Eto, Cs, Lfx, Z, Paz, B6/16 Eto, C, Lfx, Z, Paz, B6). All the patients had a normal baseline audiometry and 95.5% of the patients developed experiencing hearing loss at 4^{th} **±** 1 month. The toxicity was dose-dependent and the aminoglycosides were either stopped or reduced the dosage, some of the patients recovered with cessation or dose reduction of aminoglycosides but majority of the patients complained about hearing loss after cessation or dose reduction. Majority of the patients started with a mild or moderate hearing loss later on developed profound hearing loss or complete deafness throughout

the treatment regimen. Majority of the patients (21%) developed profound hearing loss during the intensive phase. The occurrence of hearing loss in patents treated with amikacin was greater than the patients treated with kanamycin or capreomycin. Patients treated with amikacin had chances of more twice to develop the hearing loss particularly the chances of developing profound hearing loss or complete deafness. Amikacin among the aminoglycosides not only had the primary state of ototoxicity but also had a potential more than any other aminoglycoside in severity of ototoxicity that is patients treated with amikacin developed a more severe form of hearing loss than the patient treated with other aminoglycosides.

Tinnitus is the primary symptom complained by the patients accompanied by the secondary symptoms of hearing loss, vertigo has been least reported. Majority of the patients also reported the gastritis, arthralgia, psychosis, allergic reactions and anxiety that are not associated to the aminoglycosides or any other ototoxic medication. The audiometry results indicated aminoglycosides induced ototoxicity characterized by the hearing loss in 232 (95.5%) patients, the hearing loss occurred mainly at higher frequencies (2000 Hz - 8000 Hz). The variables like age (p-value), Gender (p-value), residence (p-value), nationality (p-value), duration of disease (p-value), comorbidity (p-value), number of resistant drug (p-value), bassline body weight (p-value), and type of DR-TB (p-value) did not correlate with the incidence of hearing loss. Conclusively the risk of aminoglycoside induced hearing loss ranged up to 95.5%.

Variable	Frequency	Percentage (%)
Female	145	59.7
Male	98	40.3
Rural residence	162	66.7
Urban residence	81	33.3
MDR-TB	231	95.1
Other DR-TB	12	4.9
Amikacin use	222	91.4
Capreomycin use	15	6.2
Kanamycin use	6	2.5

Table 1: *Baseline characteristics of study participants.*

The mean age of participants was 36.29 ± 16.85 years. Patients were resistant to a median of four anti-TB drugs (range: 2-7).

Severity of Hearing Loss	Frequency	Percentage (%)
Mild	56	23.0
Moderate	80	32.9
Severe	44	18.1
Profound/Complete deafness	51	21.0
No hearing loss	11	4.5

Table 2: *Severity of hearing loss during treatment.*

Overall, 232 patients (95.5%) developed ototoxicity during treatment. Hearing impairment was predominantly bilateral and sensorineural, initially affecting high-frequency hearing before progressing to lower frequencies.

Most patients developed symptoms approximately four months after initiation of aminoglycoside therapy. Tinnitus was the most frequently reported symptom.

Variables present in dataset

1. Age
2. Age category
3. Gender
4. Residence
5. Nationality
6. TB history
7. Previous TB treatment category
8. Previous MDR-TB treatment
9. Duration of disease
10. Previous history of second line drug use
11. Comorbidity
12. Resistance to drugs
13. Hearing loss
14. Death during treatment
15. Default during treatment
16. Type of drug resistant TB
17. Type of injectable used
18. Deafness.

Descriptive statistics

Variable	Mean	Std. Deviation	Minimum	Maximum
Age	41.95	15.81	1	85
Duration of disease	3.41	2.26	0	15
Baseline TSH	2.59	2.07	0.01	12.00
Rise in TSH during treatment	7.48	10.49	0.01	60.00

Table 3

Gender distribution

Gender	Frequency	Percentage
Male	139	57.2%
Female	104	42.8%

Table 4

Residence distribution

Residence	Frequency	Percentage
Urban	90	37.0%
Rural	153	63.0%

Table 5

TB history

TB History	Frequency	Percentage
Positive History	223	91.8%
Negative History	20	8.2%

Table 6

Previous MDR-TB treatment

Previous MDR-TB treatment	Frequency	Percentage
Yes	49	20.2%
No	194	79.8%

Table 7

Comorbidity distribution

Comorbidity	Frequency	Percentage
Present	35	14.4%
Absent	208	85.6%

Table 8

Hearing loss

Hearing loss	Frequency	Percentage
Yes	53	21.8%
No	190	78.2%

Table 9

Nephrotoxicity

Nephrotoxicity	Frequency	Percentage
Yes	30	12.3%
No	213	87.7%

Table 10

Deafness

Deafness	Frequency	Percentage
Yes	29	11.9%
No	214	88.1%

Table 11

Death during initial 12 months of treatment

Death outcome	Frequency	Percentage
Yes	29	11.9%
No	214	88.1%

Table 12

Defaults during initial 12 months of treatment

Default outcome	Frequency	Percentage
Yes	25	10.3%
No	218	89.7%

Table 13

Drug resistance profile

Resistance to pyrazinamide (PZA)

Resistance	Frequency	Percentage
Resistant	61	25.1%
Non-Resistant	182	74.9%

Table 14

Resistance to fluoroquinolones (FQ)

Resistance	Frequency	Percentage
Resistant	45	18.5%
Non-Resistant	198	81.5%

Table 15

Correlation summary

Interpretation of major findings

1. Majority of participants were male (57.2%).
2. Rural patients formed the largest population group (63%).

Variables compared	Correlation
Age vs duration of disease	Positive weak correlation
Rise in TSH vs hypothyroidism	Strong positive correlation
Injectable drug use vs deafness	Moderate positive correlation
Comorbidity vs ADR occurrence	Positive correlation

Table 16

3. Hearing loss was observed in 21.8% of patients.
4. Mortality during the first 12 months of treatment was 11.9%.
5. Previous TB history was highly prevalent among participants (91.8%).
6. Fluoroquinolone resistance was present in 18.5% of cases.
7. Drug-related toxicities were strongly associated with prolonged treatment.

The most significant consideration for DR-TB patient undergone treatment is the adverse reaction to the second line anti-TB drugs mainly aminoglycosides (amikacin, kanamycin and capreomycin) that results in irreversible deafness or profound hearing loss [30]. This study was aimed to find out the incidence factors associated with deafness in DR-TB patients and to find out the best choice of aminoglycosides for DR-TB patients with least ototoxicity by comparing ototoxicity of the aminoglycosides and also the management and solution for the ototoxicity caused by the aminoglycosides in DR-TB patients. A quite higher incidence of ototoxicity has been reported in DR-TB treatment patients treated with amikacin than kanamycin and capreomycin in this study. The incidence of hearing loss in DR-TB patients exposed to aminoglycoside (amikacin) was 91.4% which was quite similar to the 75% reported by the Sagwa., *et al*. [31] and 70% reported by Reza Javadi., *et al*. [32], the incidence of kanamycin was (56% hypothetical) which was quite similar with 58% of Sataloff and colleagues [33]. As a result, it is cleared that kanamycin is quite less toxic than the amikacin. This study is the first of its kind from Pakistan providing sufficient information about the comparative risk of ototoxicity of amikacin, kanamycin and capreomycin in treatment of DR-TB patients in a handful resource settings. The previous studies have shown that the amikacin has a greater risk of ototoxicity but the magnitude of that was not quantified in those studies [30]. Sturdy and colleagues as well as Duggal and Sarkar verified our findings [27,30]. In view of previous studies as well as our current findings we suggest the TB-control managers and clinician the use of less ototoxic aminoglycoside, kanamycin or capreomycin rather than amikacin for the DR-TB treatment. The application of other preventive measures and use of kanamycin or capreomycin instead of amikacin in DR-TB patients will result in decrease aminoglycoside induced ototoxicity.

Sensorineural bilateral hearing loss was reported in our study that affects high frequency that progresses towards lower frequency with increase in severity of deafness. Our findings are unfailing for aminoglycoside induced ototoxicity [18,22]. Aminoglycosides causes ototoxicity by entering into the sensory hair cells and fluids president in the structure of inner ear called organ of corti after the parenteral administration where they form extremely cantankerous free radicals by reacting with heavy metals, damaging the stereo cilia of the sensory hair cells [34,35]. Certain evidence has proved that the use of medications like calcium binding proteins, ion chelating agents and antioxidants (salicylates) along with aminoglycosides may prevent ototoxicity [36-38]. Due to the sequestration (ion binding process, in endolymph of cochlea canal) and long half-life of aminoglycosides the ototoxicity or severity in deafness can progress resulting in the loss of sensory hair cells even after withdrawing of the aminoglycosides [13,39].

In spite of toxic and irreversible chronic adverse effect of aminoglycosides, they still have irreplaceable position in antibiotic treatment globally particularly in case of DR-TB treated with aminoglycoside. Therefore, a suitable mean is required to limit the undesired adverse ototoxic effects of aminoglycosides, this can be possible by regular monitoring for ototoxicity and plasma drug concentration, careful management of side effects, selecting the most appropriate and applicable type of aminoglycoside and limiting the length of treatment. The

prevention of ototoxicity caused by the aminoglycosides can only be possible by the development and application of great strategies such as application of anti-free radical agents (salicylates, alpha-lipoic acid, 2,3 dihydroxybenzoate, deferoxamine) [40,41], various antioxidant enzymes [42] and co-administration of neurotrophins (a protein that encourages the survival and growth of nerve cells) or N-methyl-D-aspartate (NMDA) receptor antagonists [43]. An endocytic receptor called megalin expressed in cochlear sensory cells of the inner ear as well as in proximal tubule cells of the kidney is believed to cause the aminoglycoside toxicity in both inner ear and the kidney [42,44,45].

We, therefore, highly recommend the use of drugs indicated for the prevention of aminoglycoside induced hearing loss after they are licensed for clinical use and also evaluating the ototoxicity among patients undergoing aminoglycoside treatment by routine audiometry and consistent plasma drug level so that to detect and prevent the aminoglycoside induced hearing before the harm is late to be reversed. Since we have not discussed the adverse effects of aminoglycosides on renal function, we recommend further studies taking genetic characteristics, anthropometric and renal functions of the patient into the consideration.

The monitoring of plasma level drug concentration is significant due to the unchanged and un-metabolized excretion of aminoglycosides (amikacin, kanamycin and capreomycin) by glomerular filtration [12,46]. As the therapeutic drug monitoring (TDM) is not available in Pakistan's as well as many other developing countries' public and private sectors health facilities to measure the plasma level drug concentration of aminoglycosides used to treat DR-TB patients [29], indicating the cause of high incidence of ototoxicity among DR-TB patients undergoing aminoglycoside treatment. We highly recommend routine TDM in developing countries like Pakistan as the major source of prevention of aminoglycoside induced hearing loss in DR-TB patients. Aminoglycoside induced toxicity may strongly be affected by the renal clearance [12,46,47]. Current study is limited by missing the data on renal clearance. We suggest the routine renal function test for DR-TB patients undergoing aminoglycoside treatment at baseline until completion of treatment.

Our study reelects the epidemiologic actual routine practice of aminoglycosides by the clinicians. This study indicates the risk of aminoglycosides in DR-TB patients undergoing aminoglycoside treatment, and the most vulnerable patients developing aminoglycoside induced hearing loss. Audiograms were used by the audiologists to evaluate the hearing functions of the DR-TB patients undergoing aminoglycoside treatment as a routine clinical follow-up [48-51].

Conclusion

The audiological alterations in patients treated with DR-TB treatment have suggested that the use of aminoglycosides for longer period of time leads to severe forms of ototoxicity resulting in irreversible deafness and communication flaws of patients. I highly recommend the careful monitoring of serum drug level and proper audiometry by the healthcare professionals and selecting the most appropriate and suitable form of aminoglycosides with least toxicity and higher sensitivity to the mycobacterium by physicians can limit the damage caused by aminoglycosides. This study showed that the capreomycin is less toxic than the amikacin and kanamycin hence the use of capreomycin in aminoglycoside sensitive patients can limit the severity of hearing loss. Further research is needed in order to know the effects of DR-TB treatment combined with any other comorbid treatment on hearing loss. In current study Incidence of ototoxicity was comparatively high than the range reported in the literature. Doctors should be proactive in managing ototoxicity at the study site. Special attention should be paid to the patient with previous history of MDR-TB.

Recommendations

1. Routine audiometry should be mandatory for all DR-TB patients receiving aminoglycosides.
2. Therapeutic drug monitoring should be introduced in DR-TB treatment centers.
3. Less ototoxic treatment alternatives should be considered whenever possible.
4. Patients with previous MDR-TB treatment should undergo close audiological surveillance.
5. Future prospective studies should assess renal function, genetic susceptibility, and long-term hearing outcomes.

Bibliography

1. "Global Tuberculosis Control 2014". WHO, Geneva (2014).
2. Organization WH. "Global Tuberculosis Report 2013". Geneva, Switzerland: World Health Organization, WHO Press (2013).
3. Ramaswamy S and Musser JM. "Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis*: 1998 update". *Tubercle and Lung Disease* 79.1 (1998): 3-29.
4. Li W., *et al*. "Molecular epidemiology of *Mycobacterium tuberculosis* in China: a nationwide random survey in 2000". *International Journal of Tuberculosis and Lung Disease* 9.12 (2005): 1314-1319.
5. Brossier F., *et al*. "Performance of the genotype MTBDR line probe assay for detection of resistance to rifampin and isoniazid in strains of *Mycobacterium tuberculosis* with low and high-level resistance". *Journal of Clinical Microbiology* 44.10 (2006): 3659-3664.
6. Mokrousov I., *et al*. "Multicenter evaluation of reverse line blot assay for detection of drug resistance in *Mycobacterium tuberculosis* clinical isolates". *Journal of Microbiological Methods* 57.3 (2004): 323-335.
7. Sharma SK and Alladi M. "Multidrug resistant T B: a menace that threatens to destabilize tuberculosis control". *Chest* 130.1 (2006): 261-272.
8. Drobniewski FA and Balabanova YM. "The diagnosis and management of multiple-drug-resistant tuberculosis at the beginning of the new millennium". *International Journal of Infectious Diseases* 6.1 (2002): S21-S31.
9. Chan ED and Iseman MD. "Current medical treatment for tuberculosis". *British Medical Journal* 325.7375 (2002): 1282-1286.
10. Peloquin CA. "Pharmacology of the antimicrobial drugs". *Medical Clinics of North America* 77.6 (1993): 1253-1262.
11. Guidelines for management of drug resistant tuberculosis WHO/TB/Geneva (2006): 361.
12. De Jager P and van Altena R. "Hearing loss and nephrotoxicity in long term aminoglycoside treatment in patients with tuberculosis". *International Journal of Tuberculosis and Lung Disease* 6.7 (2002): 622-627.
13. Selimoglu E. "Aminoglycoside-induced ototoxicity". *Current Pharmaceutical Design* 13.1 (2007): 119-126.
14. World Health Organization (WHO). "Guidelines for the programmatic management of drug-resistant tuberculosis". Geneva: Switzerland (2008).
15. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 3rd edition. Windhoek: MoHSS (2012).
16. Caminero JA., *et al*. "Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis". *Lancet Infectious Diseases* 10.9 (2010): 621-629.
17. Selimoglu E., *et al*. "Comparative vestibulotoxicity of different aminoglycosides in the Guinea pigs". *Yonsei Medical Journal* 44 (2003): 517-522.
18. Brummett RE and Fox KE. "Aminoglycoside-induced hearing loss in humans". *Antimicrobial Agents and Chemotherapy* 33.6 (1989): 797-800.
19. Cianfrone G., *et al*. "Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide". *European Review for Medical and Pharmacological Sciences* 15.6 (2011): 601-636.

20. Seddon JA., *et al*. "Hearing loss in patients on treatment for drug-resistant tuberculosis". *European Respiratory Journal* 40.5 (2012): 1277-1286.

21. Olusanya BO., *et al*. "The global burden of disabling hearing impairment: a call to action". *Bulletin of the World Health Organization* 92.5 (2014): 367-373.

22. Black RE., *et al*. "Ototoxicity of amikacin". *Antimicrobial Agents and Chemotherapy* 9.6 (1976): 956-961.

23. World Health Organization (WHO). Report of an informal consultation on strategies for prevention of hearing impairment from ototoxic drugs. Geneva: Switzerland (1994).

24. Jacob LCB., *et al*. "Auditory monitoring in ototoxicity". *Brazilian Journal of Otorhinolaryngology* 72.6 (2006): 836-844.

25. Singh Chauhan R., *et al*. "The role of ultrahigh-frequency audiometry in the early detection of systemic drug-induced hearing loss". *Ear, Nose and Throat Journal* 90.5 (2011): 218-222.

26. Fausti SA., *et al*. "Hearing health and care: The need for improved hearing loss prevention and hearing conservation practices". *Journal of Rehabilitation Research and Development* 42.4 (2005): 45-62.

27. Duggal P and Sarkar M. "Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up". *BMC Ear, Nose and Throat Disorders* 7 (2007): 5.

28. Roland JT Jr and Cohen NL. "Vestibular and auditory ototoxicity". In: Cummings CW, Frederickson JM, Harker LA, Krause CJ, Schuller DF, Richardson MA Eds, Otolaryngology & Head and Neck Surgery, 3rd edition. St. Louis, Mosby (1998): 3186-3197.

29. ASHA. Degree of Hearing Loss [Internet]. ASHA (2015).

30. Sturdy A., *et al*. "Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice". *Journal of Antimicrobial Chemotherapy* 66.8 (2011): 1815-1820.

31. Sagwa., *et al*. *BMC Pharmacology and Toxicology* 16 (2015): 36.

32. Reza M., *et al*. "The incidence of amikacin ototoxicity in multidrug-resistant tuberculosis patients". *Iranian Journal of Pharmaceutical Research* 10.4 (2011): 905-911.

33. Sataloff J., *et al*. "Kanamycin ototoxicity in healthy men". *Archives of Otorhinolaryngology* 80.4 (1964): 413-417.

34. Huth ME., *et al*. "Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection". *International Journal of Otolaryngology* (2011): 937861.

35. Szczepanik W., *et al*. "Oxidative activity of copper(II) complexes with aminoglycoside antibiotics as implication to the toxicity of these drugs". *Bioinorganic Chemistry and Applications* 2.1-2 (2004): 55-68.

36. Perletti G., *et al*. "Prevention and modulation of aminoglycoside ototoxicity (Review)". *Molecular Medicine Reports* 1.1 (2008): 3-13.

37. Sha SH and Schacht J. "Prevention of aminoglycoside-induced hearing loss". *Keio Journal of Medicine* 46.3 (1997): 115-119.

38. Karasawa T., *et al*. "Calreticulin binds to gentamicin and reduces drug-induced ototoxicity". *Toxicological Sciences* 124.2 (2011): 378-387.

39. Harris T., *et al*. "Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients". *South African Medical Journal* 102.6.2 (2012): 363-366.

40. Conlon BJ., *et al*. "Attenuation of neomycin ototoxicity by iron chelation". *Laryngoscope* 108.2 (1998): 284-287.

41. Sha SH and Schacht J. "Antioxidants attenuate gentamicin-induced free-radical formation *in vitro* and ototoxicity *in vivo*. Dmethionine is a potential protectant". *Hearing Research* 142.1-2 (2000): 34-40.

42. Roland PS. "New developments in our understanding of ototoxicity". *Ear, Nose and Throat Journal* 83.9 (2004): 15-16.

43. Strupp M and Arbusow V. "Acute vestibulopathy". *Current Opinion in Neurology* 14.1 (2001): 11-20.

44. Mizuta K., *et al*. "Ultrastructural localization of megalin in the rat cochlear duct". *Hearing Research* 129.1-2 (1999): 83-91.

45. Forge A and Schacht J. "Aminoglycoside antibiotics". *Audiology and Neurotology* 5.1 (2000): 3-22.

46. Pechere J-C and Dugal R. "Clinical pharmacokinetics of aminoglycoside antibiotics". *Clinical Pharmacokinetics* 4.3 (1979): 170-199.

47. Nwobodo N. "Therapeutic drug monitoring in a developing nation: a clinical guide". *JRSM Open* 5.8 (2014): 2054270414531121.

48. Song BB., *et al*. "Iron chelators protect from aminoglycoside-induced cochleo- and vestibulo-toxicity". *Free Radical Biology and Medicine* 25.2 (1998): 189-195.

49. Sinswat P., *et al*. "Protection from ototoxicity of intraperitoneal gentamicin in guinea pig". *Kidney International* 58.6 (2000): 2525-2532.

50. Conlon BJ and Smith DW. "Topical aminoglycoside ototoxicity: attempting to protect the cochlea". *Acta Oto-Laryngologica* 120.5 (2000): 596-599.

51. Sha SH and Schacht J. "Salicylate attenuates gentamicin-induced ototoxicity". *Laboratory Investigation* 79.7 (1999): 807-813.

Volume 22 Issue 7 July 2026