



OTOTOXICITY IN MULTIDRUG-RESISTANT TUBERCULOSIS: A SCOPING REVIEW OF THE INDONESIAN STUDIES

OTOTOKSISITAS PADA PASIEN TUBERKULOSIS RESISTEN OBAT: SCOPING REVIEW PADA STUDI DI INDONESIA

Okni Nugraha Putra^{1*}, Affan Yuniar.N.H¹, Fariz Hidayat², I.G.E. Sagitha³

¹Department of Clinical Pharmacy, Program Study of Pharmacy, Faculty of Medicine, Hang Tuah University - Arief Rahman Hakim 150, Surabaya, East Java – Indonesia

² Fakultas Kedokteran Universitas Diponegoro, Semarang - Indonesia

³ Institut Teknologi Kesehatan Bali - Tukan Balian 180, Renon, Denpasar, Bali – Indonesia

*Correspondence email: okni.nugraha@hangtuah.ac.id

ABSTRACT

A wide variation in ototoxicity or hearing loss due to injectable anti-tubercular drugs in patients with multidrug-resistant tuberculosis (MDR-TB) has been reported globally and in Indonesia. This scoping review assesses the ototoxicity of second-line injectable anti-tubercular drugs in Indonesian patients with MDR-TB. This review was conducted under the recommended PRISMA extension for scoping review (PRISMA-ScR). The Google Scholar and PubMed database were used to search the published articles on MDR-TB in the Indonesian population. Seven studies were included based on the inclusion criteria reporting kanamycin and capreomycin in the management of MDR-TB. Ototoxicity was observed in 39.3% (116/295) MDR-TB patients. Ototoxicity was observed in kanamycin, 38.7% (105/271 patients); capreomycin, 36.8% (7/19 patients); and kanamycin plus capreomycin, 80% (4/5 patients). Only one study reported risk factors ototoxicity in MDR-TB patients. Ototoxicity was significantly associated with older age and the length of kanamycin therapy correlates with hearing loss. This review identified a high prevalence of ototoxicity in MDR-TB patients in Indonesia treated with second-line injectable drugs. Efforts were urgently needed to develop guidelines to monitor ototoxicity, improve pharmacist and clinician awareness, and educate patients or caregivers to report hearing loss symptoms as a sign of ototoxicity.

Keywords : MDR-TB; Ototoxicity, Second-line injectable

ABSTRAK

Variasi yang luas dalam ototoksisitas atau gangguan pendengaran akibat obat antituberkulosis injeksi pada pasien dengan *multidrug-resistant* tuberculosis (MDR-TB) telah dilaporkan secara global dan di Indonesia. *Scoping review* ini mengulas ototoksisitas obat antituberkulosis injeksi lini kedua pada pasien MDR-TB di Indonesia. Tinjauan ini dilakukan menggunakan PRISMA *extension for scoping review* (PRISMA-ScR). Database Google Scholar dan PubMed digunakan untuk mencari artikel tentang MDR-TB pada penelitian di Indonesia. Tujuh penelitian diidentifikasi berdasarkan kriteria inklusi yang melaporkan kanamisin dan kapreomisin sebagai tatalaksana MDR-TB. Ototoksisitas ditemukan pada 39,3% (116/295) pasien TB-MDR. Ototoksisitas diamati pada kanamisin, 38,7% (105/271 pasien); kapreomisin, 36,8% (7/19 pasien); dan kanamisin ditambah kapreomisin, 80% (4/5 pasien). Hanya satu penelitian yang melaporkan faktor risiko ototoksisitas pada pasien TB-MDR.

Ototoksisitas secara signifikan terkait dengan usia yang lebih tua dan lamanya terapi kanamisin berkorelasi dengan gangguan pendengaran. Review ini mengidentifikasi prevalensi tinggi ototoksisitas pada pasien MDR-TB Indonesia yang diobati dengan obat injeksi lini kedua. Upaya sangat diperlukan untuk mengembangkan pedoman untuk memantau ototoksisitas, meningkatkan kesadaran apoteker dan dokter, dan mendidik pasien untuk melaporkan gejala gangguan pendengaran sebagai tanda ototoksisitas.

Kata kunci : MDR-TB; Ototoksisitas; Obat Injeksi Lini Kedua

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis resistant to two or more principal medications (isoniazid and rifampicin) used to manage tuberculosis (WHO, 2016). Drug resistance is the primary major concern, particularly multi-drug resistance, often leading to therapy failure with standard and short-term therapy (Soeroto et al, 2021; Fitriya et al, 2021). Several studies have already reported that the regimen of MDR-TB requires second-line injectable antitubercular medications that are ototoxic, namely aminoglycosides or polypeptide antibiotic, capreomycin (Nahid et al, 2019).

There are 23,000 cases of MDR-TB in Indonesia. In 2017, 442,000 TB cases were reported, of which an estimated 8,600-15,000 MDR-TB (an estimate of 2.4% of new cases and 13% of previously treated TB patients) and only 27.36% of cases were treated. Several leading causes of TB drug resistance in Indonesia have been identified: low quality of implementation of Directly Observed Treatment Shortcourse (DOTS) in hospitals and health service facilities; increased TB-HIV co-infection; weak system surveillance; and inadequate handling of drug-resistant TB cases (Ministry of Health of Indonesia, 2016). The injectable anti-tubercular drug was administered in the intensive phase along with fluoroquinolones, ethionamide, cycloserine, and pyrazinamide or ethambutol for six months. Studies reported that patients with MDR-TB were treated with second-line TB drugs may develop sensory hearing loss (Hong et al, 2018).

Ototoxic drugs affect the vestibular and cochlear parts of the inner ear and cause hearing loss by influencing the cochlear hair cells, leading to high-frequency hearing loss. Previous studies have indicated the possibility of hearing loss due to aminoglycoside administration (streptomycin, kanamycin, and gentamicin) (Wangchuk et al,

2018). An important issue related to the long-term administration of aminoglycoside in the initial phase of MDR treatment is its toxicity. Ototoxicity and nephrotoxicity are primary concerns because of the narrow therapeutic range and broad pharmacokinetics variability among patients (Shibeshi et al, 2019). MDR-TB treatment is more complex than that of TB sensitive.

MDR-TB treatment's side effects were as much as 11 times greater than that of drug-sensitive TB. Ototoxic affects the ability to communicate and reduces the quality of life of MDR-TB patients (Hong et al, 2019) and causing the discontinuation of treatment and reduce or delay the success of treatment (Mantefardo et al, 2021). Injectable second-line anti-tuberculosis drugs in the inner ear react with Fe ions to form free radicals that trigger apoptosis and cochlear hair cells' necrosis. Ototoxicity occurs initially at high frequencies without causing a complaint. If drug exposure continues to progress, the abnormality continues at low frequency, accompanied by hearing complaints, and the damage is permanent (Hong et al, 2019; Heysell et al, 2018). Ototoxic identification of the initial phase through a high-frequency audiometric examination is essential for preventing persistent hearing loss. There are variations in ototoxic incidence between different studies ranging from less than 10% to more than 50% (Hong et al, 2018; Shibeshi et al, 2019).

To prevent permanent hearing loss, the programmatic management of MDR-TB in Indonesia guidelines recommend evaluating hearing loss at baseline and each clinic visit.⁵ (Ministry of Health of Indonesia, 2016). However, in clinical practice, several studies in Indonesian patients measure ototoxicity based on symptoms, and few studies have measured it regularly regardless of symptoms, missing early ototoxicity detection. In the absence of well-designed Indonesian studies and wide variation of incidence

of ototoxicity, we tried to analyze the ototoxicity of second-line injectable anti-tubercular drugs in patients with MDR-TB throughout this scoping review including prevalence, risk factors, and management of drug-induced ototoxicity.

METHODS

The study of the ototoxicity of second-line injectable anti-tubercular drugs in MDR-TB patients in Indonesia was examined as a scoping review. This review was conducted under the recommended PRISMA extension for scoping review (PRISMA-ScR) (Tricco et al, 2018).

Search strategy

The Google Scholar and PubMed database were used to search the articles on MDR-TB in the Indonesian population. We used some combination of keywords such as *ototoxic*, *hearing loss*, *hearing impairment*, *auditory*, *cochlea*, *vestibular*, *MDR-TB*, *resistant tuberculosis*, *injectable second-line*, *aminoglycosides*, *streptomycin*, *kanamycin*, and *capreomycin*. Boolean operators with “OR” and “AND” were used with the selected keywords to make the search more specific. Database of World Health Organization and The Programmatic Management of MDR-TB in Indonesia was also searched.

Inclusion and Exclusion Criteria

The inclusion criteria in this review were conducted in MDR-TB patients exclusively in Indonesia; using second-line of anti-tubercular injectable drugs (streptomycin, kanamycin) or capreomycin; experiencing adverse effects such as hearing impairment, ototoxic, auditory or cochlea impairment; published both in Indonesia and English between 2010 and 2020; hearing assessment such as pure tone audiometry or American Speech-Language and Hearing Association (ASHA) before and after administration of injectable drugs. Articles that were not fully accessed (abstract only), guidelines or consensus,

and reviews were excluded from this study. The authors have selected and screened all titles and abstracts independently. Full-text articles were collected and reviewed to establish if the article met the criteria for eligibility

Data extraction and analysis

Each study included information such as the author, publication date, study design, sample size, ototoxic criteria, and a summary of results. Because of the heterogeneity of the studies, the results of this review are described as a narrative synthesis. The studies were organized into categories based on the characteristics of the publication and summarized in tables. Because scoping reviews aim to identify all available evidence and highlight its main characteristics, regardless of quality, no quality assessment was performed following the PRISMA-ScR

RESULTS AND DISCUSSION

The total number of articles identified through the literature search was 252 (PubMed = 53, google search = 199). Out of these, seven articles were included based on the inclusion criteria, as shown in figure 1.

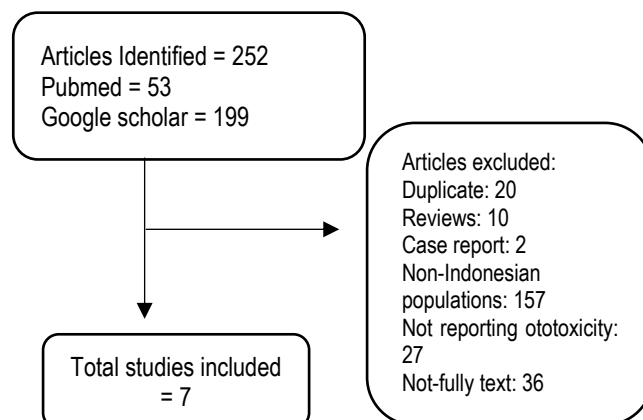


Figure 1. Study selection flowchart

Key study characteristics

The summary of the included studies as shown in table 1.

Table 1. Summary of study characteristics

No	Author and Year	Design	Sample size of MDR TB	Sex and Age (Years)	Audiometry	Injectable anti-tubercular drugs	Results
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1	Rahmawati et al, (Rahmawati et al, 2019).	Prospective Cross-sectional	72	Men:43 Woman:29 15-30 year: 19 (26.4%) 31-50 year:35 (48,6%) 51-65 year: 18 (25%)	ASHA	Kanamycin (48) Capreomycin (19) Kanamycin and capreomycin (5)	The prevalence of ototoxicity was 34 patients (47.2%). Ototoxicity was found mostly in two months of therapy, 26,5%. Ototoxicity was higher in patients with kanamycin (47.9%) compared to capreomycin (36.8%). Meanwhile, ototoxicity was found 80% in kanamycin and capreomycin group. Ototoxicity was significantly associated with increasing age (aOR:1.050, p value=0.029, CI95% 1.005-1.096). The risk of ototoxicity increased 5% every one year older.
2	Mustikaningtyas et al, (Mustikaningtyas al, 2013).	Retrospective study	41	Male: 17 Female: 24 21-30 year: 7 31-50 year: 26 51-60 year: 8	OAE	Kanamycin	Hearing loss was found in 19 patients (46.3%), 22 patients (53.7%) without any complaints. By audiometric examinations, 39 ears as mild hearing loss, 20 ears as moderate, 3 ears as moderate-severe, 1 ear as severe, 12 ears as very severe, and 7 ears as normal. By OAE examinations, 23 ears as normal cochlea, 45 ears cochlea disorders, and 14 ears were not examined.
3	Yulianti et al, (Yulianti et al, 2015).	Retrospective study	86	Male: 52 Female: 34 Age: 15-64 Mean age: 37,6	PTA	Kanamycin	Fifteen (17.4%) MDR-TB patients experienced hearing disorders and tinnitus with onset of symptoms at third month (53.3%), sixth

							month (40%), and tenth month (6.7%) of MDR-TB therapy.
4	Brahmono et al, (Brahmono et al, 2020).	Prospective Cross-sectional	15	Male: 8 Female: 7 Age: 26-56 Mean age: 39	DPOAE	Kanamycin	Cochlear dysfunction was found in 4 of 15 (26,67%) after administration of kanamycin for 4 weeks, but cochlear dysfunction was found in frequency of 10.000 Hz before and after treatment of kanamycin (p value=0.002). Tinnitus was found in 7 patients after four weeks of kanamycin. Hearing loss and vertigo were not found in all patients.
5	Wahyudin et al, (Wahyudin et al, 2018).	Prospective cohort	12	Male: 5 Female: 7 ≤ 40 year: 6 >40 year: 6	ASHA	Kanamycin	9 of 12 patients (75%) experienced ototoxicity. There was significant difference in high pitch audiometry before and after the administration of kanamycin in first, second, and until fifth month (p value <0.05). The ototoxicity events were mostly found in first month (33,3%).
6	Rakhmawati et al, (Rakhmawati et al, 2015).	Prospective cohort	36	Male: 22 Female: 16 < 20 year: 4 20-49 year: 28 ≥ 50 year: 6	DPOAE	Kanamycin	Audiometry was measured on the baseline and one month. Cochlear disorders was started to 10.000 Hz frequency on days 19-21, and 8.000 Hz frequency on days 25-27. There was no cochlea dysfunction in frequency less than 8.000Hz. Cochlea dysfunction was observed in 13,43% in 10.000 Hz and 7,04%

							in 8.000-10.000 Hz frequency
7	Irwan et al (Irwan et al, 2017).	Prospective Cross-sectional	33	Male:18 Female:15 Mean age: 39.6 ± 10.9	ASHA	Kanamycin	30 of 33 MDR-TB patients (90.9%) experienced ototoxicity. There was significant correlation between length of kanamycin and hearing threshold shift on frequency 4000 Hz and 8000 Hz (p value < 0.05, r 0,01 and 0.039, respectively). Mean kanamycin therapy was 3.73 ± 2.8 months. Based on clinical symptoms, 63.7% patients complaint were tinnitus and 45,5% had hearing loss

ASHA: American Speech Language and Hearing Association; DPOAE: Distortion Product Otoacoustic Emissions; OAE: Otoacoustic emissions

The total number of MDR-TB patients using aminoglycosides was 295 (N). All articles were observational studies, both prospective and retrospective assessing the ototoxicity during the treatment. Five studies are written in Indonesia and two studies are written in English. Patients who do not take their TB treatment properly or fail in TB category I are at risk of developing MDR-TB (Wangchuk et al, 2021). Genetic predisposition, history of TB treatment, and other factors such as diabetes mellitus, and co-infection HIV may lead to the mechanism of drug resistance. Factors associated with previous anti-tuberculosis treatments include insufficient or incomplete treatment and poor adherence to treatment. A review of the publication certainly implies that a TB history is the most significant predictor of MDR-TB (Khariani et al, 2017; Alemu et al 2018).

Out of seven studies, three studies reported the history of previous TB treatment. A study by Rahmawati et al, reported that in MDR-TB patients, the most common of the previous TB was TB category 1 (59,7%), category 1 and 2 (36,1%) (Rahmawati et al, 2019). A study by Mustikaningtyas et al, reported in MDR-TB patients, the history of the previous TB was treatment failure (44%), relapsed (31.6%), and

neglect patients (24.4%) (Mustikaningtyas al, 2013). Another study by Irwan et al, also reported the most common of the previous TB was TB category 1 (63.6%), category 2 (6.1%), category 1 and 2 (18.2%) (Irwan et al, 2017). A study in Egypt found that in MDR-TB, regimens of previous TB treatment were category I (32,1%), category II (50,8%), and category I and II (12,1%). Only less than 5% were new cases of MDR TB (Ibrahim et al, 2017). A study regarding the resistance of first-line TB drugs and prevalence of MDR-TB among naïve patients has been reported in China. The results showed the resistance to first-line TB drugs was 33,2% and the prevalence of MDR-TB was 5,7% (Wang et al, 2019). It indicated the failure treatment of category I and II were associated with the development of MDR-TB.

Numerous new cases of MDR-TB are caused by physician errors regarding drug regimens, dosing intervals, and treatment duration. MDR-TB developed from previous TB management errors like initiating an inadequate regimen using primary anti-TB drugs, adding the single medicine to an unsuccessful regimen, failing to detect preexisting resistance, and bio-availability variations anti-TB medications, which predispose the patients to MDR-TB. Non-compliance is often

underestimated and difficult to predict by physicians (Rumende et al, 2018). A study regarding risk factors in TB patients to develop MDR-TB has been reported in another country. A low patient motivation and poor adherence in taking medication were significantly associated with MDR-TB as risk factors (Wang et al, 2019).

In the present review, we reported seven studies evaluating the ototoxicity during MDR-TB treatment based on evaluation audiometry at baseline and after administration of second-line injectable anti-tubercular drugs. Six studies reported kanamycin and one study reported kanamycin and capreomycin as a cause of ototoxicity. The programmatic management of drug resistance TB in Indonesia, recommended the use of kanamycin in the intensive phase. Kanamycin is the first choice of aminoglycoside injection and is replaced with capreomycin when found resistant to kanamycin, hearing loss, or impaired kidney function. Kanamycin and capreomycin were administered in a dose 15-20 mg/kg/day, five times a week (Ministry of Health of Indonesia, 2016). Ototoxic medications affect both vestibular and cochlear parts of the inner ear, causing hearing impairment by disrupting the cochlear hair cells, especially in high frequency. In our study, ototoxicity ranged from 13.4% to 90.9% or 39.3% (116/295) in MDR-TB patients. This was similar to the previous study, which reported that the incidence of ototoxicity ranged from 4% to 62% (Dillard et al, 2021; Adetola et al, 2019). The vestibular disorders were identified based on the patient's symptoms while hearing impairment was determined by patients or by audiometry. The overall onset of symptoms of ototoxicity in this review was 1 to 3 months after administration second-line injectable anti-tubercular drugs.

A systematic review of Indian studies by Sarin et al, reported ototoxicity because second-line injectable in MDR-TB patients was 27.01% (121/448) (Sarin et al, 2019). Another systematic review reported the incidence and risk factors for ototoxicity in MDR-TB patients receiving aminoglycosides from 35 studies, but 86% of them failed to describe the specific method for the testing and classification of ototoxicity. From the five studies using standardized testing and classification of toxicity, ototoxicity was 18 to 62% (Hong et al, 2018).

The British Society of Audiology (BSA) (British Society of Audiology, 2011) and the

American Speech-Language-Hearing Association (ASHA) (ASHA, 1994) recommend hearing test at a baseline, weekly, or biweekly, and after several months of second-line injectable anti-tubercular cessation. Each evaluation should be conducted with otoscopy and tympanometry. Hearing loss must be compared to baseline values, and ototoxicity is defined as any of the following: a 20 dB decline at any one frequency; a 10 dB decline at any two consecutive frequencies, and; loss of response at three consecutive test frequencies where responses were initially provided (ASHA, 1994). If the patient is willing to cooperate, audiometry should be performed, and if no other international guidelines exist, the established ASHA guidelines should be followed. The time when hearing loss is first detected should be documented. If patients cannot cooperate, such as children, OAE should be performed as a screening test. The results should be reported as pass or refer. We recommend that hearing loss be classified using the ASHA criteria in research studies.

Although guidelines recommend several hearing test during the treatment especially in patients with changes in their audiogram, this is not universally followed in Indonesia's hospital or public center. In addition, there is a lack of coordinated guidelines recommending methods for optimal ototoxicity management in these patients. Notably, because MDR-TB patients are frequently exposed to streptomycin in the past, the hearing should be tested before initiating second-line anti-tubercular drugs (Hong et al, 2018). However, several studies reported that there was no association between streptomycin exposure and hearing loss. A study by Reviono et al, reported that 56.7% of MDR-TB patients at the Dr. Moewardi Hospital, Indonesia, experienced hearing loss, and 54.2% of them used streptomycin, even though there was no correlation between the use of streptomycin and hearing loss (p -value > 0.05). Unfortunately, their study did not examine hearing function before and after administration of streptomycin (Reviono et al, 2013). Furthermore, it was strengthened by Ratnawati et al, who stated that history of streptomycin use and body mass index were not risked factors for hearing disorders (Ratnawati et al, 2017).

In this present review, out of seven studies, only one study reporting risk factors to

develop hearing loss. Rahmawati et al, reported a significant association between age and the ototoxic incidence with a 5% increase in risk with each increase in 1 year beginning at age thirty-eight.¹³ Age is a risk factor for ototoxic, especially in the elderly. This is because of the accumulation of mitochondrial DNA mutations, which play an important role in the apoptotic mechanism of cochlear hair cells. Another study by Ratnawati et al, reported that age more 40 years old (HR=2.419, p-value=0,000, CI 95%= 1,716-3,409) and female (HR=1,549, p-value=0,015, CI95% 1,089-2,202) were significantly associated with hearing disorders after kanamycin administration in MDR-TB patients at the Dr. Moewardi Hospital, Surakarta (Ratnawati et al, 2017). A study by Irwan et al, reported a correlation between the length of kanamycin use and hearing loss at frequency 4000 Hz to 8000 Hz (Irwan et al, 2017). A study also reported that the duration of kanamycin treatment is a risk factor of hearing loss (Ernest et al, 2021).

However, there are no studies that directly compare the effects of aminoglycoside ototoxicity in MDR-TB patients in Indonesia. A study in Namibian by Sagwa et al, comparing the cumulative incidence of hearing loss between amikacin or kanamycin-based regimen in MDR-TB patients, reported that patients treated with amikacin had a higher risk of a severe form of hearing loss compared to kanamycin (OR=4.0, CI 95% 1.5-10.8) (Ernest et al, 2021). Similarly, a study by Sabur et al, stated that the use of amikacin and impaired renal function was significantly associated with hearing loss compared to capreomycin and streptomycin (Sabur et al, 2021). A low ototoxicity of capreomycin for the treatment of MDR-TB in the intensive phase was reported by Shibeshi et al, the ototoxic symptoms were found in 4.8% subjects. Capreomycin was the most common used (84,7%) and followed by kanamycin (5,6%), amikacin (4,3%), and streptomycin (0,2%) (Shibeshi et al, 2019). Fortunately, in our review, we found no studies using amikacin-based regimens in MDR-TB patients.

Identifying risk factors in patients is important to monitor the ototoxic during treatment with second-line injectable anti-tubercular drugs. Patients with risk factors prioritize audiometric tests periodically and culture conversion as an effort to shorten drug exposure. The second-line of injectable anti-

tuberculosis drugs has the side effect of ototoxic, the dose-dependent, narrow therapeutic index, and wide pharmacokinetics variations.³³ Examination of drug levels in serum is required to monitor the concentration of the drug in the body. Aminoglycosides reach the inner ear rapidly after the injectable administration. These drugs were found is in the inner ear within minutes of injection and reach a plateau 30 minutes to 3 hours after administration. The half-life elimination of aminoglycosides is about 3–5 hours, but their concentration was found in fluid in the inner ear for several months after the therapy was stoppe (Adetola et al, 2019). A prospective study reported that the total dose and therapy duration was associated with ototoxic events (Rachna et al, 2017).

Although kanamycin induced ototoxicity in mostly Indonesian studies, there was limited study analyzing the relationship between the pharmacokinetics of kanamycin and hearing loss. A recent study reported that kanamycin exposure to be significantly associated with hearing loss with a 3% increased risk of hearing loss for every 10 mcg h/L increase in kanamycin AUC 0-10. The median cumulative dose of kanamycin was not statistically higher (46,62 mg) in patients experiencing hearing loss than those without hearing loss (41,67 mg), p-value 0.390. This phenomenon occurred because clinicians tend to stop or decrease the dose of kanamycin in patients suspected of hearing loss, which may attenuate the effect of cumulative exposure to kanamycin (Ghafari et al, 2020). Furthermore, co-administration with other drugs (macrolides, loop diuretics, salicylate analgesics) with injectable anti-tubercular drugs has the risk of increasing the occurrence of ototoxicity.

Assessment of audiometry on high frequency is the most effective indicator in assessing ototoxic occurrence, especially if it uses ultra-high frequencies (> 8000kHz) and or otoacoustic emission (OAE) (de Vasconcelos et al, 2017). Detection of ototoxic premature at high frequency and is followed by good management will maintain patients' communication and quality of life. The primary management of ototoxicity is prevention. Kidney function should be measured before starting any potentially ototoxic drug therapy. Patients at high risk should be monitored their hearing regularly. All patients should be asked routinely for early symptoms of vestibular

and auditory dysfunction. In the early stages of ototoxicity, ototoxic drugs should be stopped immediately and replaced with alternative medicines that are less toxic.

There were no studies reported regarding discontinuation or replacement of therapy in patients experiencing ototoxicity in our review. This results cause a lack of information that can be provided to the health care team regarding procedures for treating ototoxic symptoms in MDR-TB patients in Indonesia. The best approach to minimize hearing loss is modifying therapy, such as switching therapy, reducing the dose, and stopping as soon as possible. A current study in Ethiopia reported a modification of treatment regimens, including switching injectable (5,3%) and discontinuation (0.9%) due to the ototoxicity of injectable anti-tubercular drugs MDR-TB patients (Shibeshi et al, 2019). Surprisingly, several studies reported the benefits of antioxidants in reducing the incidence of ototoxicity due to injectable anti-tubercular drugs.

A meta-analysis by Kranzer et al, determining the efficacy and safety of N-acetylcysteine (NAC) in preventing aminoglycosides-induced ototoxicity, reported that the co-administration of NAC at 4-6 weeks with aminoglycosides (amikacin and gentamicin) reduced ototoxicity (RR 0.14, CI95% 0.05-0.45). After the NAC administration for over six weeks for several diseases, several side effects were reported, such as abdominal pain, nausea and vomiting, diarrhea, and arthralgia, significantly increasing in the NAC group compared to placebo. However, these side effects were relatively low, from 1.6% for diarrhea to 6.1% for nausea. However, their study was performed in patients with end-stage renal disease and bloodstream infection, not in MDR-TB patients. NAC was administered 600 mg twice daily for 14 days for up to 7 days after administering of aminoglycosides was complete (Kranzer et al, 2015). A randomized controlled trial was urgently needed to clarify the efficacy and safety of NAC in MDR-TB settings.

A randomized controlled trial (RCT) by Poluan et al, reported that the administration of ginkgo biloba was significantly reduced hearing loss in MDR-TB patients after three weeks based on an audiogram and DPOAE (p-value < 0.05) compared to alfa-tocopherol (Poluan et al, 2020).

After four weeks of ginkgo biloba administration, the incidence of hearing loss was significantly lower than those in the alfa-tocopherol group. Ginkgo biloba inhibited ROS and NO synthesis, lipid peroxidase, and other radicals and prevented apoptosis. Thus it acts as a vasodilator and improves blood flow microcirculation in the cochlea.⁴⁰ However, a study by Poluan was a single-blind RCT, and the dose of ginkgo biloba and alfa-tocopherol was not stated clearly. Furthermore, the number of samples was relatively small, only in thirty-two MDR-TB patients.

This scoping review has some limitations. Most of the included studies were retrospective with a cross-sectional design, so the confounding variables was difficult to be controlled. The cumulative dose of injectable anti-tubercular drugs was not reported in most studies. The interventions for the management of hearing impairment and therapeutic drug monitoring (TDM) for aminoglycoside were not studied in this review. Furthermore, since a limited number of studies, the scoping review included few studies published in non-indexed journals. In addition, the studies have a small number of MDR-TB patients making the results cannot interpret to the entire population. Further research was needed to clarify the ototoxicity of injectable anti-tubercular drugs and its risk factors with larger sample size.

CONCLUSION

Ototoxicity was found in a high percentage of Indonesian patients in studies that used pure tone audiometry before and after administering second-line anti-tubercular drugs. Variations in the incidence of ototoxicity occurred in both the Indonesian and global populations, warranting routine ototoxicity monitoring. It is critical to raise physician and pharmacist awareness of the importance of monitoring ototoxicity during the treatment process. Patients should be informed about the potential side effects of second-line anti-tubercular drugs, report symptoms, and be involved in the decision-making process

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CONFLICT OF INTEREST

All authors declared there was no conflict of interest.

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