REVIEW ARTICLE

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-7.
https://doi.org/10.22037/orlfps.v10i1.46950

Gentamicin-induced Hearing Loss: Ototoxicity, Challenges, Pathogenesis and Mechanism

Hamid Reza Mosleh [1, 2], Hojjat-Allah Abbaszadeh [3,4,2]*, Zahra Vahdanifar [3]

1. Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Hearing Disorders Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Rayan stem cells and Regenerative medicine research center, Ravan Sazeh Company, Tehran, Iran

Article Info

Article Note:
Received: November 2024
Accepted: November 2024
Publish Online: December 2024

Corresponding Author:
Dr. Hojjat-Allah Abbaszadeh

Email:
hoomanabs@gmail.com

Keywords:
Gentamicin;
Ototoxicity;
Hearing loss;
Deafness;
Inner ear.

Abstract

Background: The most well-known side-effect of Aminoglycoside antibiotics is significant hearing loss and balance issues. For instance, Gentamicin has been widely recognized for causing hearing loss in most patients.

Aimes: This study explored the available evidence on hearing loss following Gentamicin use.

Methods: We conducted a comprehensive literature search using Web of Science and PubMed, with the keywords: "Deafness," "Hearing Loss," "Drugs," "Adverse Drug Reaction," "Ototoxicity," "Gentamicin," "Aminoglycosides," "Inner Ear," and "Audiogram." All data were independently extracted and relevant research was used to write this review article.

Results: The reviewed studies highlight the critical factors influencing the severity of Gentamicin-induced hearing loss, including the site of administration, dosage, and co-administration with other ototoxic agents like Vancomycin. The mechanisms underlying Gentamicin ototoxicity involve oxidative stress, inflammation, and apoptosis of sensory hair cells. The literature also suggests safer alternatives within the aminoglycoside class, such as apramycin and Gentamicin C1a, which could be considered for future clinical use.

Conclusion: Gentamicin has been consistently associated with significant ototoxic effects, particularly hearing loss, across various species and clinical contexts. Balancing its therapeutic benefits against potential hearing loss is essential. Developing more targeted interventions that preserve its antimicrobial efficacy while minimizing hearing loss risk may be possible.

Conflicts of Interest: The Authors declare no conflicts of interest.
Please cite this article as: Mosleh HR, Abbaszadeh H, Vahdanifar Z. Gentamicin-induced Hearing Loss: Ototoxicity, Challenges, Pathogenesis and Mechanism. J Otorhinolaryngol Facial Plast Surg 2024;10(1):1-7. https://doi.org/10.22037/orlfps.v10i1.46950

Introduction

Hearing loss is prevalent and can profoundly affect the aging process (1). It affects children, with roughly 1 in 5 burdened by Inadequate hearing rehabilitation, which can adversely impede speech, language, development, education, and cognitive abilities. In 2019, around 72.9 million individuals in the United States, equivalent to one in five, were predicted to suffer from hearing loss (3). Sensorineural hearing loss (SNHL) is the predominant type, leading to a gradual decline of the sensory hair cell and cochlear nerve functions. The inability of the human inner ear hair cells to regenerate results in irreparable damage, causing permanent hearing loss. Sensorineural hearing loss (SNHL) may be genetically inherited or acquired from aging, exposure to noise, or

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-7.
https://doi.org/10.22037/orlfps.v10i1.46950

ototoxic medications. An ototoxic medication can damage the inner and outer hair cells essential for hearing, resulting in hearing loss (5). Ototoxicity generally denotes harm to the inner ear tissues and function resulting from exposure to certain medications. The etiology of ototoxicity is frequently multifaceted, potentially harming cochlear hair cells or other cells that govern cochlear hair cell functionality. Clinical strategies to mitigate ototoxicity include identifying at-risk patients, monitoring for drug concentrations, performing routine audiometric assessments, and selecting less ototoxic alternatives where possible (6). Research indicates that between 150 and 600 pharmaceuticals may possess ototoxic properties, which can initially remain undetected (7). Aminoglycoside antibiotics induce considerable auditory impairment and vestibular dysfunction, as evidenced by animal research and human findings. Gentamicin is commonly acknowledged for inducing hearing loss in most people who receive it (8). Elevated doses of aminoglycoside antibiotics, like Gentamicin, can alter hearing thresholds by impairing inner and outer hair cells, therefore restricting their usage. Aminoglycosides constitute a category of antibiotics sanctioned by the Food and Drug Administration (FDA) for the treatment of infections. They typically target severe bacterial and mycobacterial diseases, with Gentamicin being administered for meningitis and sepsis (10). Gentamicin is well recognized for its greater vestibulotoxicity compared to cochleotoxicity, making it a prevalent option for these purposes. It is recommended to refrain from administering polymyxin B-neomycin-hydrocortisone drops, commonly employed for acute otitis externa, in instances with eardrum perforation (11). A notable adverse effect of aminoglycosides is auditory impairment, as these antibiotics are thought to induce irreversible harm to sensory cells and neurons in the inner ear, resulting in hearing loss (9). Gentamicin is recognized for its vestibulotoxic effects, impairing the vestibular system by initially impacting the cristae and then disrupting the centriolar areas of the maculi. This may lead to clinical manifestations like dizziness, ataxia, and nystagmus. The destruction of auditory sensory cells in the organ of Corti results in cochleotoxicity, frequently linked to the excessive generation of oxidative free radicals, which may present as hearing loss or tinnitus (12). Studies suggest that Gentamicin may induce hair cell death through the Hsp90/Akt signaling pathway (13). N-methyl-D-aspartate (NMDA) receptors are also involved in gentamicin-induced ototoxicity, affecting the quantity and distribution of inner hair cell ribbon synapses (14). Nevertheless, the precise mechanisms remain inadequately comprehended. If HL remains untreated, it may cause communication difficulties, perhaps leading to social isolation and depression. Treatment options for hearing loss are predominantly restricted to medical devices such as hearing aids and cochlear implants. Clinical strategies for mitigating ototoxicity encompass identifying at-risk patients, monitoring pharmacological doses, doing regular auditory evaluations, and transitioning to less ototoxic treatments when possible. Timely identification of ototoxicity with continuous monitoring is essential, as it facilitates treatment modifications to reduce or avert irreversible hearing impairment and balance disturbances. Nonetheless, certain pharmacological treatments that induce ototoxicity may remain unrecognized for prolonged durations, since healthcare professionals may fail to acknowledge the necessity of monitoring drug levels. Consequently, this investigation examined the evidence pertaining to hearing loss after the administration of Gentamicin.

Methods

We performed an extensive literature review utilizing Web of Science and PubMed, encompassing the timeframe from the

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-7.
https://doi.org/10.22037/orlfps.v10i1.46950

establishment of each database until September 2024. Our search technique employed a combination of medical topic headings (MeSH) and pertinent text keywords, including "Deafness," "Hearing Loss," "Drugs," "Adverse Drug Reaction," "Ototoxicity," "Gentamicin," "Aminoglycosides," "Inner Ear," and "Audiogram." We conducted a manual review of references from primary research and review articles to discover other pertinent studies. All data were extracted independently. For each article, we collected data on the author, publication year, journal, medications investigated, sample size, drug regimen, and follow-up period. All detected records were inputted into Reference Manager Version 11.0, and duplicates were excluded. Titles and abstracts, when accessible, were evaluated for relevance according to established eligibility criteria. Full-text articles were acquired for all potentially pertinent records (Figure 1).

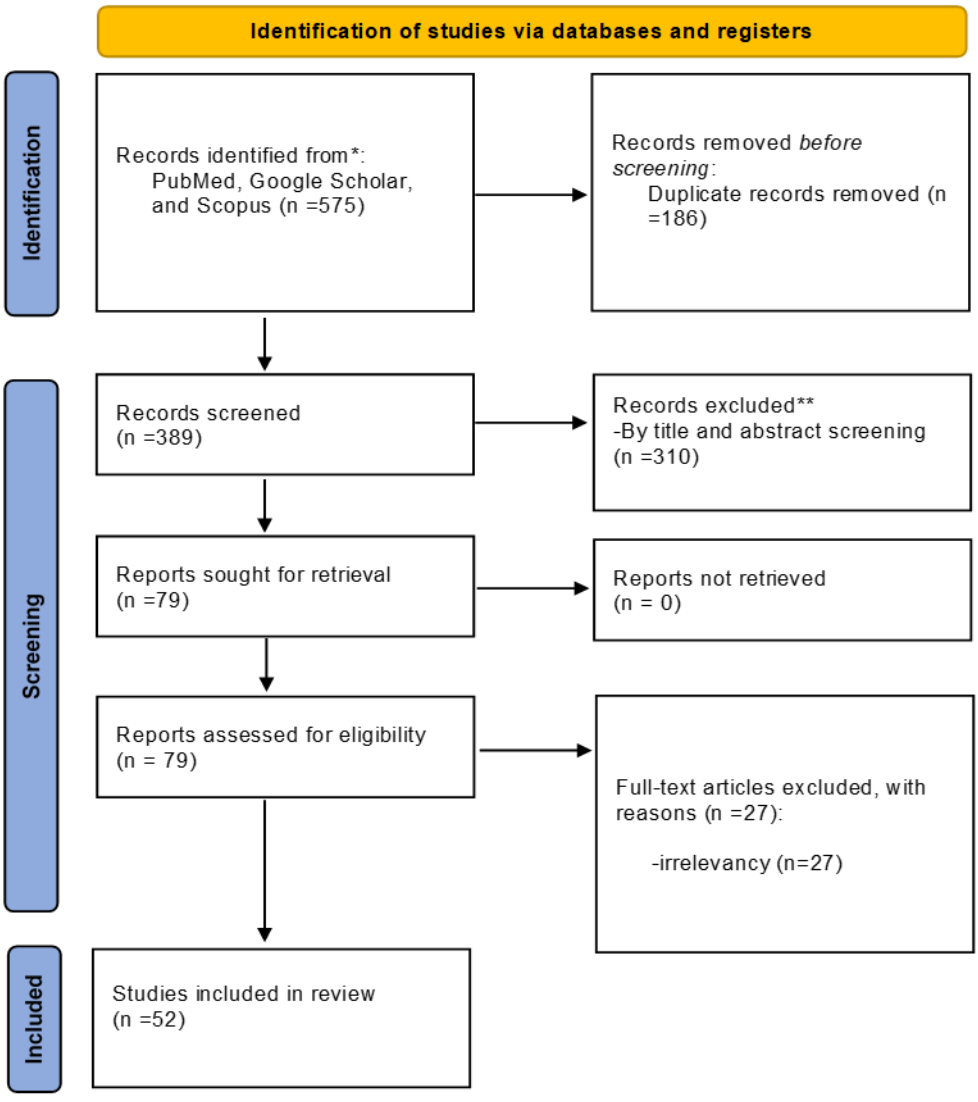

Figure 1. PRISMA flowchart of study selection process

We incorporated foreign language records into our search, translating titles and abstracts as necessary for screening. Ultimately, we employed pertinent research to compose this review piece.

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-7.
https://doi.org/10.22037/orlfps.v10i1.46950

Results

The reviewed studies emphasized the key aspects influencing the degree of Gentamicin-induced auditory impairment, including the administration site, dosage, and concurrent use with other ototoxic substances such as Vancomycin. The mechanisms of Gentamicin ototoxicity are complex, involving oxidative stress, inflammation, and death of sensory hair cells, leading to cochlear and vestibular damage. Gentamicin may be connected with genes related to oxidative phosphorylation and integrins, thus contributing to hearing loss (16). Nevertheless, research opposing this notion indicated no heightened incidence of hearing loss in children administered Gentamicin in comparison to control groups (17). Strategies including meticulous surveillance of blood levels, restricting treatment time, and investigating protective drugs such as dexamethasone, melatonin, and antioxidants have demonstrated possible alleviating therapies for Gentamicin-induced ototoxicity. The research indicates safer alternatives within the aminoglycoside class, including apramycin and Gentamicin C1a, which may be investigated for future clinical application (18).

Discussion

A comparative study using guinea pigs examined the effects of Gentamicin on either the round window membrane or the stapes footplate, emphasizing on the resultant hearing loss and related histological alterations. The animals administered Gentamicin at the stapes footplate exhibited markedly greater hearing loss in the 8-32 kHz range, a substantial decline in outer hair cell numbers in the cochlear basal turn, and a reduction in standard type I cells in the utricle; in contrast to those treated on the round window membrane or with saline controls. This indicates that Gentamicin injection onto the stapes footplate can cause more pronounced hearing loss (19). Tanaka et al. (2021) examined the correlation between different aminoglycosides and auditory impairment utilizing the FDA Adverse Event Reporting System. Their investigation of the drug-gene network indicated that Gentamicin may be associated with genes related to oxidative phosphorylation and integrins, perhaps contributing to hearing loss (16). Furthermore, Gentamicin administration has been demonstrated to cause synaptic impairment in inner hair cells, highlighting the essential function of myosin VI downregulation in Gentamicin-induced synaptic injury (20). Ishikawa et al. (2019) investigated the possible relationship between aminoglycoside ototoxicity and hearing impairment at various doses. Five aminoglycosides—Neomycin, Gentamicin, Paromomycin, Apramycin, and Gentamicin C1a—were evaluated on 45 guinea pigs. The authors found a dose-dependent correlation between compound action potential (CAP) and outer hair cell destruction, affirming that aminoglycosides, such as Gentamicin, substantially contribute to hearing loss (18). Subsequent investigations in guinea pigs revealed that Vancomycin significantly enhances the ototoxic effects of Gentamicin. Administration of Gentamicin at 50 mg/kg resulted in a little alteration in the alternating current (AC) cochlear potential. This impact was significantly amplified when administered with Vancomycin, resulting in a substantial decrease in AC cochlear potential and a pronounced increase in outer hair cell loss, particularly at elevated dosages of Vancomycin (21). A separate investigation with guinea pigs showed that noise condition did not reduce Gentamicin-induced ototoxicity. Regardless of exposure to 85 dB broadband noise for ten days, neither functional nor morphological protection were evident when the subjects were subsequently administered a high dosage of Gentamicin (160 mg/kg daily for ten days) (22). Fuchs et al. (2016) evaluated the effects of Gentamicin on sensorineural hearing loss (SNHL) in very low birth weight (VLBW) newborns. The risk of sensorineural hearing loss from Gentamicin exposure can be

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-7.
https://doi.org/10.22037/orlfps.v10i1.46950

mitigated by reducing treatment duration, monitoring serum levels, and appropriately adjusting dosages (23). Aleman et al. (2021) examined auditory impairment in horses administered intravenous Gentamicin for seven days. The research determined that even at prescribed dosages, Gentamicin may induce irreversible sensorineural hearing loss in equines (24).

Dobie et al. (2006) assessed whether individuals with vestibulotoxic responses to Gentamicin exhibited inferior hearing thresholds compared to age- and sex-matched controls. Their findings indicated that these patients had hearing thresholds comparable to the general population across most frequencies, with a minor albeit statistically insignificant decline in 1.0 and 2.0 kHz (25). Hemmingsen et al. (2020) investigated the enduring impacts of prenatal Gentamicin exposure on auditory function. Their investigation of high-dose Gentamicin (6 mg/kg) revealed no significant disparity in hearing thresholds at school age as compared to a control group (26).

Yu et al. (2014) indicated that the administration of high-concentration Gentamicin into the middle ear of guinea pigs can lead to a total loss of auditory and vestibular function. This therapy obliterated the majority of sensory hair cells in the inner ear and resulted in delayed degeneration of spiral ganglion neurons (27). In clinical environments, intratympanic Gentamicin has been utilized to treat Ménière's disease. Research indicates that individuals with early-stage Ménière's disease exhibit superior hearing preservation when administered low-dose Gentamicin compared to those with advanced disease (28–30). Low-dose, symptom-targeted Gentamicin protocols have successfully managed vertigo while reducing cochlear injury (30). Iftikhar et al. (2013) examined the safety of Gentamicin for the treatment of newborn sepsis in a community context in Pakistan. Their investigation revealed no elevated risk of hearing loss in children administered Gentamicin relative to controls. However, children with a history of ear discharge or a familial predisposition to deafness exhibited showed higher risks (17). Cross et al. (2015) and Garinis et al. (2017) identified an increased risk of hearing loss in newborns subjected to Gentamicin in the NICU, especially with prolonged treatment durations. These findings indicate that incorporating higher-frequency distortion product otoacoustic emission (DPOAE) evaluations into NICU hearing screening regimens may enhance the identification of newborns susceptible to ototoxicity (31,32).

Gentamicin-induced auditory impairment is linked to heightened oxidative stress and an inflammatory response that stimulates mitogen-activated protein kinases (MAPKs), resulting in hair cell death. Protective measures, including dexamethasone, melatonin, tacrolimus, Nigella sativa oil, Korean red ginseng, and ferulic acid, have demonstrated potential in alleviating Gentamicin-induced ototoxicity (33–37). Mannitol has been shown to inhibit Gentamicin-induced hair cell loss by functioning as a free radical scavenger, thus reducing oxidative stress (38).

Conclusion

Gentamicin, a commonly utilized aminoglycoside antibiotic, has been continuously linked to considerable ototoxic sequela, especially auditory impairment, in many animals and clinical scenarios. Despite the risks, its therapeutic efficacy is unequivocal, especially in the management of life-threatening infections. Consequently, it is crucial to weigh its therapeutic advantages against the risk of hearing impairment. Ongoing research is essential to enhance these protective techniques and to identify at-risk populations, especially vulnerable groups such as infants and persons with predisposing conditions.

As our comprehension of Gentamicin's ototoxic processes advances, it may become feasible to create more tailored therapies that maintain its

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-7.
https://doi.org/10.22037/orlfps.v10i1.46950

antibacterial effectiveness while reducing the risk of auditory impairment.

Acknowledgments
Not declared.

Conflicts of Interest
The authors declare no conflicts of interest.

Ethics
IR.SBMU.AEC.1403.051

Financial Support
Hearing Disorders Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, financially supported this work.

Authors ORCIDs
Hojjat-Allah Abbaszadeh
https://orcid.org/0000-0002-7157-1834

References
1. Nieman CL, Oh ES. Hearing loss. Ann Intern Med. 2020;173(11):ITC81–96.

2. Lieu JEC, Kenna M, Anne S, Davidson L. Hearing loss in children: a review. Jama. 2020;324(21):2195–205.

3. Lin FR. Age-related hearing loss. N Engl J Med. 2024;390(16):1505–12.

4. Tan WJT, Song L. Role of mitochondrial dysfunction and oxidative stress in sensorineural hearing loss. Hear Res. 2023;434:108783.

5. Jalkh A. Hidden Hearing Loss: Causes, Current Knowledge, and Future Directions. Int J Otolaryngol Head Neck Surg. 2023;12(3):107–23.

6. Rabiço-Costa D, Gil-da-Costa MJ, Barbosa JP, Bom-Sucesso M, Spratley J. Platinum-drugs ototoxicity in pediatric patients with brain tumors: a 10-year review. J Pediatr Hematol Oncol. 2020;42(1):e25–31.

7. Reynard P, Thai-Van H. Drug-induced hearing loss: Listening to the latest advances. Therapies. 2024;79(2):283–95.

8. Rybak LP, Ramkumar V, Mukherjea D. Ototoxicity of non-aminoglycoside antibiotics. Front Neurol. 2021;12:652674.

9. Prayle A, Watson A, Fortnum H, Smyth A. Side effects of aminoglycosides on the kidney, ear and balance in cystic fibrosis. Thorax. 2010;65(7):654–8.

10. Geyer LB, Barreto SSM, Weigert LL, Teixeira AR. High frequency hearing thresholds and product distortion otoacoustic emissions in cystic fibrosis patients. Braz J Otorhinolaryngol. 2015;81(6):589–97.

11. Rizk HG, Lee JA, Liu YF, Endriukaitis L, Isaac JL, Bullington WM. Drug- Induced Ototoxicity: A Comprehensive Review and Reference Guide. Pharmacother J Hum Pharmacol Drug Ther. 2020;40(12):1265–75.

12. Hayward RS, Harding J, Molloy R, Land L, Longcroft- Neal K, Moore D, et al. Adverse effects of a single dose of Gentamicin in adults: a systematic review. Br J Clin Pharmacol. 2018;84(2):223–38.

13. Lai R, Li W, Hu P, Xie D, Wen J. Role of Hsp90/Akt pathway in the pathogenesis of gentamicin-induced hearing loss. Int J Clin Exp Pathol. 2018;11(9):4431.

14. Hong J, Chen Y, Zhang Y, Li J, Ren L, Yang L, et al. N- methyl- D- aspartate receptors involvement in the gentamicin- induced hearing loss and pathological changes of ribbon synapse in the mouse cochlear inner hair cells. Neural Plast. 2018;2018(1):3989201.

15. Laurell G. Pharmacological intervention in the field of ototoxicity. HNO. 2019;67(6):434–9.

16. Tanaka M, Matsumoto K, Satake R, Yoshida Y, Inoue M, Hasegawa S, et al. Gentamicin-induced hearing loss: A retrospective study using the Food and Drug Administration Adverse Event Reporting System and a toxicological study using drug− gene network analysis. Heliyon. 2021;7(7).

17. Iftikhar U, Ali SA, Tikmani SS, Azam I, Saleem S, Zaidi AK. Risk of hearing loss in children exposed to Gentamicin for the treatment of sepsis in young infancy: A community based cohort study in Pakistan. J Pakistan Med Assoc. 2013;63(10):1226.

18. Ishikawa M, García-Mateo N, Čusak A, López-Hernández I, Fernández-Martínez M, Müller M, et al. Lower ototoxicity and absence of hidden hearing loss point to gentamicin C1a and apramycin as promising antibiotics for clinical use. Sci Rep. 2019;9(1):2410.

19. King EB, Salt AN, Kel GE, Eastwood HT, O'leary SJ. Gentamicin administration on the stapes footplate causes greater hearing loss and vestibulotoxicity than round window administration in guinea pigs. Hear Res. 2013;304:159–66.

20. Li G, Gao Y, Wu H, Zhao T. Gentamicin administration leads to synaptic dysfunction in inner hair cells. Toxicol Lett. 2024;391:86–99.

21. Brummett RE, Fox KE, Jacobs F, Kempton JB, Stokes Z, Allyson B. Augmented gentamicin ototoxicity induced by Vancomycin in guinea pigs. Arch Otolaryngol Neck Surg. 1990;116(1):61–4.

22. Strose A, Hyppolito MÂ, Colombari GC, Rossato M, Oliveira JAA de. Lack of protection against gentamicin ototoxicity by auditory conditioning with noise. Braz J Otorhinolaryngol. 2014;80(5):390–6.

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-7.
https://doi.org/10.22037/orlfps.v10i1.46950

23. Fuchs A, Zimmermann L, Bickle Graz M, Cherpillod J, Tolsa J-F, Buclin T, et al. Gentamicin exposure and sensorineural hearing loss in preterm infants. PLoS One. 2016;11(7):e0158806.

24. Aleman MR, True A, Scalco R, Crowe CM, Costa LRR, Chigerwe M. Gentamicin- induced sensorineural auditory loss in healthy adult horses. J Vet Intern Med. 2021;35(5):2486–94.

25. Dobie RA, Black FO, Pezsnecker SC, Stallings VL. Hearing loss in patients with vestibulotoxic reactions to gentamicin therapy. Arch Otolaryngol Neck Surg. 2006;132(3):253–7.

26. Hemmingsen D, Mikalsen C, Hansen AR, Fjalstad JW, Stenklev NC, Klingenberg C. Hearing in schoolchildren after neonatal exposure to a high-dose gentamicin regimen. Pediatrics. 2020;145(2).

27. Yu J, Ding D, Wang F, Jiang H, Sun H, Salvi R. Pattern of hair cell loss and delayed peripheral neuron degeneration in inner ear by a high-dose intratympanic gentamicin. J Otol. 2014;9(3):126–35.

28. Silverstein H, Wazen J, Van Ess MJ, Daugherty J, Alameda YA. Intratympanic gentamicin treatment of patients with Ménière's disease with normal hearing. Otolaryngol Neck Surg. 2010;142(4):570–5.

29. Delgado LP, Rodrigo JF, Peña PA. Intratympanic gentamicin in Ménière's disease: our experience. J Laryngol Otol. 2011;125(4):363–9.

30. Scarpa A, Avallone E, Carucci M, Salzano G, Chiarella G, Cassandro C, et al. Efficacy and preservation of hearing with low-dose Gentamicin in unilateral meniere's disease: A clinical symptomatology-based study. Am J Otolaryngol. 2024;45(1):104116.

31. Cross CP, Liao S, Urdang ZD, Srikanth P, Garinis AC, Steyger PS. Effect of sepsis and systemic inflammatory response syndrome on neonatal hearing screening outcomes following gentamicin exposure. Int J Pediatr Otorhinolaryngol. 2015;79(11):1915–9.

32. Garinis AC, Liao S, Cross CP, Galati J, Middaugh JL, Mace JC, et al. Effect of Gentamicin and levels of ambient sound on hearing screening outcomes in the neonatal intensive care unit: a pilot study. Int J Pediatr Otorhinolaryngol. 2017;97:42–50.

33. Bas E, Van De Water TR, Gupta C, Dinh J, Vu L, Martínez- Soriano F, et al. Efficacy of three drugs for protecting against gentamicin- induced hair cell and hearing losses. Br J Pharmacol. 2012;166(6):1888–904.

34. Edizer DT, Yigit O, Cinar Z, Gul M, Kara E, Yigitcan B, et al. Protective role of intratympanic nigella sativa oil against Gentamicin induced hearing loss. Int J Pediatr Otorhinolaryngol. 2017;97:83–8.

35. Choung Y, Kim SW, Tian C, Min JY, Lee HK, Park S, et al. Korean red ginseng prevents gentamicin- induced hearing loss in rats. Laryngoscope. 2011;121(6):1294–302.

36. Tian CJ, Kim SW, Kim YJ, Lim HJ, Park R, So H-S, et al. Red ginseng protects against gentamicin-induced balance dysfunction and hearing loss in rats through antiapoptotic functions of ginsenoside Rb1. Food Chem Toxicol. 2013;60:369–76.

37. Gu L, Cui X, Wei W, Yang J, Li X. Ferulic acid promotes survival and differentiation of neural stem cells to prevent gentamicin-induced neuronal hearing loss. Exp Cell Res. 2017;360(2):257–63.

38. Wood JW, Bas E, Gupta C, Selman Y, Eshraghi A, Telischi FF, et al. Otoprotective properties of mannitol against Gentamicin induced hair cell loss. Otol Neurotol. 2014;35(5):e187–94.