doi.org/10.36721/PJPS.2025.38.5.REG.14677.1

Evaluation of the safety of 1% voriconazole ear drops for the treatment of tympanic membrane perforation-associated suppurative otomycosis

Mao Jin[1], Yuan Zhao[2], Zhanwei Dong[2], Yuejiao Zhang[3], Lei Zhang[1,2], Xinxin Yang[2], Rui Du[2] and Shoude Zhang[1,2*]

[1]Department of Otolaryngology-Head and Neck Surgery, Sir Run Run Shaw Hospital, Medical College of Zhejiang University, Hangzhou, China

[2]Department of Otolaryngology-Head and Neck Surgery, Zhejiang University School of Medicine Affiliated Sir Run Run Shaw Hospital Xinjiang Corps Alaer Hospital, Alaer, China

[3]Nursing Department, The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China

Abstract: Otomycosis is a common otolaryngologic condition commonly complicated by tympanic membrane perforation (TMP). Although topical voriconazole has been found effective in TMP-free otomycosis, data on its safety in TMP-associated otomycosis are limited. This study was conducted to determine the safety profile of 1% ear drops of voriconazole in a rabbit model of TMP-associated suppurative otomycosis due to a clinical isolate of *Aspergillus terreus*. The local preparation was applied three times daily for seven consecutive days. Therapeutic efficacy was assessed by otoendoscopy, while safety was established by brainstem auditory evoked potential (BAEP) assessment and scanning electron microscopy (SEM) of cochlear hair cells. Serum levels of voriconazole were also quantified to assess systemic absorption. No difference was noted in pre- and post-treatment auditory thresholds (27 ± 6.75 dB vs. 27 ± 4.83 dB, $P > 0.99$). SEM examination demonstrated no damage to cochlear hair cells, and serum voriconazole concentrations remained undetectable after application. The results conclude that 1% voriconazole ear drops are safe for the treatment of TMP-associated suppurative otomycosis in this animal model. Limitations are that only one species of fungi and a preparation made at home were utilized, and further studies with other pathogens and commercial preparations are needed.

Keywords: Otomycosis, voriconazole ear drops, tympanic membrane perforation, antifungal otic therapy, auditory safety assessment

Submitted on 29-05-2025 – Revised on 06-06-2025– Accepted on 11-07-2025

INTRODUCTION

Otomycosis is a common fungal infection often encountered by otorhinolaryngologists and has been documented to present an incidence of 9% to 30% of ear symptoms that have been documented (Bojanović *et al.,* 2023; Sangaré *et al.,* 2021). Tympanic membrane perforation (TMP) affects approximately 30% of otomycosis and may lead to compromise of the middle ear structure with resulting clinical presentation in the form of hearing loss, vertigo, tinnitus, and other ear dysfunctions (Koltsidopoulos and Skoulakis, 2020; Javidnia *et al.,* 2022). Invasive otomycosis though rare, may present fatal complications (Stemler *et al.,* 2023; El Korbi *et al.,* 2022).

No standard treatment protocol has been suggested to date for otomycosis. The most common one in practice is mechanical removal of the external auditory canal debridement and topical imidazole antifungals as an ointment application (Lee *et al.,* 2021; Antunes *et al.,* 2022). Even though therapeutic in the majority, non-therapeutic effects are seen in some patients due to either resistance of fungal types, anatomical occlusion through an external auditory canal stenosis, or deep middle ear lesions to which local cream would have insufficient access (Zhang *et al.,* 2021). Since Aspergillus species are the most frequently suspected causes of otomycosis, triazole antifungals such as voriconazole could be superior to imidazoles (Ullmann *et al.,* 2018; Garcia-Vidal *et al.,* 2019; Hua *et al.,* 2003). However, their topically available commercial formulation is not common.

Intriguingly, there is also a parallel in ophthalmology, where fungal keratitis caused by Fusarium and Aspergillus species has been successfully treated with topical voriconazole. Despite the unavailability of commercially prepared topical formulations, ophthalmologists prepare 1% or 2% eye drops of voriconazole by reconstituting the intravenous powder in sterile saline solution with established safety and efficacy to treat fungal keratitis (Manikandan *et al.,* 2019; Austin *et al.,* 2017; Thomas and Kaliamurthy, 2013).

Encouraged by these ophthalmologic findings, several studies have examined the use of voriconazole drops to cure otomycosis. Chappe *et al*. reported successful treatment of chronic refractory otomycosis with self-prepared 1% voriconazole drops without corticosteroids

**Corresponding author:* e-mail: 3313002@zju.edu.cn

(Chappe *et al.,* 2018). Wee *et al*. also reported cure of refractory *Aspergillus otomycosis* with topical application of a 0.50 mg/mL solution of voriconazole (Wee *et al.,* 2022). Our November 2017 to November 2019 retrospective study contrasted the efficacy and safety of 1% voriconazole eye drops for treatment-refractory recurrent otomycosis without TMP or concurrent corticosteroid/antimicrobial treatment, and with good cure and minimal side effects (Zhang *et al.,* 2021).

Yet one of the biggest drawbacks of our previous researches and the following ones is the omission of TMP cases. In practice, otomycosis accompanied by TMP has an enhanced susceptibility and should be treated with caution because local drugs can pass into the inner and middle ear and cause ototoxicity. Up to now, there is no evidence of the efficacy and safety of voriconazole drops in treating TMP-related otomycosis.

For this gap, the present study uses a rabbit model to determine the safety profile of 1% ear drops of voriconazole for the management of perforation-positive suppurative otomycosis. The study aims to provide preclinical data which can guide future clinical utilization and fill current gaps in the scope of fungal species involved and formulation standardization.

MATERIALS AND METHODS

Animals and fungal strain

Healthy New Zealand White rabbits with a weight range of 2.5-3 kg were provided by Slac Laboratory Animal (Shanghai, China). The animals had no sign of inflammation in the ears or systemic illness. Rabbits were maintained under controlled environmental conditions at 18–22 °C and relative humidity 40-60% in the Animal Research Laboratory.

A clinical isolate of *Aspergillus terreus* was obtained from a patient who had suppurative otomycosis and tympanic membrane perforation. The isolate was cultured and subcultured on blood agar and Sabouraud gentamicin chloramphenicol agar plates (BioMerieux Biotech Co., Ltd., Marcy-l'Étoile, France), which were incubated at 37 °C and 28 °C for at least 72 hours. Plates showing no growth were incubated for an additional 72 hours. Pure colonies were identified by standard methods including colony morphology, pigmentation, lactophenol cotton blue staining (Baso Biotech Co., Ltd., China), and confirmed by the Vitek2 Compact system (BioMerieux Biotech Co., Ltd.).

Animal model establishment

Rabbits were anesthetized with 2% isoflurane (Yuyan Scientific Instrument Co., Ltd., Shanghai, China). Tympanic membranes were partially perforated with a myringotome. Three almost 0.5 cm wounds were created in the external auditory canal, deeper than the dermis. Fungal suspensions are prepared by washing three times with sterile PBS fungal tufts, centrifuging, and diluting to 1×10^6 CFU/mL in DMEM. One hundred microliters of the suspension were administered daily to each wound site for three consecutive days. A cotton ball was used in the ear canal to retain the solution. Procedures were performed under otic endoscopic guidance (Karl Storz Endoscopy, Germany).

Drug preparation and treatment protocol

The 1% voriconazole solution was freshly prepared by dissolving 200 mg of voriconazole powder (Pfizer, NYSE: PFE, USA) in 19 mL of 0.9% normal saline. The rabbits were randomly assigned to two groups: the treatment group received 1% voriconazole ear drops, and the control group received an equal volume of 0.9% saline. Treatments were administered topically to both ears three times daily for seven consecutive days. Therapeutic effectiveness was ascertained through otoendoscopy one week after treatment had been completed. Safety tests included brainstem auditory evoked potential (BAEP) testing and scanning electron microscopy (SEM) of the inner ear structures (Wee *et al.,* 2023).

Brainstem auditory evoked potential (BAEP) test

Following anesthesia, the mastoid and forehead regions were cleaned and degreased. Sterile electrodes were applied using conductive adhesive and headphones were applied. Acoustic click stimuli were delivered, beginning at 50 dB and proceeding in 10 dB increments to determine hearing thresholds. Only responses in which wave V was consistently observed in at least two replicates were accepted.

Scanning electron microscopy

Temporal bones were harvested five minutes following euthanasia and fixed in 2.5% glutaraldehyde for 24 hours. Following washes with PBS, samples were post-fixed in 1% osmium tetroxide at 4 °C for one hour, dehydrated in graded ethanol, and dried using critical-point drying with liquid CO_2. Specimens were mounted on SEM stubs using aluminum paint, sputter-coated with gold-palladium, and examined by scanning electron microscopy to evaluate the morphology of the inner ear structures, particularly the organ of Corti.

Serum voriconazole concentration analysis

Three drops of 1% voriconazole solution were instilled in the perforated ears of rabbits. Blood samples were collected from the marginal ear vein at 0, 30, and 60 minutes post-application. Samples were deproteinized with acetonitrile, centrifuged (5000 rpm, 4 °C, 10 minutes), and supernatants analyzed by high-performance liquid chromatography (HPLC). Twenty microliters of each sample were introduced into an ODS Hypersil column (150 mm × 4.6 mm; Thermo Scientific, Yokohama, Japan). The mobile phase was 1% orthophosphoric acid, 30% methanol, and 2 g/L heptane sulfonic acid (pH 5.0, adjusted

with 10 M NaOH) at a flow rate of 1.0 mL/min. Detection was at 254 nm on a CBM-20A HPLC system (Shimadzu, Kyoto, Japan) with an LC-20AT pump and SPD-10AV VP UV detector. The detection limit was 0.1µg/mL.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation (SD). Pre- and post-treatment values were compared using paired Student's t-tests. Statistical analysis was performed with GraphPad Prism 8 (GraphPad Software Inc., CA, USA). P-value < 0.05 was considered statistically significant.

RESULTS

Isolation of aspergillus terreus from a clinical case

A 54-year-old male came with a 5-day history of purulent discharge from the left ear. On otoendoscopic examination, there was a perforated tympanic membrane and erythema and edema of the external auditory canal. Microbiological culture yielded *Aspergillus terreus* as the causative organism. Despite four weeks of weekly local debridement and topical ketoconazole ointment locally, fungal plaques were still seen on the tympanic membrane and the external auditory canal (fig. 1).

Efficacy of 1% voriconazole ear drops in rabbit model of aspergillus terreus otitis media

Twenty rabbits with *Aspergillus terreus*-induced suppurative otitis media and tympanic membrane perforation were randomized into two groups (one ear per rabbit): an experimental group treated with 1% voriconazole topical drops (n=10) and a control group treated with saline (n=10). All the rabbits treated with voriconazole were cured within two weeks, as confirmed by otoendoscopic examination. None of the rabbits in the control group showed clearance of infection (fig. 2). table 1 also shows the results of infection and statistical analysis.

Auditory safety evaluation: no change in bone conduction hearing thresholds

Pre-treatment and post-treatment brainstem auditory evoked potential (BAEP) testing was done in the experimental group. The mean bone conduction threshold was 27 ± 6.75 dB pre-treatment and 27 ± 4.83 dB post-treatment, with no statistically significant difference ($P > 0.99$) (fig. 3 and 4). table 2 shows auditory threshold measurements with statistical analyses.

Maintenance of cochlear hair cell integrity after voriconazole treatment

Scanning electron microscopy (SEM) revealed no structural damage to the cochlear inner and outer hair cells after treatment with 1% voriconazole. There was morphological integrity before and two weeks after treatment (fig. 5).

Minimal systemic absorption of voriconazole after topical administration

Voriconazole serum concentrations were measured pre-treatment and at 30 and 60 minutes post-treatment. Voriconazole concentrations were below the limit of detection (0.1µg/mL) for all samples, indicating negligible systemic absorption following topical treatment to perforated ears (fig. 6).

DISCUSSION

Otomycosis is a difficult-to-treat clinical entity, especially when complicated by tympanic membrane perforation (TMP) with direct access of middle and inner ear structures to topical agents, potentially carrying ototoxic risk. While voriconazole, a triazole antifungal with broad activity, has been effective in otomycosis treatment without TMP, its safety in TMP-complicated otomycosis remains under-explored. This study attempted to bridge this knowledge gap by employing an animal model in order to ascertain the therapeutic and safety effects of 1% voriconazole ear drops in TMP conditions (Bojanović *et al.,* 2023; Sangaré *et al.,* 2021; Koltsidopoulos and Skoulakis, 2020; Javidnia *et al.,* 2022; Stemler *et al.* 2023).

Reproducible animal modeling of TMP otomycosis is important but challenging. Literature on models of otomycosis has been limited, in part due to the difficulty of routinely inducing tympanic membrane perforation and concomitant fungal infection. Partial myringectomy was performed in this study to yield uniform TMP, which allowed controlled inoculation of *Aspergillus terreus*-a clinically relevant pathogen isolated from a human patient suffering from recalcitrant otomycosis.

The technique ensured middle ear fungal colonization and permitted effective topical medication delivery. Learning from fungal keratitis research where the rabbit model is predominantly used, a tried and tested paradigm existed to assess safety through tests of auditory function and ultrastructural examination. BAEP testing offered an objective functional assessment of hearing thresholds before and after therapy, while SEM allowed for high-resolution visualisation of cochlear hair cell morphology to define submicroscopic ototoxicity (El Korbi *et al.,* 2022; Lee *et al.,* 2021; Antunes *et al.,* 2022; Zhang *et al.,* 2021).

All of the rabbits with 1% voriconazole treatment had complete infection resolution at two weeks, demonstrating robust antifungal activity against *A. terreus*. This concurs with clinical case reports where topical voriconazole effectively eradicated refractory otomycosis. However, dependence of the study on one fungal strain weakens generalizability of such evidence. Different fungal species and strains may be heterogeneously susceptible, calling for expanded antimicrobial spectrum investigation in subsequent studies (Ullmann *et al.,* 2018; Garcia-Vidal *et al.,* 2019; Manikandan *et al.,* 2019; Austin *et al.,* 2017; Thomas and Kaliamurthy, 2013).

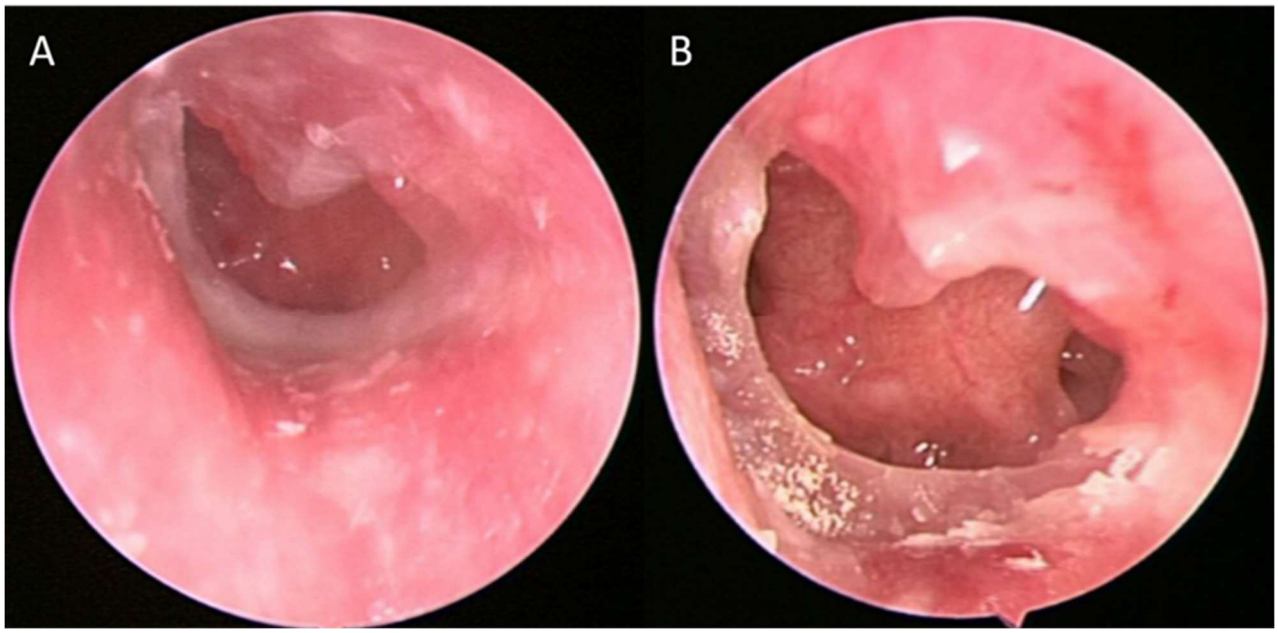

Fig. 1: Otoendoscopic examination of the patient. (A) Perforated tympanic membrane and purulent discharge prior to treatment. (B) Refractory fungal plaques after four weeks of local ketoconazole therapy.

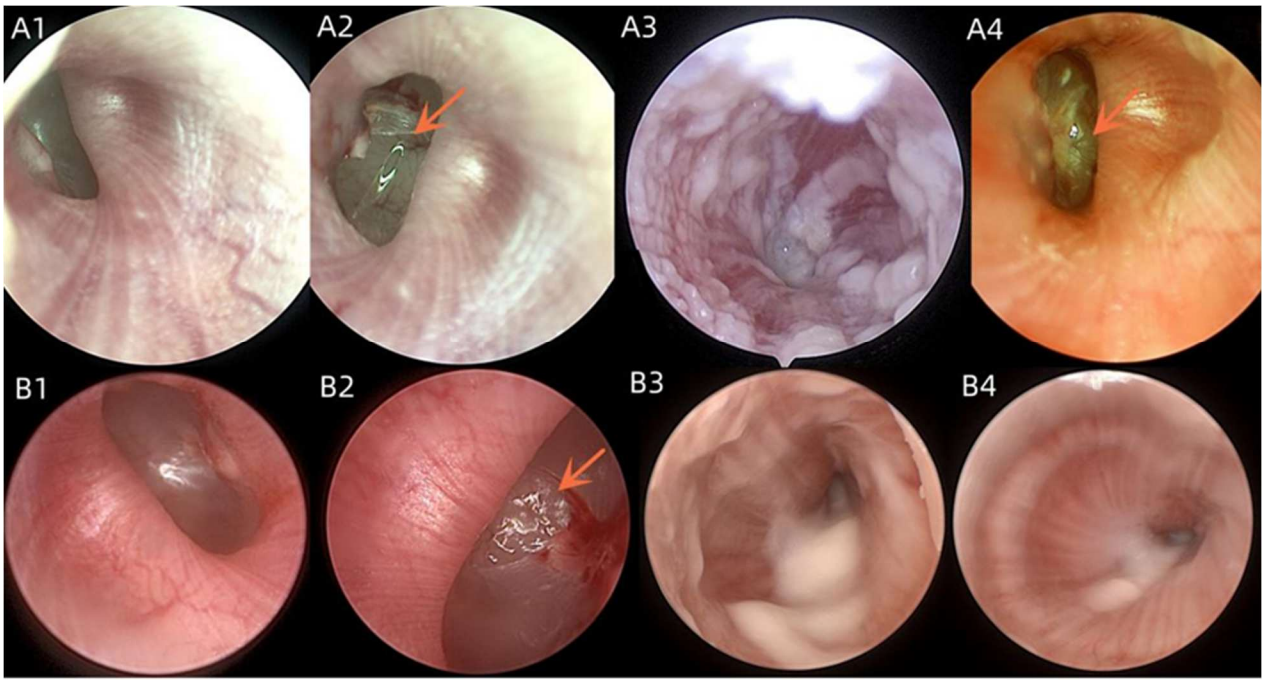

Fig. 2: Otoendoscopic photographs demonstrating treatment outcomes. A1–A4: Experimental group; B1–B4: Control group. A1, B1: Pre-intervention baseline; A2, B2: Perforation of tympanic membrane; A3, B3: Infection established; A4, B4: Post-treatment findings.

Table 1: Summary of treatment outcomes

Group	Number of rabbits	Infection resolution	Statistical significance
Experimental	10	10/10 (100%)	—
Control	10	0/10 (0%)	$P < 0.001$

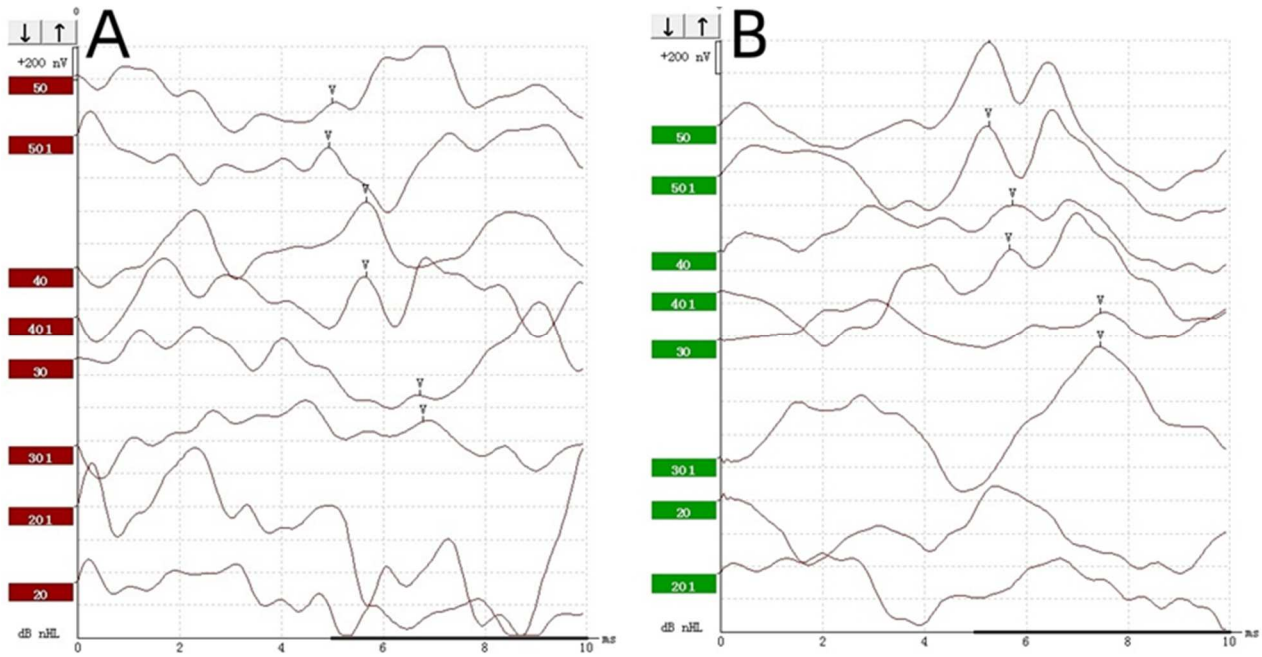

Fig. 3: Example BAEP waveforms from a rabbit ear: (A) Pre-treatment; (B) Post-treatment.

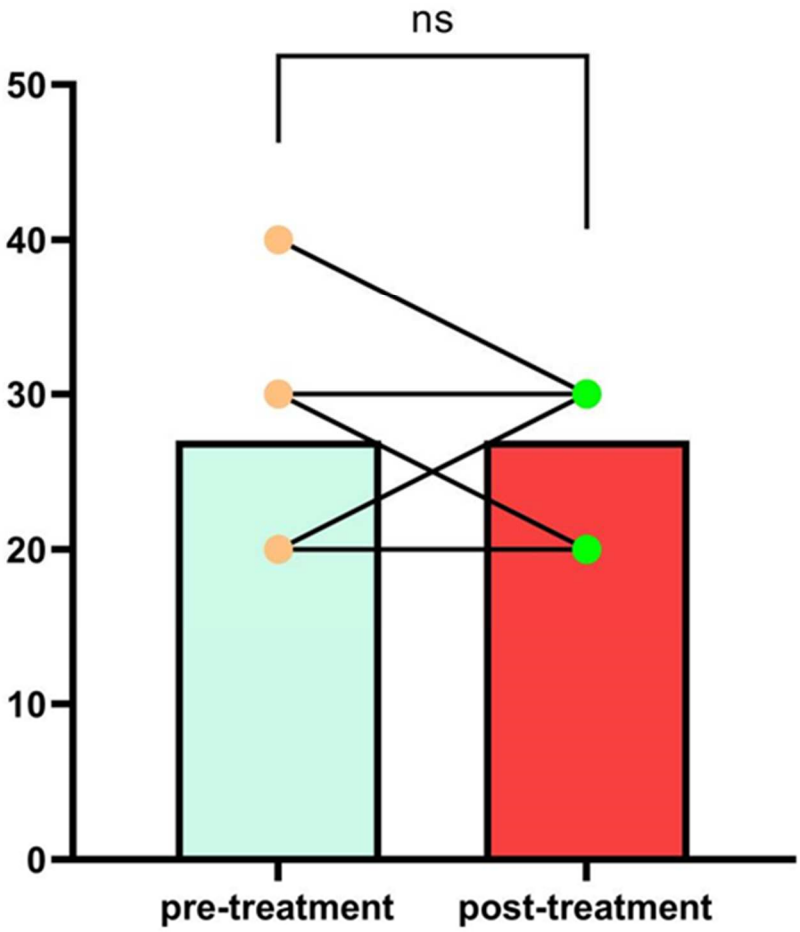

Fig. 4: Group analysis of bone conduction thresholds (n=10 ears) showing no difference between pre- and post-treatment values (paired t-test, P > 0.99).

Table 2: Bone conduction auditory thresholds pre- and post-treatment

Measurement Time	Mean Threshold (dB)	Standard Deviation	P-value (paired t-test)
Pre-treatment	27	6.75	—
Post-treatment	27	4.83	> 0.99

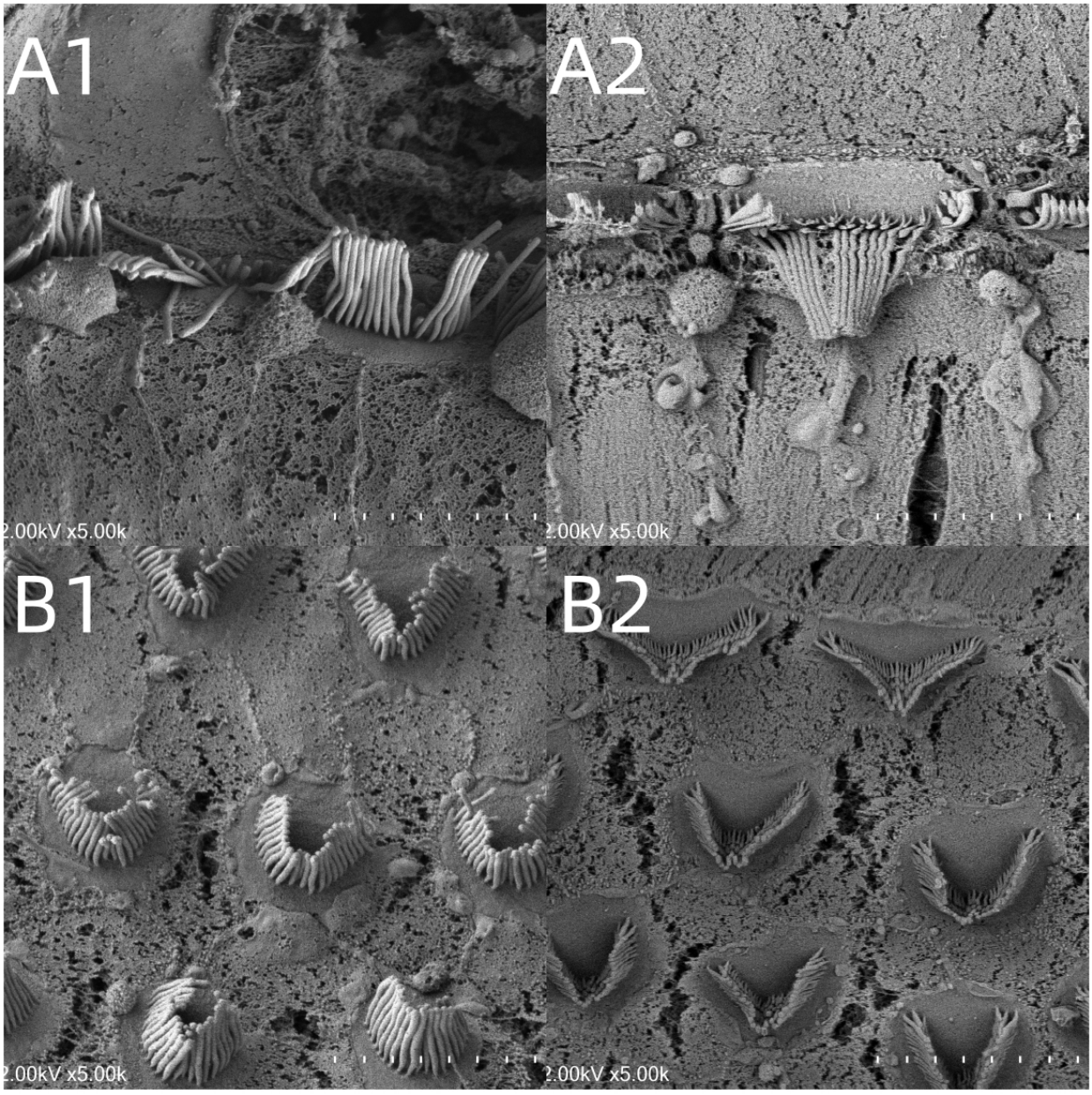

Fig. 5: SEM photos of cochlear hair cells. A1: Inner hair cells before treatment; A2: Inner hair cells after treatment; B1: Outer hair cells before treatment; B2: Outer hair cells after treatment.

The primary safety finding of the study-preservation of auditory function-was strongly established by unchanged BAEP thresholds after treatment. There were no statistically significant differences, suggesting that 1% voriconazole does not induce conductive or sensor neural hearing loss when applied to perforated tympanic membranes. SEM imaging also corroborated morphological integrity of inner and outer cochlear hair cells, offering strong proof of absence of ototoxicity. There was little systemic absorption of voriconazole, with serum concentrations below detectable levels at 30 and 60 minutes following application. These findings support

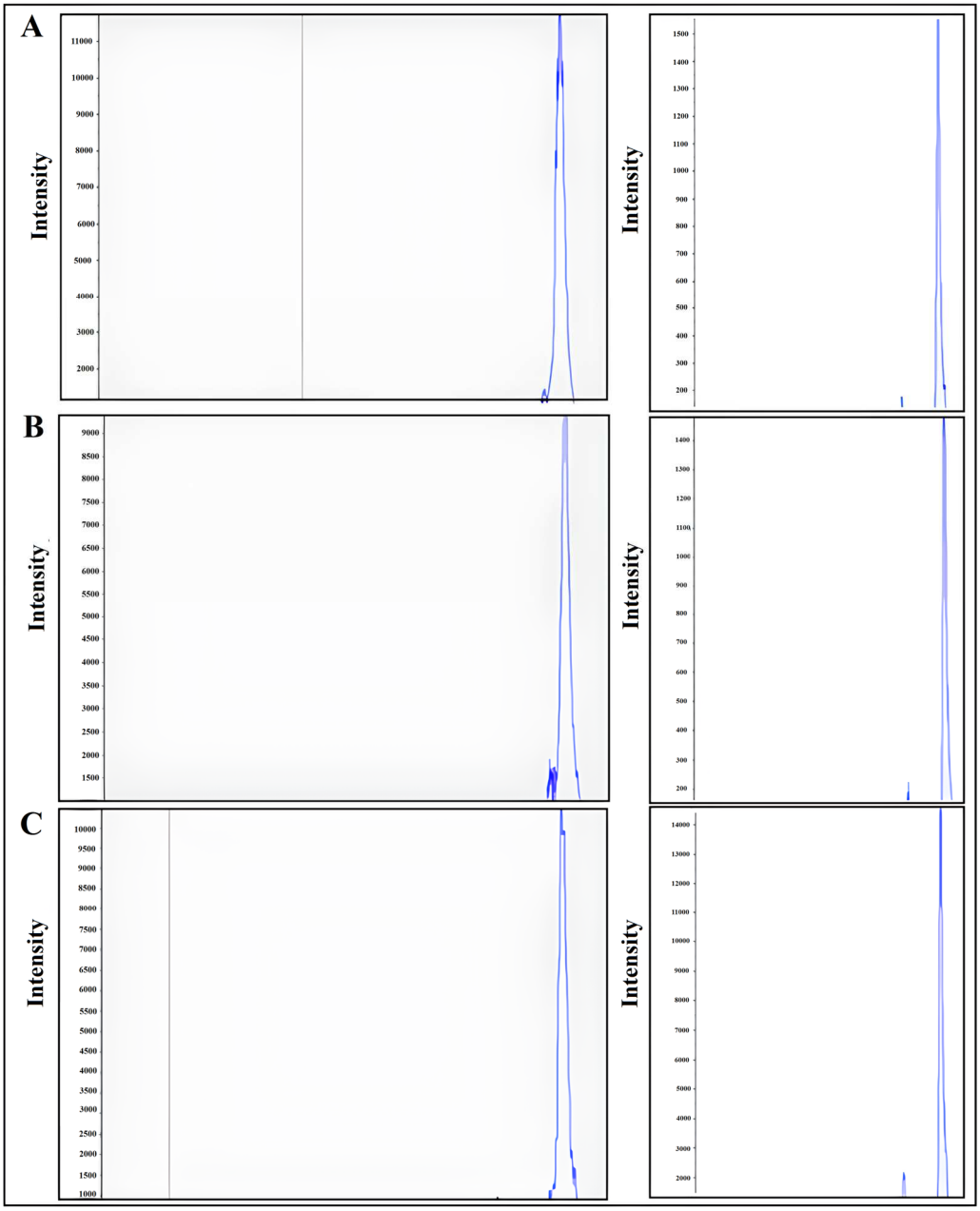

Fig. 6: Voriconazole serum concentrations. (A) Pre-treatment; (B) 30 minutes post-treatment; (C) 60 minutes post-treatment. All concentrations were <0.1 µg/mL.

earlier reports in ophthalmology in which topical voriconazole was found to have little systemic exposure. Such low absorption reduces the risk of systemic side effects and drug interactions, a valuable consideration in clinical use (Wee *et al.,* 2023; Bartochowska *et al.,* 2022; Safari *et al.,* 2022; Zahran *et al.,* 2022).

Several limitations must be acknowledged. First, no attempt was made to explore dose-response relationships or higher concentrations of voriconazole that may be associated with more efficacy or risk. Identification of the maximum tolerated dose would be useful clinically. Second, treatment duration was fixed at seven days; exploration of shorter or longer courses may optimize therapy while reducing exposure (Anazodo *et al.,* 2024; Chen and Zhao, 2024). Third, while animal models provide useful initial data, they can never replicate the human ear anatomy, physiology, and immune system. Hence, extrapolation to human clinical practice has to be with cautious interpretation. Further studies should include multi-strain fungal challenge, pharmacokinetics with tissue levels of drugs, and long-term follow-up to detect delayed toxicity. Lastly, randomized controlled trials in humans are needed to establish safety, efficacy, and optimal dosing regimens (Hagen and Baker, 2017; Noonan *et al.,* 2024; Walsh and Hanson, 2023).

CONCLUSION

This study demonstrates that 1% topical ear drops of voriconazole are effective for eradicating *Aspergillus terreus* suppurative otitis media in a model of rabbit tympanic membrane perforation without auditory toxicity or systemic drug absorption. These findings suggest that voriconazole might be an effective and safe antifungal local drug for TMP complicated otomycosis. Additional preclinical investigation and carefully controlled clinical studies are required, nonetheless, to confirm these promising findings, determine optimal dosing, and determine long-term safety in human patients.

ACKNOWLEDGEMENT

All Authors gratefully acknowledge the financial support provided by the following funding sources: (1) The Joint Fund Project of the State Key Laboratory of Pathogenesis and Prevention of High Incidence Diseases in Central Asia, co-established by national and provincial ministries and Alaer Hospital, for the year 2023 (Grant No. SKL-HIDCA-2023-ALE3); (2) The In-Hospital Scientific Research Project of the First Division Alaer Hospital, 2023 (Grant No. YNKY-202308); (3) The Science and Technology Project of Medicine and Health of Zhejiang Province, 2022 (Grant No. 2022KY817); and (4) The Science and Technology Projects of Medicine and Health of Hangzhou City (Grant Nos. A20210546 and A20240923).

Ethical approval

Animal procedures were conducted in compliance with the NIH Guide for the Care and Use of Laboratory Animals and relevant Chinese regulations, and were approved by the Animal Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Xinjiang Corps Alaer Hospital (Approval No. SRRSH-IACUC-2024-057).

Conflict of interests

The authors declare no conflict of interest.

REFERENCES

Anazodo CA, Adepeju DM, Okoli FA, Obasi CJ, Abana CC, Agu KC, Ezenwelu CO and Awari VG (2024). Umeoduagu ND. Investigating the susceptibility of otomycosis-causing microorganisms to different ear drops. *Int. Res. J. Mod. Eng. Technol. Sci.,* **6**(6): 1958-65.

Antunes J, Mendes N, Adónis C and Freire F (2022). Treatment of otomycosis with clotrimazole: Results accordingly with the fungus isolated. *Acta Otolaryngol.*, **142**(9-12): 664-667.

Austin A, Lietman T and Rose-Nussbaumer J (2017). Update on the management of infectious keratitis. *Ophthalmology*, **124**(11): 1678-1689.

Bartochowska A, Tomczak H, Podlawska P, Wierzbicka M. (2022). Aspergillosis of the middle ear in 37 immunocompetent patients. *Adv. Head Neck Surg.*, **21**(2): 25-29.

Bojanovic M, Stalevic M, Arsic-Arsenijevic V, Ignjatovic A, Ranđelovic M, Golubovic M, Zivkovic-Marinkov E, Koracevic G, Stamenković B and Otasevic S (2023). Etiology, predisposing factors, clinical features and diagnostic procedure of otomycosis: A literature review. *J. Fungi (Basel)*, **9**(6): 662.

Chappe M, Vrignaud S, de Gentile L, Legrand G, Lagarce F and Le Govic Y (2018). Successful treatment of a recurrent *Aspergillus niger* otomycosis with local application of voriconazole. *J. Mycol. Med.*, **28**(2): 396-398.

Chen Z and Zhao Z (2024). Study on the microbial diversity of ear canal secretions from patients with otomycosis. *Front. Surg.,* **11**: 1277799.

El Korbi A, Houas J, Kolsi N, Bouatay R, Ferjaoui M, Toumi A, Harrathi K and Koubaa J (2022). Fungal necrotizing external otitis: Diagnosis, management and outcomes of 15 cases. *Pan. Afr. Med. J.*, **42**: 306.

Hua G, Pennesi M, Shah K, Qiao X, Hariprasad SM, Mieler WF, Wu SM, Holz ER (2003). Safety of intravitreal voriconazole: Electroretinographic and histopathologic studies. *Trans. Am. Ophthalmol. Soc.*, **101**: 183-189.

Garcia-Vidal C, Alastruey-Izquierdo A, Aguilar-Guisado M, Carratalà J, Castro C, Fernández-Ruiz M, Aguado JM, Fernández JM, Fortún J, Garnacho-Montero J and Gavaldà J (2019). Executive summary of clinical practice guideline for the management of invasive diseases caused by *Aspergillus*: 2018 update by the GEMICOMED-SEIMC/REIPI. *Enferm. Infecc. Microbiol. Clin. (Engl Ed)*, **37**(8): 535-541.

Hagen M and Baker M (2017). Skin penetration and tissue permeation after topical administration of diclofenac. *Curr. Med. Res. Opin.*, **33**(9): 1623-1634.

Javidnia J, Ghotbi Z, Ghojoghi A, Solhjoo K, Alshahni MM, Jeddi SA, Ahmadi B, Nouripour-Sisakht S, Ansari S and Shokoohi G (2022). Otomycosis in the south of Iran with a high prevalence of tympanic membrane perforation: A hospital-based study. *Mycopathologia*, **187**(2-3): 225-233.

Koltsidopoulos P and Skoulakis C (2020). Otomycosis with tympanic membrane perforation: A review of the literature. *Ear Nose Throat. J.*, **99**(8): 518-521.

Lee A, Tysome JR and Saeed SR (2021). Topical azole treatments for otomycosis. *Cochrane. Database Syst. Rev.*, **5**(5): CD009289.

Manikandan P, Abdel-Hadi A, Randhir Babu Singh Y, Revathi R, Anita R, Banawas S, Bin Dukhyil AA, Alshehri B and Shobana CS (2019). Fungal keratitis: Epidemiology, rapid detection and antifungal susceptibilities of *Fusarium* and *Aspergillus* isolates from corneal scrapings. *Biomed. Res. Int.*, **2019**: 6395840.

Marquart ME (2011). Animal models of bacterial keratitis. *J Biomed Biotechnol*, **2011**: 680642.

Montgomery ML and Fuller KK (2020). Experimental models for fungal keratitis: An overview of principles and protocols. *Cells*, **9**(7): 1713.

Noonan KY, Gjini EK, Saunders JE (2024). External otologic infections. *Infections of the Ears, Nose, Throat and Sinuses*, 2nd ed. Springer pp.135-150.

Safari F, Madani M, Badali H, Kargoshaie AA, Fakhim H, Kheirollahi M, Meis JF and Mirhendi H (2022). A chronic autochthonous fifth clade case of *Candida auris* otomycosis in Iran. *Mycopathologia*, **187**(1):121-127.

Sangaré I, Amona FM, Ouedraogo RW, Zida A and Ouedraogo MS (2021). Otomycosis in Africa: Epidemiology, diagnosis and treatment. *J. Mycol. Med.*, **31**(2): 101115.

Sponsel W, Chen N, Dang D, Paris G, Graybill J, Najvar LK, Zhou L, Lam KW, Glickman R and Scribbick F (2006). Topical voriconazole as a novel treatment for fungal keratitis. *Antimicrob Agents Chemother*, **50**(1): 262-268.

Stemler J, Tobben C, Lass-Florl C, Steinmann J, Ackermann K, Rath PM, Simon M, Cornely OA and Koehler P (2023). Diagnosis and treatment of invasive aspergillosis caused by non-*fumigatus Aspergillus* spp. *J. Fungi (Basel)*, **9**(4): 500.

Thomas PA and Kaliamurthy J (2013). Mycotic keratitis: Epidemiology, diagnosis and management. *Clin. Microbiol. Infect.*, **19**(3): 210-220.

Thiel MA, Zinkernage AS, Burhenne J, Kaufmann C and Haefeli WE (2007). Voriconazole concentration in human aqueous humor and plasma during topical or combined topical and systemic administration for fungal keratitis. *Antimicrob. Agents Chemother.*, **51**(1): 239-244.

Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, Lass-Flörl C, Lewis RE, Munoz P, Verweij PE and Warris A (2018). Diagnosis and management of *Aspergillus* diseases: Executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin. Microbiol. Infect*, **24**(Suppl): 1:e1-e38.

Walsh EM and Hanson MB (2023). Fungal infections of the external auditory canal and emerging pathogens. *Otolaryngol. Clin. North Am.*, **56**(5): 909-918.

Wee LE, Tan MG, Tan AL and Tang JZ (2023). Relapsing *Aspergillus* otomycosis despite prolonged systemic antifungal therapy and resolution after topical voriconazole administration: A case report. *Med. Mycol. Case Rep.*, **39**: 23-25.

Zhang S, Jin M, Hu S, Zhang Y and Zhou G (2021). Administration of 1% topical voriconazole drops was effective and safe in the treatment of refractory otomycosis without tympanic membrane perforation. *Ann. Otol. Rhinol. Laryngol.*, **130**(3): 273-279.

Zahran EM, Mohamad SA, Yahia R, Badawi AM, Sayed AM and Abdelmohsen UR (2022). Anti-otomycotic potential of nanoparticles of *Moringa oleifera* leaf extract: An integrated *in vitro*, *in silico* and phase 0 clinical study. *Food Funct.*, **13**(21): 11083-11096.