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Effectiveness of voriconazole in treating refractory otomycosis: A systematic review

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Abstract
Background: Otomycosis is a fungal infection of the external auditory canal, affecting 9% to 30% of the global population. Although not life-threatening, otomycosis is challenging to treat due to high recurrence and antifungal resistance. Topical antifungals, such as clotrimazole and nystatin, are standard treatments, often combined with steroids or antiseptics. Voriconazole, a newer antifungal, has shown promise for refractory cases due to its broad spectrum and strong anti-Aspergillus activity. However, research on its optimal use in otomycosis remains limited.
Objective: While a systematic review exists for fungal keratitis, none have assessed voriconazole for otomycosis. Therefore, a systematic study was conducted to evaluate its effectiveness in treating refractory otomycosis.
Methods: We conducted a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search in PubMed, Scopus, ScienceDirect, and Google Scholar was conducted from inception to February 2025. Duplicate publications, review articles, and incomplete articles were excluded. The database searches identified a total of 1400 articles. A thorough review of the abstracts and titles led to the exclusion of 862 items.
Results: Finally, we identified 5 articles through full-text reading and analysis, which included 89 cases. All reported cases were successfully treated with voriconazole.
Conclusion: Voriconazole appears to be a potentially effective treatment, especially for refractory cases of otomycosis.

Keywords: Voriconazole, refractory otomycosis, topical antifungal therapy, systematic review, aspergillus infection

Introduction

Around 9% and 30% of people worldwide have otomycosis (OM), a superficial fungal infection of the outer auditory canal [1]. One About four out of every 1,000 people are afflicted with the acute type each year, whereas 3% to 5% of persons are affected with the chronic form [2]. Many fungus, mostly saprophytes, can cause otomycosis, although the most prevalent ones are Aspergillus and Candida. Although not usually life-threatening, the disease has a significant chance of recurrence and requires prolonged treatment and monitoring, making its course challenging and burdensome [3].

Ear instrumentation, high humidity in the outer auditory canal, the accumulation of epithelial particles, long-term use of broad-spectrum antibiotics or steroids, immunocompromised status, and underlying conditions like diabetes and dermatological diseases are some of the local and systemic factors thought to predispose people to otomycosis [4, 5]. Common symptoms include itching, ear pain, aural fullness, tinnitus, hearing loss, a blocked sensation, and ear discharge [6]. Previous systematic review found that the most prevalent otomycosis risk factor is the application of several oils and wax solvents after the administration of ototopical antibiotics, either with or without steroid drops. Additionally, trauma to the outer auditory canal due to compulsive cleaning or instrumentation also contributes to the risk [7].

Otomycosis is commonly handled with topical antifungal, either alone or in combination. The primary approach involves removing visible debris and fungal elements [2]. Steroids, solutions of acid, and antibacterial agents may be used in addition to antifungals. Despite being widely used, otomycosis can be difficult to treat because they don't always provide a full recovery, many people develop resistance to antifungal, and the rates of recurrence are High [8, 9]. The recommended first-line treatment for otomycosis in France is nystatin, which is frequently taken for up to 15 days in combination with oxytetracycline, polymyxin B, and dexamethasone [10]. In the United States, clotrimazole, a topical imidazole, is the preferred

treatment for uncomplicated otomycosis [11]. Numerous studies have shown that otomycosis can be effectively treated with a single topical application of 1% clotrimazole [12, 13, 14]. Furthermore, oral triazole medications, such as voriconazole, posaconazole, and isavuconazole, have good penetration into bone and the central nervous system and are effective against fungal infections like Aspergillus [15]. Voriconazole is one of the newest agent against fungal infections [16]. Voriconazole offers distinct advantages in treating otomycosis due to its broad spectrum, powerful anti-Aspergillus potency, and good long-term tolerance [17]. Another therapy option for resistant otomycosis that does not improve with conventional medications is topical voriconazole [10, 18].

Up to this point, several studies analyzed the effectiveness of Voriconazole as the alternative antifungal, not only as an initial therapy but also as an adjuvant for the treatment of fungal infections, especially for the refractory cases. Significant research gaps persist regarding the optimal use of voriconazole for otomycosis, despite its growing clinical relevance. Existing studies often produce inconsistent results due to variations in study design, populations, and outcome measures, with limited data on factors such as fungal species, severity of infection, and routes of administration. While a systematic review has evaluated the effectiveness of voriconazole in treating fungal keratitis, no such review has been conducted for its use in otomycosis. For these reasons, a systematic study was conducted to assess and conclude the effectiveness of voriconazole in treating refractory otomycosis.

Methods

The aim of this study was to evaluate the effectiveness of Vocarizole in treating refractory otomycosis. To ensure an objective approach, the assessment was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines [19].

Search Strategy

This data acquisition was obtained by searching for basic data electronically in PubMed, ScienceDirect, Scopus and Google Scholar. The data search ended on February 2, 2025. One of the reviewers (AR) stated the development of the data search strategy by using related keywords and referring to medical subject headings (MeSH) such as “refractory”, “otomycosis”, "fungal otitis", "mycotic otitis", "antifungal agents", "antifungal", "voriconazole". The results of this search were then combined and removing the duplicates.

Eligibility Criteria

To assess the eligibility was carried out on the entire study, whose inclusion criteria accompanied patients who diagnosed refractory otomycosis whose treatment was through voriconazole in any form or without comparison to placebo or other types of antifungal agents. Each of these studies was designed to review studies that were not limited to language, country, and date of publication. In this case there is an exception.

In this study, the method was applied according to the PRISMA statement guidelines, which were based on its inclusion and exclusion criteria. In the process of selected studies and duplications that were removed using Rayyan AI and the review was carried out by AR and HR then to analyze this text was carried out on the entire study in order to identify the formulation of appropriate problems to be included in this study. ARA acts as a mediator if there are differences of opinion in the writing process, which if this happens, then a joint discussion will be held as a solution.

Data Extraction and Quality Assessment

For the extraction of this data is held by AR and HR as the authors, which are poured into a table via Google Sheets to extract the data according to this study. If there are differences of opinion between the authors, then the role of mediator is held by ARA and then a discussion is carried out together. Data extracted were author, study design, region, age, gender, medical history, clinical features, interventions, intervention effects and reported findings. Finally, the articles are screened and synthesized into a qualitative systematic review. The JBI (Joanna Briggs Institute) Critical Appraisal Tool was used in this research to assess the quality [20]. Risk assessment was performed by AR and ARA.

	Yes	No	Unclear	Not applicable
1. Is the review question clearly and explicitly stated?	✓	☐	☐	☐
2. Were the inclusion criteria appropriate for the review question?	✓	☐	☐	☐
3. Was the search strategy appropriate?	✓	☐	☐	☐
4. Were the sources and resources used to search for studies adequate?	✓	☐	☐	☐
5. Were the criteria for appraising studies appropriate?	✓	☐	☐	☐
6. Was critical appraisal conducted by two or more reviewers independently?	✓	☐	☐	☐
7. Were there methods to minimize errors in data extraction?	✓	☐	☐	☐
8. Were the methods used to combine studies appropriate?	✓	☐	☐	☐
9. Was the likelihood of publication bias assessed?	✓	☐	☐	☐
10. Were recommendations for policy and/or practice supported by the reported data?	✓	☐	☐	☐
11. Were the specific directives for new research appropriate?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐

Fig 1: JBI Critical Appraisal Tool for quality assessment

Results

In this study, the basic data was searched and identified with a total of 1400 articles (Figure 2), which were then filtered on these articles based on their inclusion criteria and exclusions which then accompanied the selected studies. This filtering reached 862 articles that were disrupted because the title and abstract did not include otomycosis and voriconazole. Then, identification was carried out on 5 articles through full-text reading and analysis, which included 89 cases of refractory otomycosis treated with voriconazole. The summary of included studies that have been selected is been listed in Table 1.

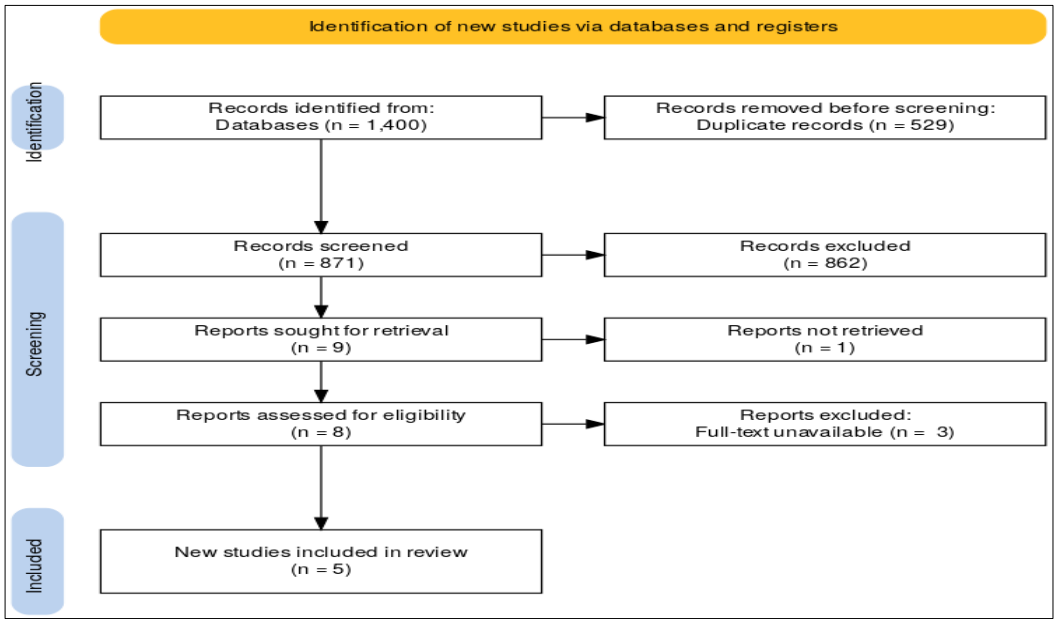

Fig 2: PRISMA flow chart

Research Methods

The summary of included studies that have been selected is been listed in Table 1. Of the five studies that met the inclusion criteria, two used a cross-sectional design, two were case reports, and one used a retrospective analysis design. The number of participants varied from one (for a case report) to 55 participants (for a retrospective study in China). The five studies aimed to evaluate the effectiveness and safety of topical voriconazole in treating recurrent otomycosis that had not responded to previous therapies such as oral antibiotics or antifungals [20-25].

Data collection in the studies included clinical examinations, patient interviews, and microbiological tests to identify the cause of the infection. Data collected included patient characteristics, clinical symptoms, fungal culture results, therapy effectiveness, side effects, and clinical outcomes after treatment [21-25].

Basic Characteristics

The total number of participants across the five studies was 89. The basic characteristics of the patients varied, but there were several similarities. The majority of patients were women, accounting for approximately 53.9% (48 patients), while 46.1% (41 patients) were men. The average age of patients varied, with a range from 44.5 to 75 years in some studies, while other studies did not provide specific details. Most patients had recurrent otomycosis, meaning they had a fungal infection in the ear that recurred despite previous treatments. Most patients had received both topical and oral therapies before switching to topical voriconazole, but did not show significant improvement and, in some cases, experienced side effects from oral therapy.

Clinical Symptoms

From the data available, common clinical symptoms included: pruritus (88.2%, 78 patients), otorrhea (55.5%, 49 patients), otalgia (56.7%, 50 patients), and hearing loss before therapy (41.2%, 37 patients). Patients also reported redness and inflammation in the external ear canal (variable, but frequently observed) [21-25]. It was noted that only one patient experienced a mild adverse event in the form of tinnitus after using topical voriconazole [25].

Identification of the Fungus Causing Otomycosis

Microscopic examinations and microbiological cultures revealed that the main pathogen causing otomycosis in patients across four studies was Aspergillus species (71 patients total) [21, 24]. In research by Piernavieja *et al.* (2020), it was found that only 55.5% of cases underwent microscopic examination and fungal culture. Of these, 33% were caused by Candida species, 22% by Aspergillus species, and the remainder could not be identified [25].

Medical History

Patients typically underwent various treatments before being prescribed topical voriconazole, including prior use of oral antibiotics (29 patients, 32.6%), oral antifungals (19 patients, 21.3%), topical antibiotics (17 patients, 19%), and topical antifungals (12 patients, 13.5%).[22-25] It is unclear whether therapy was provided before topical voriconazole in some studies [21].

Side Effects of Oral Antifungals

Many patients in this study had previously undergone therapy with oral antifungals, such as itraconazole and voriconazole, but had to stop treatment due to severe side effects. These side effects included elevated liver enzymes (hepatotoxicity), [22] visual disturbances such as blurred vision or photophobia, [22-24] gastrointestinal symptoms like nausea, vomiting, and stomach discomfort, [22-24]. as well as skin phototoxicity, where the skin becomes more sensitive

and develops rashes due to sun exposure after prolonged use of oral voriconazole. These serious side effects often led to discontinuation of oral therapy, with patients switching to topical voriconazole, which proved to be safer and more effective. Additionally, the long-term use of oral antifungals (averaging over three months) imposes an economic burden on patients [25].

Interventions and Outcomes in Reseach

The interventions provided in the studies included: [21-25].

- Discontinuation of oral antifungal therapy in patients who experienced side effects or did not show a satisfactory clinical response.
- Topical voriconazole 1% was administered as 1-2 drops, 2-3 times a day for an average of 4 weeks.

According to research by Piernavieja *et al*. (2020), there was a significant improvement in symptoms after administering topical voriconazole for 4 weeks [25]:

- 93.3% of patients experienced overall improvement in symptoms.
- Symptoms of otorrhea decreased from 100% to 6.7% (P<0.05).
- Pruritus reduced from 41.2% to 7.7% (P<0.05).
- Hearing loss improved in 36.4% of patients (P<0.05.

Chappe *et al*. (2018) stated that topical voriconazole therapy is particularly effective in treating Aspergillus niger, which is resistant to nystatin drops [23] Cueh Ho *et al*. (2014) reported that topical voriconazole successfully treated invasive Aspergillus in otitis externa without requiring surgical debridement.24 For refractory otomycosis with tympanic membrane perforation, Zhang *et al*. (2021) discovered that topical voriconazole therapy was secure and efficient in just two weeks [21].

Safety of Topical Voriconazole Use

Compared with oral antifungals, topical voriconazole has an excellent safety profile. In all the studies reviewed, only one patient experienced mild tinnitus, which was well tolerated and did not interfere with the course of therapy [25]. There were no reports of any severe side effects, such as hepatotoxicity or visual abnormalities, which are typical of oral medication. Additionally, patients using topical voriconazole did not require regular liver function monitoring, which is typically necessary with oral therapy.

Table 1: Summary of Included Studies

Author (Year)	Study Design	Region	N	Medical History	Interventions	Findings
Pierna-vieja *et al*. (2020) [25]	CS	Spain	18	Prior attempts at oral (83.3% antibiotics, 22.2% antifungals) and topical (94.4% antibiotics, 55.5% antifungals) medications had failed for all patients.	Sterile formulation of topical voriconazole ear drops (VE)	Improvement in symptoms was reported by 93.3%. Humidity, otorrhea, earache, and itching all significantly decreased, and 36.4% reported an improvement in their hearing. There was only one recorded mild adverse event, which was tingling. In conclusion, patients with recurrent otomycosis who did not react to existing treatment options found that VE was a safe and effective way to greatly lessen their symptoms.
Zhou *et al*. (2020) [21]	RA	China	55	RO	1% topical VE	All instances of otomycosis were satisfactorily cured following two weeks of topical voriconazole drops at 1% concentration. Before and after therapy, there were no discernible changes in bone conduction. In summary, 1% topical voriconazole was found to be a quick, safe, and efficient treatment for refractory otomycosis without tympanic membrane perforation.
Liang *et al*. (2022)	CR	Singa-pore	1	Multiple relapses of Aspergillus otomycosis in spite of standard topical and systemic antifungal treatment, along with the use of hyperbaric oxygen therapy as an adjuvant	Topical 1% voriconazole	Over eight weeks, 1% topical voriconazole was administered without adverse effects, leading to successful resolution. No relapse occurred during six months of follow-up. Topical voriconazole is an effective and safe treatment for resistant *Aspergillus* otomycosis, even in cases unresponsive to other topical or systemic antifungals.
Chappe *et al*. (2018) [23]	CR	Franch	1	Topical nystatin or econazole, as well as other antibiotic therapies, did not help a patient with recurrent otomycosis.	Voriconazole solution daily for 14 days (3 drops, 3-4 times a day)	A full recovery was made with no serious side effects, and a year later there was no recurrence. Further research is necessary to confirm the promising treatment of voriconazole 1% solution for refractory otomycosis.
Chueh Ho *et al*. (2014)	CS	Taiwan	14	Topical medications, antibiotics, or local therapy had not worked for any of the patients.	Voriconazole	Following voriconazole medication, two individuals experienced a return of their symptoms. After a second 12-week regimen, one was cured, but the other needed surgical debridement. Without surgery, the remaining 11 patients made a full recovery. Voriconazole is emphasized in this study as a practical and efficient treatment for refractory *Aspergillus* otomycosis.

Table abbreviations: CR= Case Report, CS= Case Series, VE= Voriconazole Ear Drops, RA= Retrospective Analysis, RO= Refractory Otomycosis,

Discussion

Factors Influencing the Prevalence of Otomycosis in Women

Although epidemiological data regarding the sex distribution of otomycosis vary among studies, several findings and hypotheses help explain the tendency for a higher incidence in women. First, hormonal and anatomical factors may play a role; hormonal differences between men and women can influence the composition of cerumen and the humidity of the ear canal, which in turn affects fungal growth [26]. Second, habits and lifestyle contribute significantly. Women are more likely to use various hair care products, wear hijabs or other head coverings, and use earphones, all of which may create a moist environment around the ears that favors fungal proliferation [27, 28]. Third, exposure to water through swimming, bathing, or using saunas can further increase the moisture within the ear canal, supporting fungal growth [27, 28] These findings are multifactorial; the variation between studies suggests that

environmental, behavioral, and biological factors collectively increase the risk of otomycosis in women.

Clinical Findings

The available data indicate that common clinical symptoms include pruritus (88.2% in 78 patients), otorrhea (55.5% in 49 patients), otalgia (56.7% in 50 patients), and hearing loss prior to therapy (41.2% in 37 patients). These results are consistent with research by Shuaib (2020) in Nigeria, which reported that 73% of 275 otomycosis patients experienced ear pruritus, followed by otalgia in 66.5%, a sensation of blockage in 57%, otorrhea in 19.6%, tinnitus in 11.6%, and hearing loss in 9.8% of the overall sample [29]. Similarly, Mehreen (2022) in India noted that the most common clinical symptoms were itching (74%) and otalgia (60%), followed by a feeling of blockage in 50% of patients; other symptoms included hearing loss (44%), discharge (36%), and tinnitus (8.9%) [30]. Itching, otorrhea, and the sensation of ear canal obstruction are among the symptoms that are commonly linked to otomycosis. Other symptoms like headache, tinnitus, and pain (of different intensities) are also typical. Additionally, these individuals often exhibit hearing loss, desquamation of the epithelium, and edema and redness of the external auditory canal (EAC). [31]

Effectiveness of Topical Voriconazole Compared to Oral Therapy

A study by Zhang *et al*. (2021) demonstrated that administration of 1% voriconazole ear drops for two weeks resulted in complete healing in cases of refractory otomycosis without tympanic membrane perforation. The primary advantage of topical therapy is that the drug is directly applied to the infection site, achieving high local concentrations. In contrast, oral therapy relies on systemic absorption, which may be limited.[24] Furthermore, a case report by Wee *et al*. (2023) indicates that despite prolonged oral therapy, the infection may recur due to inadequate drug penetration into the ear canal and the presence of a biofilm that protects the fungus.[22] Chappe *et al*. (2018) also support the notion that topical application can treat infections more quickly and effectively than oral therapy, which often fails even when administered for extended periods.[23]

Side Effects of Oral Voriconazole

The toxicity of voriconazole is concentration-dependent, according to pharmacokinetic studies. Patients with mean plasma voriconazole concentrations above 3.52 µg/ml much higher than the therapeutic threshold of 2.05 µg/ml for invasive aspergillosis have been confirmed to exhibit visual impairments. The plasma concentration is far higher than what is required for a therapeutic effect when visual defects emerge [23]. In research conducted by Zonios *et al*., patients initially showed normal liver function tests before starting voriconazole; however, abnormalities began to appear within 7 days of treatment in all but one patient. In one instance, a patient experienced an increase in the liver enzyme alkaline phosphatase on day 7 after initiating voriconazole, despite prior treatment for 8 days [32].

The Occurrence of Relapse in Otomycosis after Systemic Therapy

Even though blood level of the drug have reached therapeutic levels, the concentration that accumulates in the ear canal particularly in areas with limited blood circulation may not be sufficient to eradicate the fungus completely. This insufficient local concentration allows fungal remnants to persist, leading to relapse [22]. Additionally, Aspergillus species are known to form biofilms on the surface of the ear canal; these biofilms act as physical barriers that impede drug penetration. Consequently, even continuous systemic therapy may not reach and neutralize the fungus embedded within the biofilm [22]. Several studies emphasize that topical application overcomes these challenges by delivering higher drug concentrations directly at the infection site, ultimately leading to successful eradication of the fungus [23, 24]

Considerations for Using Topical Voriconazole as First-Line Treatment

Given its high effectiveness in treating refractory otomycosis, topical voriconazole may be considered as first-line therapy, particularly in patients without tympanic membrane perforation [21]. Several cases of refractory otomycosis have been successfully treated with voriconazole [10, 15, 24, 33] The ability to achieve optimal drug concentration at the infection site, coupled with the minimal risk of systemic side effects, renders topical therapy a more attractive option compared to oral treatment which is associated with greater risks and a higher potential for relapse. Furthermore, the ease of use and convenience of ear drops enhance patient compliance, a critical factor in treatment success. Cost and resource considerations also favor topical therapy, as it may reduce the need for hospitalization and the intensive monitoring typically required for systemic therapy. However, further research is needed to standardize application protocols, including dosage and duration, to optimize treatment on a larger scale.

Conclusion

In conclusion, voriconazole possibly effective for the cases of refractory otomycosis. The findings can be a basis for further studies with high-level evidence studies such as cohort or clinical trials to confirm the effectiveness of voriconazole for refractory otomycosis.

Declarations

The review procedures were created by AR, who also helped with data gathering, article screening, data analysis, and manuscript drafting. Data gathering, article screening, and manuscript preparation were all done with assistance from HR and ARA. ARA also helped English editing, proofread and made revisions to the paper. The final manuscript has been read and approved by all writers.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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