

Mycological spectrum and efficacy of clotrimazole versus 4% boric acid in otomycosis patients presented at Assiut university hospitals clinic

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Abstract:

Background: Otomycosis affects one or sometimes both ears. Immunocompetent people can have superficial infections such as fungal otitis externa. *Aspergillus* and *Candida* isolates in individuals with fungal otitis externa have been documented. Local debridement, systemic and local antifungal medications, and stopping topical antibiotics have all been suggested as treatments.

Patients and Methods: Seventy suspected patients who visited the otolaryngology department at Assiut University Hospitals were screened for otomycosis. The results of the culture and the sensitivity test for both clotrimazole and 4% boric acid indicated that the treatment was administered locally for a minimum of two weeks. After the first week, second week, and month, all of the patients were checked on. The two antifungal reagents were tested for efficacy and side effects.

Results: The mean age of the studied cases was 33.85 ± 15.1 years old. Males represented 55% of cases. The majority of patients aged between 19-30 years old representing 36.6%. The present study revealed that most cases have an infection in the left ear (54.8%). The duration of the infection was 13.73 days. The study also revealed that most cases have no comorbidities, 11.7% have diabetes mellitus (DM) and only 1.7% have both DM and hypertension (HTN). Filamentous organisms' infection compared to the *Candida* spp. was (70% vs. 30%, respectively). Sensitive to Clotrimazole was (65%) followed by boric acid 4% (21.7%) while (10%) were sensitive to both and (3.3%) were resistant to both.

Conclusion: So, we can conclude that fungal cultures for patients with otomycosis are a must.

Keywords: Otomycosis, Clotrimazole, Boric acid, *Aspergillus*, *Candida*

Introduction

One or occasionally both ears may be affected by otomycosis, a fungal infection. The majority of those impacted are those who live in warm or tropical regions. Fungal otitis externa, a noninvasive, acute, and chronic infection caused by protracted colonization, can occur in immunocompetent individuals. Additionally, people with diabetes,

regular swimmers, and those with other chronic illnesses and skin disorders are often impacted.¹

The affection usually involves the external auditory meatus. The tympanic membrane and middle ear cavity are rarely involved.²

Risk factors include immunocompromised hosts, those who have had open cavity mastoidectomy,

the presence of cerumen, ear instrumentation, increased topical antibiotic and steroid preparation use, a humid environment, and users of hearing aids with occlusive ear mold. The infection is typically unilateral and presents with inflammatory pruritis, scaling, and otalgia.³⁻⁴

Many authors have reported finding isolates of *Aspergillus* and *Candida* in patients with fungal otitis externa. Other species such as *Mucor*, *Fusarium*, *Scedosporium*, *Hendersonula*, *Rhodotorula*, and *Cryptococcus* are quite rare.⁵ Individuals frequently exhibit edema, erythema of the meatal epithelium of the auditory canal and tympanic membrane, persistent white or colorless otorrhea with or without tympanic membrane perforation, and whitish, cotton like, or greasy debris in the external auditory canal, occasionally on the tympanic membrane or in the cavity after cholesteatoma surgery. Additionally, patients frequently report developing hearing loss, chronic discharge, itching, and earache.⁶

Otitis externa is diagnosed using a patient's clinical history, physical examination, otoscopic examination conducted under microscopic control, head imaging tests, and laboratory fungal detection.⁷ Treatments have included ceasing topical antibiotics, systemic and local antifungal drugs, and local debridement. Even while otomycosis still has a high recurrence rate, it can occasionally emerge as a challenging condition to treat and monitor over time.⁸

So, the aim of the present study was to screen the etiological agents of otomycosis and to compare the clinical effectiveness and adverse events of clotrimazole solution versus 4% boric acid in distilled water for the treatment of otomycosis.

Patients and methods:

A prospective randomized clinical trial study included 70 suspected patients with otalgia, itching, hearing loss, ear fullness, and tinnitus who visited the otolaryngology department at Assiut University Hospitals have been done from August 2022 to April 2023. Any patient on systemic antifungal drugs, sensitive to any of the two drugs under comparison, pregnant ladies or those who refused to participate in the study were excluded. The study was approved by the hospital's human ethics committee and participants had to agree to participate by local guidelines defining human protection. On a questionnaire sheet, clinical data was entered.

The diagnosis of otomycosis relies on the patient's clinical history, the physical examination, and otoscopic examination. Treatment effectiveness was determined based on the Otoscopic absence of fungus and fungal culture after the 1st week, 2nd week and after 1 month.⁹

Mycological Assay

Two sterile cotton swabs were used to collect samples, which were then moistened with sterile normal saline (0.85% NaCl, pH 7) and sent in cooler boxes to the Assiut University, Faculty of Science's Microbiology Lab for analysis. Every sample has undergone direct microscopic examination and phenotypic & microscopic identification.¹⁰⁻¹¹

Sensitivity test

Agar well diffusion method¹² was used to test and compare the antifungal activities of the two antifungals under the study on fungal isolates species that have been isolated in the first part according to the inhibition zone.

Statistical analysis:

Data was managed by Microsoft Excel and Statistical analysis of the data was performed using the SPSS-22 software package, Data was presented in the form of frequency and percent, and the studied groups were compared and evaluated by analysis of variances:

- P-value < 0.05 was considered significant.

- P-value < 0.001 was considered as highly significant.

- P-value > 0.05 was considered insignificant.

Results

This randomized clinical trial included 70 patients with symptomatic otomycosis. 10 patients were excluded due to missing the follow up appointments. Then 60 patients were divided into two groups according to the treatment modality: 4% boric acid group (n=30) and clotrimazole group (n=30).

Regarding the demographic characteristics, the present study indicated that the mean age of the studied cases was 33.85 ± 15.1 years old. The majority of patients were from the age group 19-30 years old followed by the age group 31-50 years old, then <18 years old then >50 representing 36.6% vs 35% vs. 15% vs 13.4% respectively (P value=0.042). Males represented 55% and females represented 45% of the total cases .

The present study revealed that most cases have no comorbidities, while 11.7% have DM and only 1.7% have both diabetes mellitus (DM) and hypertension (HTN). Regarding medical history, 8.3% of cases were on insulin, 5% were on oral hypoglycemic, additionally, 1.7% of cases were on hearing aids. There were no statistically significant differences between the studied groups regarding age, gender, and comorbidity .

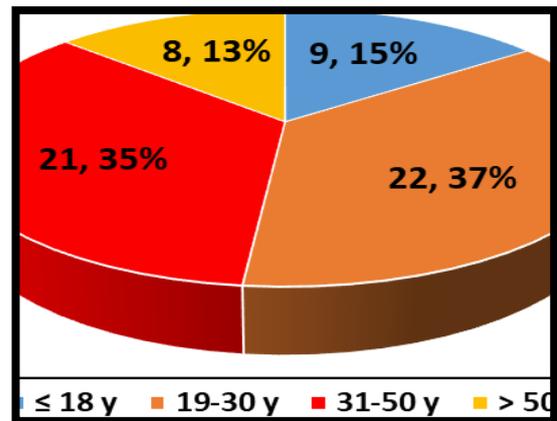


Fig 1. Age Group Distribution of the studied

Most cases were infected with *Aspergillus flavus* followed by *Aspergillus niger* then *Candida krusei* (35% vs. 28.3% vs, 20%, respectively). There was a statistically significant increase in the infection with filamentous organisms compared with the candida spp. (70% vs. 30%, respectively) .

Regarding the sensitivity test, the majority of organisms were sensitive to clotrimazole (65%) followed by 4% boric acid (21.7%). Additionally, (10%) were sensitive to both and (3.3%) were resistant to both.

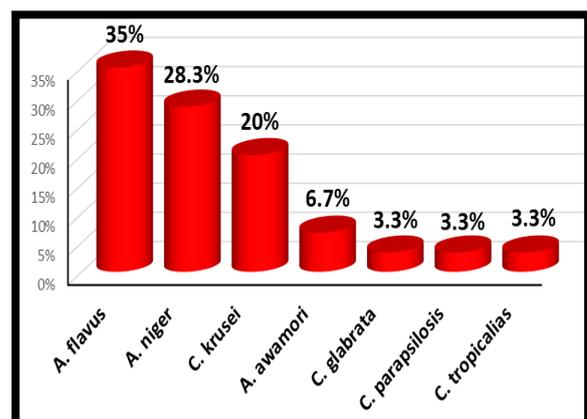


Fig 2. Distribution of the studied Cohort according to Fungal Species

The present study revealed that there was a statistically significant difference between the studied groups regarding the follow-up results. 100% of cases treated with Clotrimazole got cleared from the infection; meanwhile, in 6.7% of patients treated with Boric acid 4% were still positive for infection, most such infections were *Candida krusei*.

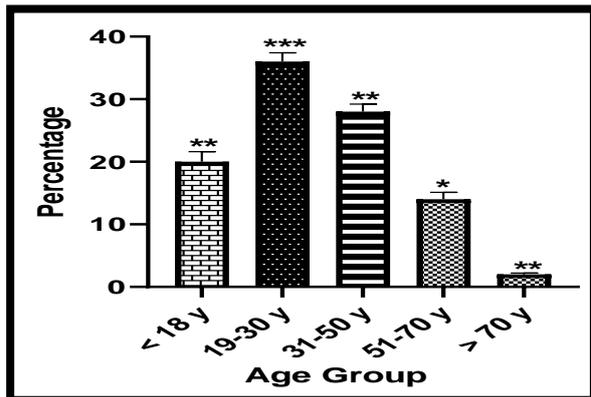


Fig 3. Age Group Distribution of the studied Cohort



Fig 4. Sensitivity to clotrimazole in *Aspergillus awamorii*

Discussion:

These days, the long course of treatment for otomycosis, the risk of recurrence, and the emergence of more antifungal-resistant fungal strains make managing the disease challenging for both patients and physicians. Clotrimazole, miconazole, and nystatin are examples of topical treatments that are specific; gentian violet and

acidifying chemicals are examples of non-specific treatments.

By dissolving the fungus's cytoplasmic membrane penetrability barrier, clotrimazole creates fissures in the cell membrane that let the fungus' materials seep out. This eliminates the fungus and treats the disease.¹³

Acidifying medications are mostly used to treat patients who are at risk of developing recurrent acute or chronic external otitis. They can be applied to minor otalgia in moderate, acute, or chronic cases. An alkaline pH has been associated with the development of either acute or chronic otitis externa, with the severity of the condition affecting the acidity loss. Boric acid has fungicidal and fungistatic properties.¹⁴

Because males spend more time outside, they are more likely to come into touch with fungus spores, which could account for the male predominance. Fungal flora that is common in the area is known to be significantly spread by outside air. The difference in surface lipids between males and females may potentially help to explain this discovery, since sex hormones control surface lipids.¹⁵⁻¹⁶ Our results concur with those of **Ali et al., (2018)**¹⁷, who studied 122 patients with a clinical diagnosis of otomycosis and found that 59% of the patients were male. Their ages varied from 9 months to 71 years, with the age group of 21 to 30 years having the largest share (27%), with a median age of 25.7 years.

Yahia and Alsayed (2021)¹⁸, who examined 194 patients with a clinical diagnosis of otomycosis and found that 15% of patients had diabetes and 9% had hypertension as underlying comorbid illnesses. In a similar vein, **Abdelazeem et al., (2015)**¹⁹ earlier research revealed a tenuous connection between otomycosis infection and other systemic conditions like diabetes, hypertension, and pregnancy. The

majority of patients with underlying diseases had hypothyroidism (34.37%), followed by heart and coronary diseases (17.18%), allergies (17.18%), diabetes (12.5%), gastrointestinal diseases (9.37%), and cancer (9.37%), according to a study conducted by **Kiakojuri et al., (2021)**²⁰ on 1040 patients with otomycosis.

The primary causes of otomycosis have been inconsistently reported in the literature. These discrepancies can be attributed to variations in geographic distribution and environmental factors, as the fungi that cause otomycosis are saprophytes, or secondary invaders, of skin that has previously been affected by eczema, psoriasis, seborrheic dermatitis, bacterial infections in the past, physical trauma, or an excessive buildup of cerumen. These results concur with those of **Roohi et al., 2023**²¹, who reported that *Aspergillus* section Nigri (58.57%) was the most common isolate in terms of fungus, followed by *Aspergillus* section Flavi (19.23%) and *Candida parapsilosis* (14.96%). On the other hand, the predominant fungal pathogens in otomycosis were different in various literature reports. In a study conducted by **Javidnia et al., 2022**²² on 211 individuals suspected of having otomycosis, it was shown that *Aspergillus tubingensis* was the most often isolated species (52.77%), with *Aspergillus niger* coming in second (25.92%) and 16% of instances, otomycosis as a result of *Candida* species infection was noted. Furthermore, the **Antunes et al., 2022**²³ investigations found that *Candida* was a more common cause of otomycosis. *Aspergillus*, the mold that causes aspergillosis, is very common both indoors and outdoors. It is often found in soil, decaying vegetation, seeds, and grains, where they thrive as saprophytes. It also exists in the air, so most people breathe in fungal spores daily, which

helps to explain the high incidence of *Aspergillus* fungal infection, according to **Anh-Tram 2019**²⁴. There's probably no way to prevent breathing in *Aspergillus* spores. It is safe for those with strong immune systems to breathe in *Aspergillus*. Breathing in *Aspergillus* spores, however, can result in an infection in the sinuses or lungs that can spread to other areas of the body in those with compromised immune systems.

Clotrimazole has the best or most significant effect in treating otomycosis for patients experiencing pain, itching, swelling, and hearing loss, according to a review study by **Yassin et al., 2023**¹⁴ on eight trials. Clotrimazole is the best treatment for fungal infections, according to **Mehreen and Prasad 2022**²⁵. It works by reducing the permeability barrier of the fungi's cytoplasmic membrane, which results in holes appearing in the cell membrane and leaking out of the organism, killing the fungus and curing the infection.

Conclusion:

Fungal cultures for patients with otomycosis are a must, to determine the most effective treatment and to avoid resistance to treatment. Also, the probability of the development of new strains or expansion of pathogens' resistance to standard antimycotics from one perspective and the progression of new techniques for cultures and, the development of new generations of antifungals highlights the necessity to reevaluate our treatment plan from time to time.

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Conflicts of interest: No

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