



# Single application of clotrimazole cream in the management of fungal otitis externa

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**Background:** Fungal otitis externa (FOE) is a common infection of the external ear canal. FOE is often associated with tympanic membrane perforation (TMP). This may be pre-existing or caused by the infection. The potential risk of ototoxicity from topical medication provides an additional treatment challenge for these patients. In this audit, a comparison is made of outcomes for patients with FOE managed with three different treatments. We compare two topical treatments licensed for use in Australia: flumetasone pivalate/clioquinol ear drops and triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin ointment, with the off-label use of clotrimazole 1% cream. This is to determine if clotrimazole (the only treatment of the three without risk of ototoxicity) is as efficacious as the current licensed treatments.

**Methods:** A review of patients diagnosed with FOE from a single Victorian specialist Ear, Nose and Throat (ENT) hospital Emergency Department (ED) was undertaken. Data from a 6-month period (March 2021–September 2021) were collected. Any patient who had presented to the ED, was subsequently confirmed on microscopy results to have FOE, and was reviewed 2 weeks post-treatment in ENT clinic was included. Successful treatment was defined as no further treatment requirement at the 2-week review.

**Results:** Fifty-eight patients met the inclusion criteria. Ten of 16 patients (63%) were successfully treated with flumetasone pivalate/clioquinol eardrops. Twenty of 30 patients (67%) were successfully treated with triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin ointment. Seven of 12 patients (58%) were successfully treated with clotrimazole 1% cream. There was no statistically significant difference between successful treatment rates between the topical treatments (Chi-square: 0.27, P=0.87).

**Conclusions:** Clotrimazole appears to be as efficacious in the management of FOE as other topical antifungal agents. Although used off-label, it is not associated with ototoxicity. It should be considered an appropriate first-line treatment for patients with FOE, especially in the setting of TMP.

**Keywords:** Otitis externa; mycosis; clotrimazole; tympanic membrane perforation (TMP)

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## Introduction

### Background

Otitis externa is a common infection of the skin of the external ear canal and patients often present to a General

Practice (GP) or Emergency Department (ED). A fungal infection is responsible for approximately 9–25% of these and the common pathogens are *Aspergillus* and *Candida*. Predisposing factors include trauma to the ear canal, water exposure and antibiotic usage (1). Patients can present with

pruritis, otalgia, aural fullness, reduced hearing and aural discharge. Recurrence rates are high, with some literature reporting 15% recurrence despite adequate treatment (1). Fungal otitis externa (FOE) can also often be associated with tympanic membrane perforation (TMP) either as a pre-existing problem or caused by the fungal infection (2,3). The risk of ototoxicity from topical medications provides an additional treatment challenge in the management of these patients. Antifungal treatments that are proven safe for the middle and inner ear are limited. Common topical antifungal treatments including flumetasone pivalate/clioquinol ear drops (Locacorten-Vioform<sup>®</sup> ear drops) and triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin (Otocomb<sup>®</sup> ointment) carry potential for ototoxicity to the inner ear causing hearing loss. Although there is no literature reporting ototoxicity in humans, animal studies demonstrate that both of these treatments may be ototoxic (4,5). Clotrimazole 1% cream, however, is not associated with this risk of ototoxicity in animal studies (4,5). Flumetasone pivalate/clioquinol ear drops (Locacorten-Vioform<sup>®</sup> ear drops) and triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin (Otocomb<sup>®</sup> ointment), unlike Clotrimazole 1% cream, are approved by the Australian Therapeutic Goods Administration for treatment of FOE (6).

### **Objectives**

The aim of this study was to compare the success rate of treatment of acute FOE comparing a single application of clotrimazole 1% cream, or a single application of triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin ointment, or repeated application of flumetasone pivalate/clioquinol ear drops. The usage of clotrimazole 1% cream in this study was off label. The Clinical Practice Guideline (CPG) of this hospital is utilized by the broader medical community, and if clotrimazole was shown to be efficacious for the management of FOE, approval would be sought from the Pharmacy Safety Committee for the CPG to be updated to recommend clotrimazole treatment for FOE management, especially when a TMP is present. We present this article in accordance with the STROBE reporting checklist (available at <https://www.theajo.com/article/view/10.21037/ajo-23-4/rc>).

### **Methods**

#### **Ethics**

The study was conducted in accordance with the Declaration

of Helsinki (as revised in 2013). This project was endorsed by the Royal Victorian Eye and Ear Hospital as a clinical audit and did not require review by the Human Research Ethics Committee (reference number 21/1512HQ). Because of the retrospective nature of the research, the requirement for informed consent was waived.

#### **Patient population**

A review of patients who were diagnosed with FOE from a single Victorian specialist Ear, Nose and Throat (ENT) hospital ED was undertaken. Data from a 6-month period (March 2021–September 2021) was collected. Patients were managed initially by a registrar or consultant specializing in the field of otolaryngology or emergency medicine. There were 125 patients initially identified. Sixty patients had a positive culture for fungi and remained eligible for inclusion. Only 58 of these patients attended ENT clinic review approximately 2 weeks after the ED presentation and were therefore suitable for the final review population. All patients except one were adult. The average patient age was 48 years. There were 27 male patients and 31 females. Two patients had FOE of both ears, 27 only the right ear and 29 the left ear.

The 58 patient records were analyzed. Data from the initial consultation was collected; specifically, patient demographics, initial treating clinician specialty, treatment type, treatment duration, fungal culture result, tympanic membrane integrity and past history of FOE. Data were collected from the ENT clinic review encounter related to further treatment requirement, subsequent treatment type and duration, as well as tympanic membrane integrity. It was not always possible to ascertain if the TMP was pre-existing. These patients were still included, given that the main outcome for assessment was successful treatment of FOE, rather than resolution of the TMP.

Prior to the instillation of topical treatment, hospital standard practice dictates that microbiological swab of the ear is performed, followed by thorough ear clean. An ear clean was noted to involve visualization of the ear canal with microscope and a combination of: suction, curettage and instillation of 3% hydrogen peroxide solution. Once clean, topical treatment were applied. Single application treatments were delivered via small syringe (1–2 mL) with or without the attachment of a micro ear suction tube. Topical treatments compared were: single application of triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin ointment; a single application of clotrimazole 1%

cream, or repeated application of flumetasone pivalate/ clioquinol drops. The patients included had FOE confirmed on microbiological testing and had returned for follow-up at least once. Successful treatment was defined as no further treatment requirement at the initial ENT clinic review at 2 weeks after the presentation.

Chi-square testing was performed to assess the significance of results.

## Results

Fifty-eight patients met the inclusion criteria. Overall, 64% of patients were successfully treated from the ED, meaning that they did not require further management at 2-week ENT clinic review. Ten out of 16 patients (63%) were successfully treated with flumetasone pivalate/cliquinol ear drops. Twenty out of 30 patients (67%) were successfully treated with triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin ointment. Seven out of 12 patients (58%) were successfully treated with clotrimazole 1% cream. There was no statistically significant difference between successful treatment rates between the topical treatments (Chi-square: 0.27,  $P=0.87$ ).

### Treating clinician

When an emergency medicine clinician initially managed the patient (ear clean and application of topical treatment), 50% of patients were successfully treated. Comparatively, when an ENT clinician initially managed the patient, 79% of patients were successfully treated. Chi-square testing confirmed this to be a significant difference (Chi-square =5.1186,  $P=0.02$ , at  $P<0.05$ ). If the initial management included a single application of topical treatment there was a statistically significant difference between the success of treatment if the patient was seen initially by an ED clinician (43% success) vs. an ENT clinician (77% success) (Chi-square =4.75,  $P=0.02$ , significance at  $P<0.05$ ). However, when Chi-square testing with significance  $P<0.05$  was performed there was no statistically significant difference between the ED and the ENT clinicians for any individual topical treatment.

### Pathogen

*Aspergillus* species alone was cultured in 43 out of 58 patients (74%). *Aspergillus niger* was most prevalent and was cultured in 40 patients (69%). Two patients grew both *Candida*

species and *Aspergillus* species. A further five patients grew *Aspergillus* and bacteria. Six patients grew *Candida*. One patient grew *Candida* and bacteria. One patient grew *Penicillium*.

Further information is provided in *Table 1*.

### TMP

In 11 patients (19%) there was a tympanic membrane present at the initial presentation. At the 2-week review, 55% of these had healed. Owing to the risk of ototoxicity, none of the patients who had a perforation were treated with flumetasone pivalate/cliquinol ear drops. For each treatment there was one patient who had a new perforation at the review. *Aspergillus* was the causative organism for all patients with TMPs. One patient also grew *Candida* on culture. For the eight patients who had a persistent perforation three have had a myringoplasty and the remainder did not attend further follow-up or are awaiting review.

## Discussion

FOE is common in Australian society. Humid weather, large surfing communities and regularity of water sports all contribute to infection rates. Recurrent infection rates are high and the risk of TMP adds further complexity (2,3). Given the low risk for ototoxicity and the ease of once-off application, clotrimazole 1% cream to manage this pathology deserves further consideration.

No human studies testing the ototoxicity of common topical treatments for FOE have been conducted. Triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin ointment and flumetasone pivalate/cliquinol ear drops, despite being licensed for the treatment of FOE in Australia, have been shown to be ototoxic to the guinea pig (4,5). Guinea pigs are likely to be more susceptible to topical ototoxins than humans (4,5) but did not develop ototoxicity with clotrimazole (4,5). All treatments in our study were well-tolerated and no patient developed middle or inner ear pathology. This result is in keeping with the literature, whereby, once-off application of clotrimazole 1% cream did not cause ototoxicity when applied in the ears of children with tympanostomy tubes and otomycosis (7).

The efficacy of a once-off application of clotrimazole cream has been reviewed previously in the literature. A systematic review comparing flumetasone pivalate/cliquinol and clotrimazole found no significant difference

Table 1 Treatment summary

Variables	Flumetasone pivalate/ clioquinol ear drops (n=16), n [%]	Triamcinolone acetonide/ neomycin sulphate/gramicidin/ nystatin ointment (n=30), n [%]	Clotrimazole (n=12), n [%]
Pathogen			
Aspergillus alone	12 [75]	22 [73]	9 [75]
Aspergillus + bacteria	0	3 [10]	2 [17]
Candida	3 [19]	2 [7]	1 [8]
Candida + bacteria	0	1 [3]	0
Aspergillus + Candida	1 [6]	1 [3]	0
Penicillium	0	1 [3]	0
Presence of tympanic membrane perforation			
Initial	0	10 [33]	1 [8]
Review	1 [6]	6 [20]	1 [8]
New at review	1 [6]	1 [3]	1 [8]
Resolved at review (% of initial)	0	5 [50]	1 [100]
Required further treatment at review	6 [38]	10 [33]	5 [42]
Re-presentation to emergency after initial treatment period	1 [8]	0	0
Total requiring further treatment	7 [44]	10 [33]	5 [42]

in the efficacy between the two treatments (8). Our study also demonstrated no significant difference between the three topical treatments, as confirmed with Chi-square testing. All three antifungal preparations resulted in successful treatment for approximately 60% of patients. Interestingly, this is significantly lower than other literature, where flumetasone pivalate/clioquinol and clotrimazole efficacy was noted to be 73% and 85% respectively (8). Cochrane review of topical '-azole' treatments for FOE did not find any studies comparing topical '-azole' treatment to a placebo or no treatment, which is an important consideration when assessing efficacy and something that needs investigation in the future (9).

Thorough cleaning of the external auditory canal before the application of topical therapy is essential (1,10,11). It is assumed that the ENT clinicians have greater experience in aural toilet, and this accounts for the improved success rate for their patients. When once-off topical treatments were compared, the success rate for treatment between specialties was significantly different, with those treated by ENT clinicians more likely to have successful management with a topical treatment. The significance of extensive aural toilet alone is unable to be specifically assessed, given no patient

received this as the only treatment.

Clotrimazole cream is noted to be less viscous than triamcinolone acetonide/neomycin sulphate/gramicidin/nystatin ointment and in our experience, patients treated with clotrimazole cream required less extensive microsuction at review, with reduced patient discomfort and possibly less trauma to the skin of the ear canal.

It should be noted that during this period flumetasone pivalate/clioquinol ear drops were not readily available. These ear drops could cost more than \$A35 per bottle which is a significant consideration for those who require treatment for an extended period. Patient socioeconomic factors, although not specifically documented, were considered.

### Limitations

Although this study compares the efficacy of anti-fungal preparations, there were many confounding variables. There are many patients who attend the hospital with chronic ear disease, and it is not known how many of the patients had a pre-existing perforation. Clinical notes are often unreliable; with severity of infection, amount of

cream or ointment applied and advice on water precautions during the treatment period, all poorly documented. Broad clinician experience level is another variable that cannot be accounted for. This ED is staffed by consultant ED physicians and registrars and ENT consultants and registrars. The ED registrars rotate from other hospitals for 3 months, and in general have less experience in performing aural toilet. Furthermore, only a small number of patients were treated with clotrimazole, as this treatment is not in the current hospital CPG and is therefore less commonly utilized.

A randomized control study with uniformity amongst treatment clinician and a larger population sample should be considered.

## Conclusions

Once off application of topical clotrimazole 1% cream is as efficacious in the management of FOE as other topical antifungal agents, with no statistically significant difference in treatment success rates found in this study. It should be considered an appropriate first-line treatment for patients with FOE, especially if there is a TMP.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://www.theajo.com/article/view/10.21037/ajo-23-4/rc>

*Data Sharing Statement:* Available at <https://www.theajo.com/article/view/10.21037/ajo-23-4/dss>

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*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <https://www.theajo.com/article/view/10.21037/ajo-23-4/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This project was endorsed by the Royal Victorian Eye and Ear Hospital as a clinical audit and did not require review by the Human Research Ethics Committee (reference number 21/1512HQ). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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