Otomycosis - a review of current management trends

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Abstract

ABSTRACT Otomycosis is increasing in prevalence and can account for up to 20% of ENT outpatient consultations in warm and humid regions. Objectives: The aim of this review was to investigate the treatment strategies and antifungal agents used in various institutions and to highlight current trends. Design: PubMed, Cochrane Library and Google Scholar electronic databases were searched for freely-accessible articles spanning January 2001 and December 2020. Results: 59 full-text English-language articles were retrieved. Aspergillus spp. were the commonest species isolated followed by Candida spp. Clotrimazole-resistant Aspergillus spp. were encountered more frequently among immunosuppressed patients. Topical medications included drops, creams, ointments, powders, lotions and sprays. Systemic treatment was given orally or intravenously. Antifungal agents used were azoles, polyenes, echinocandin, allylamine, thiocarbamate, hydroxyquinoline and griseofulvin. Antiseptics employed included Betadine, Gentian Violet, N-chlorotaurine, Castellani's Paint, Cresylate drops and Tincture Merthiolate. Steroids (beclomethasone, betamethasone, dexamethasone and hydrocortisone) were generally used in combination therapy. Acidifying agents administered were 3% boric acid, 2% acetic acid and 2% salicylic acid. Lignocaine and tetracaine formed part of some formulations. Conclusions: Topical applications are the mainstay of treatment of otomycosis, but occasionally oral or intravenous agents are required. Aural toilet and specific antiseptics have an important role. Clotrimazole remains an essential antifungal against a variety of fungi, but other antifungals may be needed against resistant species and in immunocompromised patients.

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Conclusions: Topical applications are the mainstay of treatment of otomycosis, but occasionally oral or intravenous agents are required. Aural toilet and specific antiseptics have an important role. Clotrimazole remains an essential antifungal against a variety of fungi, but other antifungals may be needed against resistant species and in immunocompromised patients.

Keywords: otomycosis, otitis externa, management, antifungals

FIVE KEY POINTS

Otomycosis can account for up to 20% of ENT outpatient consultations in some regions

Aspergillus and Candida species are the frequent culprits

Tympanic membrane perforation is an infrequently reported feature of otomycosis which physicians are not always aware of, but yet is not uncommon

Ear toilet is an important initial step in the management of otomycosis

Specific antiseptics have a useful role. Clotrimazole remains a workhorse antifungal, but other antifungals may be needed against resistant species and in immunocompromised patients

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INTRODUCTION

Otomycosis, a fungal infection of the external auditory canal, is increasingly common in general practice and ENT clinics, accounting for up to 20% of ENT outpatient consultations in some regions (1,2). Fungi are believed to cause from 2 to 15% of cases of otitis externa (3-5).

Otomycosis is more prevalent in warm and humid climates and among aquatic sports enthusiasts. Other postulated predisposing factors include frequent or prolonged use of antibiotic and steroid ear drops, regular ear manipulation, aural hygiene measures that disturb the acidic pH of the ear canal, sharing of earphones and stethoscopes, presence of hearing aids, chronic skin conditions, acute or chronic otitis media with otorrhoea, anatomical abnormalities, previous ear surgery, evidence of fungal infection elsewhere, immunosuppression and working in mouldy environments (6). Otomycosis is less common in children compared to adults in temperate climates. However, children and adults are affected to similar extents in tropical places - possibly due to families sharing swimming pools.

Itchy ear is a common presentation. Other symptoms include aural fullness, deafness, otalgia, discomfort, wetness, otorrhoea and tinnitus (7). In its florid form, the ear canal is full of moist fungal mycelia, hyphae, conidiophores, spores, desquamated epithelial cells, pus and bloody discharge. Microsuction of debris may reveal pustules, polyps and ulcerations of the ear canal skin and tympanic membrane. Inflammation of the tympanic membrane can lead to sequential breakdown of its layers leading to a perforation. Tympanic membrane perforation is an infrequently reported feature of otomycosis which physicians are not always aware of, but yet is not uncommon (8). Some authors have attributed perforations to mycotic thrombosis of blood vessels supplying the tympanic membrane (8,9).

Studies have identified Aspergillus and Candida species as the frequent culprits (10). The diagnosis of otomycosis requires a high index of suspicion. Usually, an empirical diagnosis is made based on clinical features and treatment is instituted without microbiological confirmation (5). Otolaryngologists are more likely to take a microbiological swab if patients have not responded to initial treatment (5).

The literature shows a wide variety of medications being used in the management of otomycosis with no general consensus (11,12). The aim of this review was to investigate the treatment strategies and antifungal agents used in various institutions and to highlight current trends.

METHODS

Article searches were conducted via PubMed, Cochrane Library and Google Scholar electronic databases spanning January 2001 and December 2020. MeSH terms used in PubMed were: 'otomycosis', 'fungal otitis externa', 'treatment', 'therapy' and 'therapeutics'. Articles that were not freely accessible, non-English language studies, those related to mixed otitis externa, fungal malignant otitis externa, complicated otomycosis (e.g those associated with tympanic membrane perforation) and alternative medicine for otomycosis were excluded. The PRISMA 2020 Checklist (13) was used as a guideline for reporting although the article is not a full systematic review per se.

RESULTS

59 full-text English-language articles were retrieved (see Tables 1 and 2). The mean age of patients was 36.6 ± 10.6 years. Otomycosis was diagnosed in immunocompetent patients in 54 studies. 3 studies involved immunosuppressed patients, while 2 studies involved both immunocompetent and immunosuppressed patients.

Characteristics of the organisms

Aspergillus spp. (53%) were the commonest species isolated among the studies (Table 1). In terms of specific organism, Aspergillus niger, Candida albicans, Aspergillus flavus and Aspergillus fumigatus were found in 53%, 41%, 33% and 31% of studies respectively. At least one Aspergillus organism was routinely isolated in studies involving immunocompromised patients. Opportunistic organisms were isolated in immunocompetent patients in two studies: a case of external ear mucormycosis was reported in India and a case of otomycosis caused by Pseudallescheria apiosperma was reported in Tunisia.

Treatment received

Ear toilet

Forty studies mentioned aural toilet which included clearance of fungal mass, suctioning, dry mopping with or without the aid of a cleansing solution, before the administration of therapeutic agents (Table 2).

Therapeutic agents

Topical

The topical formulations included drops, creams, ointments, powders, solutions, lotions and sprays which were given alone or in combination. Eardrops were prescribed in 38% of studies, solutions in 18%, creams in 15%, ointments in 2% and powders in 2%. Among eardrops, clotrimazole-containing drops were used most frequently (33%). Among topical solutions, antiseptic-containing ones were the most popular (45%). 1% clotrimazole cream was preferred over 1% clotrimazole drops in one study as it required a single application. The use of impregnated strips, wicks and gauze was mentioned in a few studies. Nagl M et al (14) used a cotton strip soaked in N-Chlorotaurine and dexamethasone which was changed daily for 8 days in a recalcitrant case. Arifullah et al (15) impregnated gauze with 1% clotrimazole lotion or cream. Dorasala SP & Dorasala S (1) introduced medicated absorbable gelatin sponge pieces (Gelfoam) in layers under the microscope and advised patients to instil a combination of antifungal and antibiotic ear drops for 3 days.

Systemic

Systemic therapy included oral drops, tablets, capsules or intravenous route of administration.

Antifungals

The antifungal agents included: azoles (clotrimazole, fluconazole, miconazole, voriconazole, ketoconazole, itraconazole, luliconazole, econazole, serticonazole, posaconazole and bifonazole), polyenes (amphotericin B and nystatin), echinocandin (caspofungin), allylamine (terbinafine), thiocarbamate (tolnaftate), hydroxyquinoline (clioquinol) and griseofulvin. Azoles were chosen in a majority of studies (61%). Clotrimazole was the commonest azole used (46%), followed by fluconazole (15%) and miconazole (12%).

In studies where an oral antifungal was prescribed, such as in immunosuppressed patients who were unresponsive to topical antifungals, voriconazole was chosen frequently (36% of studies). One prospective study documented the efficacy of oral fluconazole in immunosuppressed patients. Amphotericin B was frequently chosen when intravenous treatment was required.

Jimenez-Garcia L et al (16) reported 75% resolution with clotrimazole cream compared to 45% with tolnaftate eardrops after a week of treatment. Other studies found the efficacy of clotrimazole eardrops to exceed 90% with little adverse effects. Kiakojuri K et al (17) noted a reduction in the relapse rate with a prolonged course of clotrimazole eardrops.

Clotrimazole-resistant Aspergillus spp. were encountered more frequently among immunosuppressed patients. These organisms were found to be susceptible to fluconazole and tolnaftate solution. Luliconazole showed strong activity against Aspergillus niger complex in two in-vitro studies where the minimum inhibitory concentration was the lowest compared to other antifungals.

Antiseptics

Various antiseptics have been employed including Betadine (povidone-iodine), Gentian Violet (methylrosanilin), iodine, N-chlorotaurine, boric acid, Castellani's paint, Cresylate drops, Mercurochrome and Tincture Merthiolate. Two studies found 10% Betadine and 1% clotrimazole to be equally effective at treating otomycosis. One study found better results with Tincture Merthiolate compared to clotrimazole drops. Another study showed resolution of otomycosis in 77% of cases when treated with topical 4% boric acid in alcohol.

Steroids

Steroid use was mentioned in 8 studies. Most of the steroids (beclomethasone, betamethasone, dexamethasone and hydrocortisone) were used in combination therapy. However, Arndal E et al (5) reported on topical hydrocortisone cream use in some patients.

Anaesthetics

Lignocaine and tetracaine formed part of some formulations used to treat otomycosis.

Acidifying agents

2% acetic acid was chosen in 8 out of 9 studies where acidifying agents were employed. One study used 2% salicylic acid.

Combination therapy

Among the studies retrieved, 24 evaluated combination therapy as follows – antifungal/antibiotic 17%, antifungal/acidifying agent 17%, antifungal/steroid 12.5%, two antifungals 8%, antifungal/antiseptic 8%, antifungal/antibiotic/steroid 8%, antifungal/anaesthetic 8%, acidifying agent/antiseptic 8%. One study each evaluated antifungal/steroid/anaesthetic, antifungal/antibiotic/steroid/antiseptic/anaesthetic and antiseptic/steroid combinations.

Arifullah et al (15) achieved a resolution rate of 57.3% with an antifungal and acidifying agent mixture (clotrimazole and acetic acid). Kiakojori K et al (18) found that a mixture of miconazole and acetic acid was not superior to topical miconazole alone. Anwar K & Gohar MS (9) recorded a similar outcome when they substituted 1% clotrimazole for miconazole.

Atypical cases

An unusual case of otomycosis was reported in an adolescent caused by multi-drug resistant Candida auris where topical nystatin and oral terbinafine were used to treat this emerging organism. In one case of invasive otitis externa affecting a female diabetic patient, Aspergillus niger, resistant to several topical agents, was treated effectively with intravenous voriconazole. Oral voriconazole was administered in two atypical cases caused by Aspergillus niger - one with relapsing polychondritis and otomycosis, the other with diabetes and invasive otomycosis. Sander R (18) reported on the use of oral itraconazole to treat clotrimazole-resistant

Aspergillus infection. A rare case of otomycosis in a healthy male patient caused by Lichtheimia corymbifera was treated aggressively with debridement of devitalised tissue and a prolonged course of intravenous amphotericin B.

DISCUSSION

Saprophytic fungi which exist in nature or form part of the commensal flora of healthy ear canals can cause otomycosis. Aspergillus niger has been identified as the commonest culprit, followed by Candida albicans, Aspergillus flavus and Aspergillus fumigatus.

Ear toilet is an essential initial step in the management of otomycosis. The removal of fungal mass and debris allows a complete assessment of the ear canal and tympanic membrane. It also ensures that the administration of topical medication is not compromised.

Topical agents remain the mainstay of treatment. Eardrops were used more frequently than solutions, creams, ointments or powders. Among the various antifungal agents used, clotrimazole was the most popular. This inhibitor of ergosterol synthesis renders fungal cell walls leaky resulting in cellular disruption.

The efficacy of clotrimazole was found to exceed 90% in many studies. Kiakojuri K et al (17) noted a reduction in relapse rate with an extended course of clotrimazole drops. Mishra D et al (20) preferred 1% clotrimazole cream over drops as it provided a longer duration of contact with the infected ear canal skin. Clotrimazole-resistant Aspergillus spp. were encountered more frequently among immunosuppressed patients. These organisms were found to be susceptible to fluconazole and tolnaftate solution.

Systemic antifungals have an important role in specific cases of otomycosis, for example in immunosuppressed patients unresponsive to topical antifungals, in multi-drug resistant Candida auris and Aspergillus infections and in invasive otitis externa.

Antiseptics have inhibitory effects on fungal mycelial growth, are cheap, non-ototoxic and do not induce resistance. 10% Betadine was found to be as effective as 1% clotrimazole eardrops in two comparative studies. Tincture Merthiolate, a keratolytic agent with antifungal properties, was more effective than clotrimazole drops. Özcan KM et al (21) showed that topical 4% boric acid in alcohol can be beneficial, though is less effective than clotrimazole. N-Chlorotaurine, a long-lived oxidant produced by activated human granulocytes and monocytes and a novel anti-infective agent with an oxidising and chlorinating mechanism of action leading to attacks of multiple targets in microorganisms, may require further investigation.

In-vitro studies have shown that the choice of antifungal agent depends on the organism involved. Moulds, being high protease producers, show sensitivity to voriconazole, but resistance to fluconazole. Yeasts which are weak enzyme-producers are sensitive to nystatin and amphotericin B, but resistant to terbinafine. Filamentous fungi, like Aspergillus species, possess high enzymatic activity which makes them more virulent (10). If clotrimazole-resistant Aspergillus spp. is suspected or isolated, fluconazole or thiocarbamate eardrops are an option. If Candida albicans is responsible, nystatin eardrops can be effective.

During the initial treatment, a combination of drugs may be useful - topical steroids, antiseptics, antibiotics and local anaesthetics may help to reduce pain, pruritus, oedema and superadded bacterial infection. Topical antifungal eardrops after suction clearance of debris can then proceed for three weeks to eradicate fungal spores. The patient needs to be advised to keep water out of the ears. The use of a cottonwool ball coated in petroleum jelly provides a snug, effective and comfortable water-repellent earplug (22). The patient needs to be informed about the self-cleaning mechanism of the ear and its microenvironment which must not be altered with chlorinated water, soap or shampoo. Cerumen is a natural emollient with antifungal and antibacterial properties which helps to maintain an acidic environment (23).

The main limitation of our study is that it is not a systematic review of the subject per se. Only English-language articles that were freely-accessible online were included. Nevertheless, studies from institutions across many countries were retrieved which gave us an insight into how otomycosis is managed globally. Another limitation is that studies involving complicated otomycosis such as with tympanic membrane perfo-

rations were excluded. The presence of a tympanic membrane perforation poses its own specific challenges. This may be investigated further in future studies.

CONCLUSIONS

The management of otomycosis can be tricky. Topical applications are the mainstay of treatment, but occasionally oral or intravenous agents are required. Aural toilet and specific antiseptics have an important role. Clotrimazole remains an essential antifungal against a variety of fungi, but other antifungals can be useful against resistant species and in immunocompromised patients.

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Table 1. Characteristics of the studies

Research ID	**Study design**	**Mean age of patients (years)**	**Organisms isolated**	**Immune status (ImC/ ImS/ both)**
Cimolai N, 2020	Review	Not specified	Broad spectrum fungi	ImC
Jimenez-Garcia L *et al*, 2020	Randomised controlled trial	55	*Aspergillus niger* & other *Aspergillus* spp., mycelium	ImC
Mohammed W *et al*, 2020	Prospective study	38	*Aspergillus flavus*	Both
Moslem M & Mahmoudabadi AZ, 2020	Experimental study	Not applicable	*Aspergillus flavus*	ImC
Abastabar M, 2019	Case report	14	*Candida auris*	ImC
Al-Hashimi *et al*, 2019	Descriptive study	Not specified	*Candida albicans* & *Aspergillus niger*	ImC
Teharia RK & Narvey VP, 2019	Comparative study	Not specified	Not specified	ImC
Sumbria D *et al*, 2019	Prospective study	26	*Aspergillus* spp., *Candida albicans* & *Trichophyton*	ImC

Kiakojori K *et al*, 2019	Descriptive study	45	*Aspergillus niger, Aspergillus flavus, Candida albicans, Aspergillus terreus, Aspergillus fumigatus*	ImC
Dundar R & Iynen I, 2019	Prospective study	29	*Aspergillus* spp., *Candida* spp.	ImC
Hivary S *et al*, 2019	Experimental study	Not applicable	*Aspergillus nigri* complex	ImC
Kanade SM, 2018	Randomised double blind prospective study	40	*Aspergillus niger, Aspergillus flavus, Aspergillus fumigatus, Candida albicans*	ImC
Ahmed MR *et al*, 2018	Descriptive study	41	*Aspergillus fumigatus, Aspergillus niger, Candida albicans, Aspergillus flavus, Aspergillus terreus, Candida tropicalis*	ImC
Kiakojori K *et al*, 2018	Cross-sectional study	45	*Aspergillus flavus, Aspergillus niger & Candida albicans*	ImC
Mofatteh MR *et al*, 2018	Single blind clinical trial	39	*Aspergillus* spp., *Candida albicans*	ImC
Mahdavi OS *et al*, 2018	Clinical trial	50	*Aspergillus* spp. & *Candida* spp.	ImC
Ali K *et al*, 2018	Experimental descriptive study	26	*Aspergillus niger*, *Aspergillus flavus* & *Candida* spp.	ImC
Nagl M *et al*, 2018	Descriptive study	Not specified	*Aspergillus* spp. & *Candida* spp.	ImC
Chappe M *et al*, 2018	Case report	45	*Aspergillus niger*	ImC
Baumgardner DJ, 2017	Review	Not specified	*Candida* spp. & *Aspergillus* spp.	ImC

Agarwal P & Devi LS, 2017	Prospective study	25	*Aspergillus niger complex, Aspergillus flavus and Aspergillus fumigatus, Candida* spp., *Penicillium, Mucor & Trichophyton mentagrophyte*	ImC
Mishra D *et al*, 2017	Prospective randomised study	Not specified	*Aspergillus niger, candida albicans & Aspergillus fumigatus*	ImC
Arndal E *et al*, 2016	Descriptive study	Not specified	Not specified	ImC
Arifullah *et al*, 2016	Observational study	31	Not specified	ImC
Nandyal CB & Choudhari AS, 2015	Prospective study	Not specified	Not specified	ImC
Vadisha SB *et al*, 2015	Review	Not specified	*Aspergillus niger*	ImS
Zarei Mahmoudabadi A *et al*, 2015	In vitro study	Not applicable	*Aspergillus* spp. & *Candida* spp.	ImC
Abed AR & Hussein IM, 2015	Experimental study	Not applicable	*Aspergillus niger, Candida albicans*	ImC
Navaneethan N & YaadhavaKrishnan RP, 2015	Prospective study	Not specified	*Aspergillus niger, Candida albicans, Aspergillus flavus, Aspergillus fumigatus*	ImC
Naqi S *et al*, 2014	Descriptive case series	35	*Aspergillus* spp. & *Candida* spp.	ImC
Anwar K & Gohar MS, 2014	Prospective study	38	Not specified	ImC
Adoga AS & Iduh AA, 2014	Retrospective study	46	*Candida* spp.	ImC
Nemati S *et al*, 2014	Cross-sectional study	38	*Aspergillus niger, Candida albicans & Aspergillus fumigatus*	ImC

Prasad SC *et al*, 2014	Prospective study	26	*Aspergillus niger* complex, *Aspergillus fumigatus* complex, *Aspergillus flavus* complex, *Penicillium* spp. & *Candida albicans*	ImC
Philip A *et al*, 2013	Single blinded prospective randomised case control study	23	*Aspergillus niger, Aspergillus flavus*	ImC
Khan F *et al*, 2013	Descriptive study	40	Not specified	ImC
Neji S *et al*, 2013	Case report	32	Graphium stage of *Pseudallescheria apiosperma*	ImC
Dorasala SP & Dorosala S, 2013	Descriptive study	Not specified	Not specified	ImC
Shraga S *et al*, 2013	Clinical study	Not applicable	*Aspergillus* spp., *Candida albicans.*	ImC
Kolling WM *et al*, 2013	Case report	59	Not specified	ImC
Block TK & Munson E, 2012	Case report	19	*Aspergillus niger*	ImC
Schaefer P & Baugh RF, 2012	Review	Not specified	*Aspergillus* spp. & *Candida* spp.	ImC
Viswanatha B *et al*, 2012	Prospective study	46	*Aspergillus niger, Aspergillus fumigatus, Candida albicans, Penicillium chrysogenum*	Both
Edward *et al*, 2012	Review & case report	41	*Aspergillus niger, Aspergillus fumigatus, Candida albicans*	ImC
Vyas DH & Shah PD, 2011	Case report	55	*Lichtheimia corymbifera*	ImC
Viswanatha B & Nasseruddin K, 2011	Review	Not specified	*Aspergillus* spp., *Candida albicans*, *Pseudallescheria boydii*	ImS

Hsu CL *et al*, 2011	Case report	35	*Aspergillus niger*	ImC
Lee A *et al*, 2011	Review	Not specified	Not specified	ImC
Yaganeh Moghadam A *et al*, 2010	Clinical study	37	*Aspergillus niger, Candida albicans* and other *Aspergillus* spp.	ImC
Mgbe R *et al*, 2010	Retrospective study	26	Not specified	ImC
Chalabi EY & Ahmed TS, 2010	Randomised prospective comparative study	Not specified	*Aspergillus niger, Candida albicans, Aspergillus fumigatus, Aspergillus flavus*	ImC
Parize P *et al*, 2009	Case reports & Review	46	*Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger*	ImS
Malik MF *et al*, 2009	Prospective study	26	*Aspergillus niger, Aspergillus flavus, Aspergillus fumigatus, Candida tropicalis and Mucor* spp.	ImC
Ibiam FA, 2009	Prospective study	28	*Aspergillus niger, Aspergillus fumigatus, Aspergillus flavus, Candida albicans*	ImC
Kiakojori K *et al*, 2007	Clinical study	36	*Aspergillus niger & Candida* spp.	ImC
Ong YK & Chee G, 2005	Review	Not specified	*Aspergillus* spp. & *Candida* spp.	ImC
Özcan KM *et al*, 2005	In vitro study	Not applicable	*Aspergillus niger, Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus & Candida albicans*	ImC

Panizza BJ, 2002	Descriptive study	Not specified		*Aspergillus niger* & *Candida* spp.	ImC
Sander R, 2001	Review	Not specified		*Aspergillus* spp. & *Candida* spp.	ImC
ImC - Immunocompetent ImS - Immunosuppressed spp. - Species	ImC - Immunocompetent ImS - Immunosuppressed spp. - Species	ImC - Immunocompetent ImS - Immunosuppressed spp. - Species	ImC - Immunocompetent ImS - Immunosuppressed spp. - Species	ImC - Immunocompetent ImS - Immunosuppressed spp. - Species	ImC - Immunocompetent ImS - Immunosuppressed spp. - Species

Table 2. Treatment regimens used

Research ID	Class of drugs used (Topical unless specified)	Treatment (Detailed)	Duration of treatment	Ear toileting
Cimolai N, 2020	Hydroxyquinoline	1% - 3% Clioquinol	Unspecified	Unspecified
Jimenez-Garcia L *et al*, 2020	Azole versus thiocarbamate	Group 1 - Clotrimazole cream was applied to ears and left for 7 days Group 2 - Patients were instructed to apply Tolnaftate solution 2 drops every 12 h for 7 days	1 week	Group 1 - Cream residue removed from EAC after 7 days Group 2 - EAC cleaned and dried after 7 days
Mohammed W *et al*, 2020	Azoles (topical & oral) and polyene	Clotrimazole, fluconazole, nystatin or miconazole. If no response, patient treated with systemic antifungal (fluconazole and voriconazole)	Unspecified	Clearance of fungal mass
Moslem M & Mahmoudabadi AZ, 2020	Azoles versus echinocandin versus polyene	Luliconazole, voriconazole, caspofungin and amphotericin B	Not applicable	Not applicable
Abastabar M, 2019	Cephalosporin (oral), aminoglycosides, polyene and allylamine	Oral Cefixime 400 mg/d and topical gentamicin Topical nystatin 100 000 U/g TDS and terbinafine 250 mg TDS	Unspecified	Unspecified

Al-Hashimi *et al*, 2019	Azole versus thiocarbamate versus combination of azole and steroids	1st group - Clotrimazole solution / clotrimazole cream 2nd group - Tolnaftate solution 3rd group for severe candida infection- Clotrimazole mixed with steroid for 2 days, then extraction of mass, then clotrimazole with steroid for a further 5 days, then steroid cessation and continuation of clotrimazole for 2 weeks For severe Aspergillus niger infection - Tolnaftate mixed with steroid for 2 days, then extraction of mass, then tolnaftate with steroid for a further 5 days, then steroid cessation and continuation of tolnaftate for 2 weeks	2 weeks	Suction of ear canal and cleaning by dry method For severe infection, extraction of mass, after washing, complete cleaning and drying of ear
Teharia RK & Narvey VP, 2019	Antiseptic versus azole	Group A - Betadine (povidone iodine 10%) 10 ml solution ear wash using syringes at each visit Group B - 4 drops of clotrimazole 1% QID	20 days	Ear washing with 10% betadine 10 ml solution using syringes at each visit

Sumbria D *et al*, 2019	Azole versus azole versus thiocarbamate versus combination of azole, antibiotic and steroids	Group 1 - 1% Luliconazole lotion Group 2 - 2% Sertaconazole cream Group 3 - 1% Terbinafine hydrochloride cream Group 4 - 0.5% Fluconazole gel Group 5 - 1% Clotrimazole lotion Group 6 - Combination of 1% clotrimazole, chloramphenicol and beclomethasone eardrops	4 weeks	Dry aural toileting with swab stick
Kiakojori K *et al*, 2019	Azole	Clotrimazole 2 drops 3 times per week	4 weeks	Cleaning and drying of ear canal
Dundar R & Iynen I, 2019	Azole	The ear canal was filled with 1% clotrimazole cream	7-15 days	Cleaning of ear canal by microsuction
Hivary S *et al*, 2019	Azoles versus polyene versus echinocandin	Luliconazole, amphotericin B, posaconazole and caspofungin	Not applicable	Not applicable
Kanade SM, 2018	Azole versus Azole	Group A - 1% Clotrimazole eardrops, 3-5 drops TDS instilled by the patient Group B - 0.3% Fluconazole eardrops, 3-5 drops TDS instilled by the patient For proper administration of eardrops, instructions were given by a trained nurse assistant	3 weeks	Patients were advised to keep the ear dry
Ahmed MR *et al*, 2018	Azoles versus polyene macrolide antibiotic	Ketoconazole 2% cream, Miconazole 2% cream Nystatin 100 000 U/g cream was used for Candida spp.	2 weeks	Removal ear canal debris

Kiakojori K *et al*, 2018	Azole	2% Miconazole ointment	Unspecified	Suction clearance and removal of colonies ± 2% oxygenated solution / distilled water / normal saline followed by drying of the ear
Mofatteh MR *et al*, 2018	Antiseptic alone versus azole, thiocarbamate & antiseptic	Group 1 - washed by physician using 10 ml betadine 10% with syringe Group 2 - 8 drops of clotrimazole 8 hourly For resistant cases, tolnaftate and Gentian Violet were used	20 days	Ear washing with 10 ml betadine 10% with syringe
Mahdavi OS *et al*, 2018	Combination of cephalosporin and azole versus azole alone	1% Clotrimazole cream injected into ear canal under the microscope for both groups Intervention group received ceftizoxime 1 g powder sprayed in ear canal using insufflation	Unspecified	Suction clearance
Ali K *et al*, 2018	Polyenes versus azoles versus allylamine	Amphotericin B 100 units and nystatin 100 units fluconazole 25 ug, ketoconazole 10 ug, clotrimazole 10 ug, voriconazole 1 ug and itraconazole 10 ug Terbinafine 25 ug	Not applicable	Not applicable
Nagl M *et al*, 2018	Chloramine, steroids and azole	Cotton strip soaked with 1% N-chlorotaurine (NCT) plus 0.1% dexamethasone. The strip was changed daily 1% clotrimazole strip was used in case of relapse Treatment was changed again to 1% NCT plus 0.1% dexamethasone	8 days	Unspecified

Chappe M *et al*, 2018	Polyene & azole	Nystatin (Auricularum®, Grimberg) BD for 1 month Econazole cream was started 7 months later due to relapse, but was difficult to apply. Finally, 1% voriconazole solution was used TDS / QID for 14 days	14 days after relapse	Ear canal suction
Baumgardner DJ, 2017	Mixture of acidifying agent and alcohol or azole	2% acetic acid in propylene glycol or 1% clotrimazole solution	Unspecified	Unspecified
Agarwal P & Devi LS, 2017	Azole	Clotrimazole drops, 4-5 times daily	10-14 days	Thorough aural toilet
Mishra D *et al*, 2017	Azole versus azole	Group A - Patients were instructed to instil 1% clotrimazole 3 drops TDS Group B - 1% clotrimazole cream was squirted into 2 ml syringe and ear canal was filled with this cream under endoscopic guidance	1 week	Unspecified
Arndal E *et al*, 2016	Azoles versus polyene versus steroids versus antiseptics versus allylamine	Clotrimazole, miconazole Nystatin Hydrocortisone Methylrosanilin (Gentian Violet) Terbinafine	Unspecified	Unspecified
Arifullah *et al*, 2016	Acidifying agent & azole	1% clotrimazole lotion or cream (impregnated gauze)	1-3 weeks	Local debridement, ear cleaning with dilute aluminium acetate solution combined with acetic acid
Nandyal CB & Choudhari AS, 2015	Azole versus Azole	1% Clotrimazole eardrops TDS were used in 70 cases 1% miconazole eardrops TDS were used in 65 cases	2 months	Cleaning of fungal mass and debris in infected ear canal either by dry mopping (98%), microsuction (4.4%) or syringing (0.74%)

Vadisha SB *et al*, 2015	Azoles	Topical clotrimazole was widely used For patients who did not respond to clotrimazole, fluconazole was an alternative	3 weeks	Suction clearance of fungal debris
Zarei Mahmoudabadi A *et al*, 2015	Azoles versus polyene versus allylamine	Clotrimazole 50 ug/disk Miconazole 10 ug/disk Nystatin 100 ug/disk 10% terbinafine (Lamisil) stock was prepared with dimethyl sulfoxide 12 ug/disk	Not applicable	Not applicable
Abed AR & Hussein IM, 2015	H2O2 versus antiseptic versus acidifying agent	3% H2O2, 1% Iodine, 2% Acetic acid	Not applicable	Not applicable
Navaneethan N & YaadhavaKrishnan RP, 2015	Azole versus azole	Group A - 1% Clotrimazole eardrops, 3-5 drops TDS Group B - Two application of miconazole cream, once during initial visit and second application during first week review for persistent disease Group C - Fluconazole drops, 3-5 drops TDS	2 weeks	Aural toileting
Naqi S *et al*, 2014	Azole	Clotrimazole lotion BD	2 weeks	Unspecified
Anwar K & Gohar MS, 2014	Azole / acidifying agents in alcohol / polyene (oral)	Clotrimazole 1% lotion or cream / 2% salicylic acid in alcohol / ototopical drops with propylene glycol / antimicrobial / fluconazole / nystatin (Nilstat)	1 week	Aural cleaning

Adoga AS & Iduh AA, 2014	Combination of azole, antibiotic, local anaesthetics, steroid, alcohol, hydroxyquinoline / steroid	Discontinuation of antibiotics Combination of clotrimazole, Chloramphenicol, lignocaine hydrochloride, Beclomethasone, glycerine (Candibiotic®) in 98.0%, Clioquinol / Flumethasone (Locacorten Vioform®) in 2.0%	2 weeks	Aural toileting
Nemati S *et al*, 2014	Azoles & polyene	Clotrimazole, fluconazole, ketoconazole and nystatin	Not applicable	Not applicable
Prasad SC *et al*, 2014	Azole	Clotrimazole 4-5 drops TDS	7-14 days	Aural toilet by suctioning and removal of fungal debris
Philip A *et al*, 2013	Antiseptic versus combination of azole with local anaesthetic	Group 1 - 3 drops of 1% clotrimazole & 2% lignocaine in propyl glycerol were instilled in the affected ear OD Group 2 - 3 drops of 7.5% povidone-iodine were instilled in the affected ear OD	2 weeks	Thorough toileting of the ear canal
Khan F *et al,* 2013	Azole	Clotrimazole lotion 5 drops TDS	2 weeks	Unspecified
Neji S *et al*, 2013	Azole	Ecorex ® (econazole nitrate) 5 drops BD	10 weeks	Intense cleaning
Dorasala SP & Dorasala S, 2013	Antifungal & antibiotic	Pressed and cut medicated Gelfoam pieces soaked in topical antifungal and antibiotic ear drops Patients advised to instil eardrops over Gelfoam for 3 days	3 days	Cleaning of all fungal debris

Shraga S *et al*, 2013	Antifungal	Shraga Cream: 0.1% Betamethasone, 10% Griseofulvin, 35% Lanolin, 20% Petroleum jelly (Vaseline®) , 15% Tea tree oil and 20% Distilled water Shraga Ear drops: 0.1% Betamethasone, 10% Griseofulvin, 15% Tea Tree oil, 25% Petroleum jelly (Vaseline®) and 50% Distilled water OD	1 week	Unspecified
Kolling WM *et al*, 2013	Combination of azole and anaesthetic vs azole alone vs analgesic (oral)	1% clotrimazole 4 drops TDS Oral ibuprofen 2 drops of 1% topical tetracaine in propylene glycol 5 minutes followed by 4 drops of 1% clotrimazole	2 weeks	Cleaning of ear canal
Block TK & Munson E, 2012	Azole	1% Clotrimazole eardrops	Improvement noted following 2 days of therapy	Unspecified
Schaefer P & Baugh RF, 2012	Acidifying agent, half acidifying agent/ half alcohol or antifungals	Acetic acid 2% (Vosol) otic solution 2 drops BD	7 to 10 days	Meticulous cleaning of ear canal
Viswanatha B *et al*, 2012	Azole versus Azole	Discontinuation of topical antibiotics Initial treatment regimen - clotrimazole eardrops. Patients who did not respond to clotrimazole were switched to fluconazole eardrops.	3 weeks	Microscopic suction clearance of fungal mass

Edward *et al*, 2012	Antiseptics, polyene, azoles	Boric acid, Gentian Violet 1%, Castellani's paint, Cresylate Otic drops, Mercurochrome, Nystatin cream / ointment / powder, Clotrimazole, ketoconazole, fluconazole, miconazole cream 2%, Bifonazole 1% solution, Itraconazole Case report - Gentian Violet	5 days	Mechanical debridement
Vyas DH & Shah PD, 2011	Polyene (IV)	IV Amphotericin B	Unspecified	Suction clearance & debridement
Viswanatha B & Nasseruddin K, 2011	Azoles	Clotrimazole eardrops / fluconazole eardrops	3-4 weeks	Microscopic suction clearance of fungal mass
Hsu CL *et al*, 2011	Azoles (oral & IV), aminoglycoside (oral), polyene (oral), beta-lactams (oral)	Initially, oral ketoconazole 400 mg QID for 2 weeks IV fluconazole 200 mg QID, gentamicin 160 mg QID, gentamicin replaced after 3 days by amphotericin B 30 mg QID and piperacillin and tazobactam 2.25 g 8 hourly for 4 days After obtaining culture result, IV voriconazole (loading dose 300 mg every 12 h for 1 day; maintenance dose 200 mg every 12 h for 5 days) Oral voriconazole 200 mg BD was administered for 5 further days	4 weeks	Daily clearing of ear discharge
Lee A *et al*, 2011	Azole	1% clotrimazole	14 days	Suction clearance and dry mopping of debris

Yaganeh Moghadam A *et al*, 2010	Mixture of alcohol & acidifying agent	Mixture of 90 ml of 70% isopropyl alcohol + 10 ml of 2% acetic acid every 8 h	3 weeks	Unspecified
Mgbe R *et al*, 2010	Hydroxyquinoline / steroids / azole / local anaesthetics / antiseptic	Ears packed with wick impregnated with either clioquinone / flumethasone (Locacorten Vioform eardrops/cream) or beclomethasone dipropionate / clotrimazole / lidocaine hydrochloride (Candibiotic ear drops) or Gentian Violet changed thrice daily	2 weeks	Aural syringing
Chalabi EY & Ahmed TS, 2010	Azole drops	1% clotrimazole 2 drops BD	3 weeks	Group A - Suction cleaning (dry ear cleaning) Group B - Gentle (wet ear cleaning) syringing by using clean water at body temperature or normal saline

Parize P *et al*, 2009	Azoles (oral), polyene (oral), echinocandin (oral)	1st case: Oral voriconazole 200 mg BD 2nd case: Oral voriconazole first at 200 mg BD, then at 300 mg BD to obtain a trough concentration of more than 1 mg/L Review: 17 patients received 2 g amphotericin B, 9 of the 17 patients received amphotericin B and itraconazole. 1 patient first received itraconazole and was switched to amphotericin B because of a relapse In 3 cases, itraconazole was used as the only antifungal 1 patient received both voriconazole and caspofungin	3 months for the 1st case 12 months for the 2nd case	Unspecified
Malik MF *et al*, 2009	Antiseptic versus azoles	Tincture Merthiolate or clotrimazole or miconazole 4 drops BD	14 days	Cleaning by dry mopping
Ibiam FA, 2009	Hydroxyquinoline	Locorten-Vioform® 2-3 drops QID	3 weeks	Aural dry mopping
Kiakojori K *et al*, 2007	Azole versus combination of azole and acidifying agent	First step - 2% miconazole Second step - Combination of 2% miconazole and acidic acid drops (acetic acid 3% in ethanol 97%)	21 days	Suction clearance
Ong YK & Chee G, 2005	Acidifying / drying agent and azole	Acetic acid 2% and topical clotrimazole eardrops	Unspecified	Aural toilet
Özcan KM *et al*, 2005	Antiseptic in distilled water versus antiseptic in alcohol	Boric acid solution in 70% distilled water, boric acid solution in 70% ethanol	Not applicable	Not applicable

Panizza BJ, 2002	Combination of antibiotic, corticosteroids and antifungal	Combination of ciprofloxacin, hydrocortisone and antifungal ear drops	1 week	Suction clearance, dry mopping of canal with probe
Sander R, 2001	Acidifying drops / azoles (topical / oral)	2% acetic acid TDS / QID If symptoms persist, 1% clotrimazole (Lotrimin) Aspergillus infection resistant to clotrimazole required oral itraconazole (Sporanox)	1 week	Cleansing of ear canal by suctioning
BD - Twice daily OD - Once daily QID - Four times a day TDS - Three times daily NCT - N-Chlorotaurine EAC - External auditory canal	BD - Twice daily OD - Once daily QID - Four times a day TDS - Three times daily NCT - N-Chlorotaurine EAC - External auditory canal	BD - Twice daily OD - Once daily QID - Four times a day TDS - Three times daily NCT - N-Chlorotaurine EAC - External auditory canal	BD - Twice daily OD - Once daily QID - Four times a day TDS - Three times daily NCT - N-Chlorotaurine EAC - External auditory canal	BD - Twice daily OD - Once daily QID - Four times a day TDS - Three times daily NCT - N-Chlorotaurine EAC - External auditory canal

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