



## Efficiency of 5 Day Course Oral Itraconazole in Management of Recurrent Otomycosis in Diabetic Patients- a Randomized Control Clinical Trail

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**ABSTRACT**

Otomycosis (or fungal Otitis externa) is a troublesome infection of External ear usually by Aspergillus or Candida. Chronic and recurrent Otomycosis is frequently seen in Diabetic and elderly patients. This study highlights that Oral Itraconazole at a daily dose of 200mg/day for 5 days is an effective and safe remedy for treatment of Otomycosis in Diabetic patients. In addition early and quasi-urgent eradication of fungus provides for prevention of Fungal Malignant Otitis externa, (Invasive Otitis externa) or Skull base osteomyelitis.

**KEYWORDS**

Aspergillus, Candida, Aspergillus niger, Otitis externa, Otomycosis, Swimmer’s ear, Itraconazole, Oral anti fungal, Diabetes mellitus

**INTRODUCTION**

Otomycosis (or fungal Otitis externa) is a common and recurrent complaint in patients living in Hot and humid environment. This is often offset by usage of Steroid ear drops and Antibiotic use. Patients with Diabetes mellitus are at higher risk developing a complicated form Otitis externa known as Malignant Otitis externa, (Invasive Otitis externa) or Skull base osteomyelitis.

**Methodology**

A cohort of 20 type 2 Diabetes mellitus patients was selected from the Out-patient clinic at our Hospital from 1 May 2015 till 1 October 2015.

**research Design of the study**

The type of clinical trial was Randomized control trial unblinded (open) Parallel group design, both groups were managed local treatment like suction, irrigation and topical Clotrimazole ear drops. The study group was administered oral antifungal and control group was not given any oral drugs.



**Figure 1: Research Design followed in our study**

Study groups were assigned to random groups by Simple random number table. Patients were not blinded as patients had no active role in the outcome. The final grading outcome was carried out by our colleague doctors who were blinded and did not have any knowledge of the administered treatment.

Trail was carried on for 3 to 6 weeks, at the end of which patients was released from trial. The goal of the study was to show superiority or higher cure rates with Oral-Antifungal Itraconazole.

**Selection criteria**

1. Confirmed Diabetes mellitus for duration of 1 year and onwards
2. Age greater than 40 years
3. More than 1 episode of Fungal Otitis externa – Proven by Culture of ear swab, and treatment by using toilet and removal of the debris and topical anti-fungal drop.

4. Free from any Diabetes related complications like Chronic Renal failure

**Disease criteria**

1. Clinically proven Fungal disease by Oto-endoscopy, Oto-microscope, 2 Ear swabs were taken.

First swab material was examined in the ward side lab after heating with 10% potassium hydroxide solution and a search was made for (hyphae, conidia and Aspergillus heads).The second Ear swab inoculated on Sabouraud’s Dextrose Agar (SDA) with antibiotics and 25°C and 37°C for a minimum period of 4 weeks. The culture tubes were examined for the presence of growth every day.

2. Identification of mycelium (hyphae, conidia and Aspergillus heads) was done by Gram’s Stain followed by Lactophenol Cotton Blue Mount preparation and Slide culture examination was used for differentiation of morphology.

**CONSENT and Ethical consideration**

Hospital ethical approval was obtained and also written consent was obtained from each patient before inclusion into study.

**End POINT / Cure criteria**

Observing a dry ear free of fungal debris using Oto-endoscope and Oto-microscope. (Grade 0)

Following that patients were followed up to 3 to 6 weeks to ensure no recurrence of the pathogen.

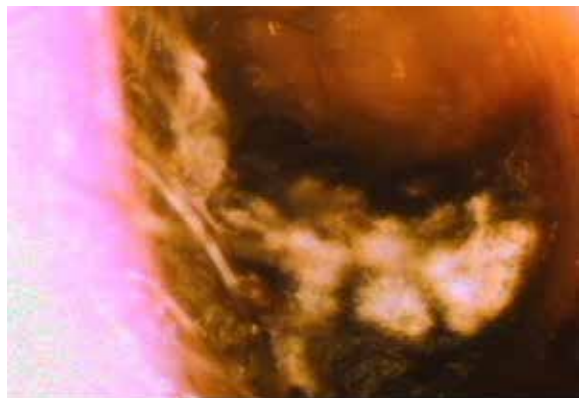
**GRADING OF DISEASE**

Grading of disease severity was done as the following table; Grading was done at first visit followed up till final visit or end-point 6 weeks

**TABLE – 1 grading of otomycosis (developed by authors)**

Observation criteria	Grade of Disease
External Auditory canal dry No fungal debris Tympanic membrane pearly white	Normal ear 0 Zero
External Auditory canal wet Minimal fungal debris in floor of EAC	Minimal Grade 1
External Auditory canal wet Fungal debris around 50% of EAC	Moderate Grade 2

External Auditory canal wet Fungal debris completely filling up the EAC	Severe Grade 3
External Auditory canal wet Fungal debris completely filling up the EAC Excoriation of pinna and EAC	Super added bacterial infection Grade 4



**Figure 2: A Grade 2 Otomycosis with Aspergillus colonies filling up almost half of External auditory canal.**

**Treatment methodology**

**Patients were randomly treated with Oral Itraconazole or**

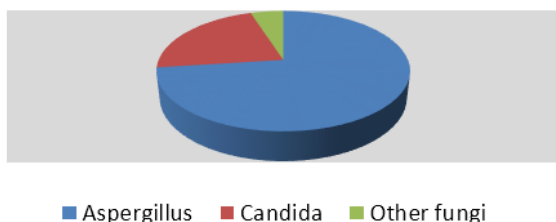
1. Removal of fungal debris on the first visit using Suction or gentle ear irrigation under Endoscope or Microscope guidance
2. Topical Clotrimazole ear drops 5 drops twice a day for all patients. No oral medicines for Control wing.
3. Cap Itraconazole at 200mg Once a day for 5 days for trial group.

**Observations**

Ear swab was cultured on Sabouraud's dextrose agar, growth was stained and observed to identify the fungal pathogen, and fungal species profile that was observed is as follows in the figure 1.

Most common fungus isolated was Aspergillus niger , fumigatus and flavus 73% of cases, Candida albicans/ pseudotropicalis /tropicalis was found in 22% of cases, other miscellaneous fungi like Mucor, Alternaria, Fusarium 5% cases.

**Species wise distribution**



**Figure 3: Species wise distribution of pathogen**

**RANDOMIZATION of treatment**

Using a simple random number table participants were assigned study group or Control group. Patients were not blinded as they were passive, the grading doctors were blinded and did not know which group patient belonged when estimating the clinical grade of Otomycosis. The effectiveness of the therapy was tested by Bio-statistical methods.



**Figure 4 Candida species growing with curd white (yeast) colonies on Sabouraud's dextrose agar from ear swab of a case**

**Adverse effects**

No serious adverse effects were seen on using Cap Itraconazole at 200mg Once a day for 5 days, though a subset of patients did complain of nausea following ingestion of capsule. This was fortunately a small cohort comprising of 3 out of 15.

**Effect on Itching symptom**

All the treatment limb patients had remarkable relief from itching which was one of their most troublesome symptoms on first presenting to our clinic.

**Biostatistic analysis of Randomized control trial results**

Simple Analysis of data was done using statistical test. Since the trial uses grading to measure outcomes, this qualifies as nominal data and hence we had to use Non-Parametric statistical test for analysis of the trial data.

Kolmogorov–Smirnov was employed to test and ascertain normality of data. For sample sizes of 20, approximation using the normal distribution is fairly good.

Null hypothesis is that treatment has not made any difference and since failure and cure are possible 50% times (Equally possible if solely by chance  $p=q=0.5$ ). Setting up variables

Null hypothesis  $H_0: E(X) =$  There is no difference in cure rates in either limbs of study (median difference between the pairs is zero)

Alternate Hypothesis:  $H_a: E(X) =$  Itraconazole has produced a significant difference in cure rate. (median difference is not zero)

We used Non-parametric Wilcoxon-Mann-Whitneys test and Median Test to find the p Value which was computed to N1=15(Trail) N2=5(Control), the computed U value based on grading 0-5 and ranked was found to be

U=11 (Table value at p=0.05 Significance N1=15 and N2=5 is 14)

Our obtained U of 11 is less than this, and so we conclude that there is significant (95%) difference between our two groups and we reject the null hypothesis and agree that the treatment has made a significant impact.

### Discussion

Andrall and Gaverret were the first ascribe this infection of the ear to fungal pathogen (Rafique R and Udaipurwala 2014) Recurrence and recidivism are a common phenomenon in Otitomycosis in Diabetic patients (Vennewald I, Klemm 2009).

The following are predisposing factors identified for causation of Otitomycosis.

**TABLE – 2**  
**Predisposing factor for Otitomycosis**

Predisposing factors described in literature
1.Absence of wax
2.Hot and humid climatic conditions
3.Use of systemic or topical antibiotics and steroids
4.Use of occlusive hearing aids or dress
5.Previous mastoid surgeries
6.Immuno-compromised condition like HIV
7.2nd and 3rd decades of life
8.Lower socioeconomic status keeping poor hygiene
9.Instillation of oil (Haja Abdul N & Shaik K M 2015

Aspergillus genus or yeast-like fungi, particularly Candida spp are known to inhabit the External Auditory canal EAC as commensals (Murray P. A 1995). This flora is non pathogenic as long some predisposing factor does not reduce immunity and bring about a fungal infection. So the treatment has to be vigorously directed towards management of the predisposing factor. In Diabetics it is particularly difficult to control the infection there is where Oral anti-fungal with a broad spectrum of activity comes into picture.

### Role of Oral Anti-fungal in Recurrent cases

Fluconazole is a first-generation triazole anti-fungal drug

which has high activity against Candida species (Except species Candida krusei or glabrata) and some Dermidaceous fungi but is quite ineffective against Aspergillus. Though Fluconazole can be used and does have a high safety profile, Oral Fluconazole can be used in patients culture proven Candida (Susceptible species).

Itraconazole has a broad spectrum of activity than Fluconazole and is effective specifically against the most common pathogen Aspergillus(Gilbert DN 2006). Itraconazole cannot be used for deep CNS infections as it does not have any CSF penetration. Itraconazole also is being clinically trailed as an adjunct Chemotherapy agent for Non Small cell carcinoma of lungs (Aftab BT & Dobromilskaya 2010).

### The following adverse effects are seen with the use of Itraconazole

1. Elevated liver enzyme due to Hepatocellular damage and Acute liver failure. (Serious adverse effect)
2. Congestive cardiac failure CCF can be precipitated and Acute Cardiac failure (Serious adverse effect)
3. Other adverse effect are Sensori-neural hearing loss, Neuropathy, loss of libido, depression, palpitations, fever, chills, or sore throat, hair loss, increased or uncontrolled urination ,joint pain, loss of appetite, myalgia, fatigue, weakness, or cramping, numbness, burning, or tingling of the hands, arms, legs, or feet, pain, redness, or swelling at the injection site, pale stools etc
4. Minor adverse effects are Diarrhea, dizziness, abdominal distension, headache, nausea, abdominal pain and vomiting.

In our study we did not experience any serious adverse effects, only minor Gastrointestinal upset Nausea and abdominal distension were reported by few patients. In fact a majority of patients reported a remarkable relief from itching which was one of their most troublesome symptom on first presenting to our clinic.

### Conclusions

1. The predominant agent fungus was Aspergillus niger in most of the cases.
2. Cap Itraconazole 200md OD given for 5 days is a very effective therapy for Recurrent Otitomycosis in Diabetic patients
3. A short course of Oral broad spectrum Anti-fungal is very effective in management of troublesome Otitomycosis.
4. Early intensive management in Diabetic patients prevents Malignant Otitis externa.
5. Pruritis is also much reduced after using Cap Itraconazole.

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