EFFECTIVENESS OF 7.5 PERCENT POVIDONE IODINE IN COMPARISON TO 1 PERCENT CLOTRIMAZOLE IN THE TREATMENT OF OTOMYCOSIS

A

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

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CERTIFICATE

This is to certify that the dissertation entitled **"Effectiveness of 7.5 percent povidone iodine in comparison to 1 percent clotrimazole in the treatment of otomycosis"** is a bonafide original work of **Dr Ajay Philip,** submitted in partial fulfillment of the rules and regulations for the MS Branch IV, Otorhinolaryngology examination of The Tamil Nadu Dr. M.G.R Medical University to be held in April 2012.

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CERTIFICATE

This is to certify that the dissertation entitled '**Effectiveness of 7.5 percent povidone- iodine in comparison to 1 percent clotrimazole in the treatment of otomycosis**' is a bonafide original work of **Dr Ajay Philip**, carried out under my guidance, in partial fulfillment of the rules and regulations for the MS Branch IV, Otorhinolaryngology examination of The Tamil Nadu Dr. M.G.R Medical University to be held in April 2012.

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CONTENTS

Abstract

Title- Effectiveness of 7.5 percent povidone iodine in comparison to 1 percent clotrimazole in the treatment of otomycosis.

Key words- otomycosis, fungal otitis externa, fungi, antifungals, clotrimazole, povidone –iodine, aspergillus, candida

Objectives

This was a prospective randomized case control study and its objective was to establish the effectiveness of povidone iodine in treatment of otomycosis to a commonly used antifungal, clotrimazole. Our secondary objective was to identify the most common fungal isolate in our hospital. The two drugs were compared on the improvement in symptoms and signs of the affected individuals.

Review of literature

Otomycosis or fungal otitis externa is a condition seen in any otolaryngology set up and can be quite frustrating for the patient and the doctor due to its recurring nature. It is a superficial, sub-acute or chronic infection of the outer ear canal, usually unilateral characterized by inflammation, pruritus, pain and scaling (1). Prevalence is more in the tropical and subtropical humid climates(4). Candida and aspergillus are the most common fungi isolated (2). The most common aspergillus isolate was the niger species (3)(4) followed by the species of flavus and fumigatus.

Treatment mainly comprises of thorough lavage of the ear and clearing all fungi debris mainly seated in the anterior recesses of the ear canal (5). Predisposing factors must be addressed and topical antifungals initiated. Clotrimazole is the most commonly used antifungal. This drug acts on the fungal wall making them to be more permeable and lead to their instability and later cell death(6).

Povidone iodine, is a widely used antiseptic, easily available, cheap and seen to be effective in the treatment of bacteria, fungi, virus, protozoa and spores (7). No resistance is known so far to this antiseptic (8). Hence we planned to use povidone iodine in this study in view of its above properties.

Methodology

We conducted a prospective randomized case control study of individuals who were clinically diagnosed with otomycosis in our ENT OPD. The individuals who satisfied the inclusion criteria were randomized and blinded to the drug they would receive. The symptoms and signs were noted and a pretreatment ear swab was taken for culture. On follow up after 2 weeks, their symptoms, signs were noted and a post treatment ear swab taken. Each of the pretreatment and post treatment variables were compared and efficacy of the drug assessed.

Results and Conclusion

34 patients, clinically diagnosed as otomycosis who fulfilled the inclusion criteria were assessed, 8 were lost to follow up.

In our study, the condition was more prevalent in females below the 30 age group. Unemployed individuals topped the list followed by housewives. The left ear was most commonly affected involving 74 % of the cases. Pruritus was seen in 76.5% of our patients followed by otorrhoea. There was a close relation between self-cleaning and absence of wax. Mixed infection was more common (35.4%) and aspergillus niger formed 60.86% of fungal isolate. Pseudomonas aeruginosa and non-fermenting GNB was the most common bacterial isolate. Both drugs showed a good response in symptoms and signs after treatment and though comparable, were not statistically significant(p value>0.05). The result of this study supports the use of Povidone-iodine in the treatment of otomycosis, thus avoiding emergence of resistant organisms. Future studies in larger groups of patients are necessary to see which is more effective. This study has opened a window in the application of povidone –iodine in clinically diagnosed case of otomycosis in humans in addition to the management of chronic suppurative otitis media.

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INTRODUCTION

Fungal external otitis (otomycosis) is a common disease throughout the world. Its frequency varies according to different geographic zones. It is a prevalent disease in the tropics (1) and is sometimes associated with complications, involving the middle ear (2). It has been an entity which has perplexed many an otologist because of its recurrent nature.

Since its description about 100 years ago by Andral and Cavarret in 1843 and by Mayer in 1844, (3) many attempts have been made in the diagnosis and the treatment of this condition. The disease is seen worldwide and it is estimated to constitute approximately 5-25% of the total cases of otitis externa (4).

In a routine otolaryngology clinic, its prevalence ranges from about 9 percent to about 30.4 percent in individuals presenting with otitis externa (5). It was believed that fungi were secondary invaders in external canal infections and that one third of the external otitis was caused due to fungi and the remaining were attributed to gram negative bacilli (Syverton et al)(3).

Traditionally, the treatment of otomycosis revolved around good personal hygiene and avoidance of self-cleaning. But the management varied as time progressed which ranged from copious lavage to insertion of metacresylacetate wick, boric acid, sulphathiazole ointment, topical ketoconazole, cresylate otic drops, and aluminum acetic drops in the affected ear(5). In recalcitrant cases, treatment with 75 rads of X-rays (6) has also been attempted. The use of metacresylacetate however had produced dermatitis and hence its use was discontinued. The medical treatment has abundant literature describing the use of various classes of drugs mainly antifungals in the topical treatment of otomycosis (7).

However there has never been a study which evaluated the role of iodine as an antifungal in otomycosis. It is a well-known fact that iodine is a routinely used antiseptic solution in surgical wards, because of its antibacterial property which has never been resisted or conquered by any organism. This present study plans to evaluate the antifungal (8) property of povidone-iodine and to provide a cheaper alternative in the treatment of otomycosis.

AIMS AND OBJECTIVES

Aim

To evaluate the effectiveness of 7.5 percent povidone-iodine in the treatment of otomycosis as compared to 1 percent clotrimazole ear drops.

Objectives

Primary Objective:

1. To establish the effectiveness of povidone iodine in the treatment of otomycosis in comparison with clotrimazole.

Secondary Objective:

1. To establish povidone iodine as an antifungal agent.
2. To establish the most common fungal isolate in our hospital set up.
3. To detect the presence of any other pathogen.

REVIEW OF LITERATURE

Otomycosis or fungal infection of the ear has been described since time immemorial. A number of studies have been done on the epidemiology, geographical distribution and clinical features of this disease and its association with chronic middle ear infection (7).

It has many synonyms such as Singapore ear, hot weather ear and mildew ear. Since the early 1950s, there has been increasing awareness of this entity (Sood et al 1967, Mugliston and O`Donoghue), fungal infections are usually found in association with bacterial infections with fungus being the sole cause in only 15-20 percent of the cases(9).

Anatomy of the external acoustic meatus

The external ear

The external ear or the meatus *acusticus externus* extend from the bottom of the concha to the tympanic membrane. It is about 4 cms in length if measured from the tragus and 2.5 cms when measured from the bottom of the concha. It is divided into a cartilaginous and bony part which forms a S shaped curve as it proceeds towards the tympanic membrane. It first curves inwards, forwards and slightly upwards (pars externa) and then it passes inwards and backwards (pars media) and finally downwards (pars interna).

The ear canal is oval and cylindrical in shape and has 2 constrictions:

- The first is at the inner end of the cartilaginous canal.
- The second is at the isthmus, in the osseous segment about 2 cms from the concha.

The length of the cartilaginous canal is about 8 mm in length and the osseous segment about 16 mm in length. The cartilage is continuous with the auricular cartilage and is deficient in the upper and the posterior part of the meatus. There are two to three deep fissures seen in the anterior part of the cartilage.

The osseous portion is also known as *meatus acusticus externus osseus*. It is narrower than the cartilaginous canal and its anterior wall is about 4mm longer than the posterior. Its medial end is lined by a groove deficient in its superior aspect-the tympanic sulcus where the pars tensa find its attachment (Pic 1).

The skin lining the meatus is adherent to the cartilaginous and the osseous canal wall and is very thin and forms the epithelial layer of the tympanic membrane. The subcutaneous tissue of the cartilaginous portion is thick and contains numerous wax secreting ceruminous glands which resemble sudoriferous glands.

Blood supply- branches from the posterior auricular, internal maxillary and temporal arteries.

Nerve supply- nerves are chiefly derived from the auriculotemporal branch of the mandibular nerve and the auricular branch of the vagus.

Fungi

Fungi are eukaryotic organisms comprising of moulds, yeasts, mushrooms and are almost found everywhere. The word Fungi is derived from the Latin word fungus which has its origin from the Greek word *Sphongos* which means sponge. The Egyptians have documented the presence of fungi as early as 4500 B.C. A number of hieroglyphic

depictions of plants (many of which are psychedelic) on walls and within texts could be found throughout Egypt. Temples with countless pillars shaped like huge mushrooms with tall stems, umbrella caps, and mushroom engravings were also distributed all over the country (Pic 2)

They differ from plants in that they lack cellulose. Classically fungi are broadly divided into 2 groups, the yeasts and the moulds.

Among the medically important fungi, the Aspergillus genus is the most common fungi causing otomycosis (10). It is present worldwide and niger is the most common species. The niger species are referred to as black aspergillus as they produce black colonies. The niger species have 8 morphologically distinct taxa (11). Other species of Aspergillus like the awamori and tubingenisis (2) have also been isolated in otomycosis.

Fungi reproduce both sexually and asexually. Sexual reproduction involves meiosis. Certain species of fungi mate with the individuals of opposite mating type while others mate with themselves or individuals of the same mating type, the former are known as the heterothallic and the latter, the homothallic (12).

The asexual phase involves formation of spores, also known as conidia. Spores maintain clonal populations and help in rapid dispersion of the fungus (13). This is a very significant clinical finding in diagnosing a case.

Under unfavorable conditions, fungi form spores. Fungal spores have a characteristic robust cell wall which help in its biological behavior.(Good day -1994) The spores have germ tubes which germinate from the sides and elongate to form cylindrical filaments which are called as hyphae (Pic 3).

The hyphae get entangled and form mycelia. The hyphae have numerous compartmental walls known as septae. These compartments communicate with each other for the passage of nutrients and organelles such as nuclei (14).

The structure of the filamentous fungal cell wall

Polysaccharides and glycoproteins are the two components of the cell wall of which polysaccharides contributes a major portion. The fungal cell wall is not homogenous and is composed of different layers, a feature which is highlighted with electron microscopy. The four components of the cell wall include the beta (1-3) glycan, beta(1-6 glycan), chitin(N-acetyl glucosamine) and glycoproteins. The beta glycans and the chitins form the inner fibrous layer and the glycoproteins form the more flexible outer layer (14) (Pic 4)

Hydrophobins are a group of proteins which protect the hyphae and spores from aggregating and render the fungi resistant to desiccation.

Mechanism of growth of fungal hyphae

Fungal hyphae grow by tip extension via apical growth. These apices have vesicles rich in carbohydrate rich monomers and cell wall synthetase enzymes. Increased branching of the hyphae are seen during increased nutritional supply. Many survival strategies are available for fungus during starvation, the main two being (14) :

a. Autolysis
b. Cryptic growth

Autolysis is a process in which proteolytic activity of fungi increases significantly, leading to self-digestion. White et al proposed that the digestion of the fungal cell wall

was by hydrolytic enzymes. The hydrolytic enzymes broadly fall into three categories- chitinases, gluconases and proteases. These enzymes are inhibited by feedback mechanism as the number of end products increase. The end products are used for providing nutrition to the hyphal ends. This metabolism is known as endogenous metabolism (Righelato et al) and the phenomenon as cryptic growth and probably the cause why these infections are hard to eradicate (14).

Clinically significant fungi in otomycosis

Aspergillus

Kingdom: Fungi

Phylum: Ascomycota

Order: Eurotiales

Family: Trichocomaceae

Genus: Aspergillus

In 1729, Michelle described the microscopic structure of an organism which looked similar to a device used by Roman clergy men to sprinkle holy water during the liturgy – The Asperga (Ainsworth 1976)(15). It is derived from the Latin word, "Thou will sprinkle". These organisms are saprophytes and grow on decaying vegetation, in this instance dead human skin. The spores of Aspergillus are components of aerosols and they disperse themselves with the air current to get deposited over either a solid or liquid media. They then germinate (Kanaani et al. 2008). This ability to be carried in air currents

and be dispersed anywhere makes them ubiquitous (14). The fungi are heterotrophic and differ in the feeding mechanisms from other scavengers in that they secrete acids and enzymes into the surrounding environment and digest organic material. Their hyphal tips grow into and through food substrate and derive nutrition.

Microscopic Features

The basic morphology of all the species of Aspergillus is the same. There are some features unique to certain species and some similar features (16)(17)(18).

The common features

They have septate and hyaline hyphae. The conidiophores arise from the basal foot cell on the supporting hyphae and terminate in a vesicle at the apex. Vesicle formation is typical of aspergillus. Morphology and colour of the conidiophores varies among species. The phialides are flask shaped structures which when they completely cover the vesicle, are called radiate head. When they partially cover the vesicle, they are called columnar head. The conidia form radial chains around the phialides.

Aspergillus Niger

This filamentous Ascomycota fungus (Pic. 5) is ubiquitous in the environment and has been involved in opportunistic infections of humans. It is a citric acid producer and is attributed to be one of the most common species isolated in otomycosis. It was discovered by Van Tiegham in 1867. The microscopic morphology describes the hyphae as septate and hyaline. The conidial spores are radiate initially and at maturity split into columns. They produce vesicles which support the conidiogenus phialides and are hence called

biseriate. The conidiophores are about 400-3000 micrometer, smooth and hyaline and become dark at the apex which terminate in a globose vesicle each of 30-75 micrometer in diameter. The entire vesicle is covered with metulae and phialides. The conidia are rough, black, globose and measure about 4-5 micrometer in diameter (19).

When grown on potato dextrose agar at 25°C, they initially become white, then quickly turn black and start producing conidia. In agar medium the growth is initially pale yellow and may produce fissures on the same.

The Aspergillus niger 'aggregate' is a complicated taxonomic subgroup containing 8 morphologically indistinguishable taxa: Aspergillus niger, Aspergillus tubingensis, Aspergillus acidus, Aspergillus brasiliensis, Aspergillus costaricaensis, Aspergillus lacticoffeatus, Aspergillus piperis, and Aspergillus vadensis. The awamori, first described by Nakazawa, has been compared taxonomically with other black aspergilla and recently it has been considered a synonym of A. niger (11).

Aspergillus fumigatus

The fumigatus species was first described by Fresenius in 1863. The hypha is septate and hyaline and it belongs to the thermophilic group of fungi. Their conidial heads are columnar in an undistributed culture and their conidiophores are uncolored, smooth–walled and have a length of 300 micrometers. They are uniseriate with compact phialides seen on the upper portion of the vesicle. The conidia are subglobosal with a diameter of 2-3.5 micrometer and are smooth and finely roughened (20)(15)(21).

On dextrose agar at 25 degrees, they are smoky gray–green and have a cottony to granular texture. Atypical colonies are white with sparse conidiation. Their hyphae in tissue usually demonstrate a branching at 45 degrees although this may vary.(20)(19)(21).

Aspergillus flavus

This member of the Aspergillus genus has a remarkable ability to survive in high temperatures, thus making it a predominant organism in the Middle East, Africa and South East Asia. In the northern hemisphere it is seen in the harvest time. The fungi can grow anywhere between 25-42 degrees Celsius and may grow at an optimal temperature of 37 degrees. It is thermo tolerant up to 55 degrees Celsius. It accounts for about 50-80% of ENT and ocular related cases like sinusitis, keratitis and cutaneous infections. They are the pathogens implicated in the production of aflatoxins.

On microscopy, the hypha show septations and have a 45 degree angle branching. The conidial heads are arranged in a radiate manner and lose their columnarity with age .Their conidiophores are about 400-850 micrometers in length and 15-20 micrometers wide. The conidia are uncolored and coarsely roughened. They are biseriate and have metulae covering the entire vesicle. At times they may be uniseriate, pale green and may be conspicuously echinulate. Cleistothecium are usually absent in this species (22)(23)

Candida

Kingdom: Fungi

Phylum: Ascomycota

Subphylum: Ascomycotina

Class: Ascomycetes

Order: Saccharomycetales

Family: Saccharomycetaceae

Genus: Candida

This yeast is the most common cause of opportunistic mycoses in the world, and usually colonizes skin and the mucous membrane. It appears in either a mitosporic or a teleomorphic state to produce asexual spores and consists of about 150 species of which 6 are known to cause disease in humans. The most important and frequently encountered species is the albicans. The other species encountered are Candida tropicalis, Candida glabrata, Candida parapsilosis, Candida krusei, and Candida lusitaniae. There has been a recent surge of infections caused by the non albicans candida species, the Candida glabrata and Candida krusei(24)(25)(26)

Pathogenicity and clinical significance

The candida species cause candidiasis and this disease has an extreme diverse spectrum, affecting almost any system or organ of the body. They have an ability to adhere to the host cell, produce enzymes such as aspartyl proteases and phospholipase enzymes and change from the yeast to the hyphal state(27)(28)(29).

This is the most commonly isolated yeast in human disease and causes both systemic and superficial infection. There are reports of this organism causing infection of the cornea, nail, ear and blood stream. (30)(31)(32). It is also the predominant species in fungal biofilms on medical devices.(33)

The macroscopic and microscopic appearance

Macroscopic morphology- On Sabourauds dextrose agar at 25°C the colonies are white to cream, soft, smooth and wrinkled. The isolate grows at 42°C on media containing cycloheximide.

Microscopic morphology- On cornmeal following 72 hours incubation at 25°C, Candida show abundant branched pseudohyphae. True hyphae with blastoconidia in a grape like cluster are present. On extended incubation, terminal chlamydoconidia are seen (19) . (Pic.6.)

Candida tropicalis

Macroscopic morphology of Candida tropicalis

On Sabourauds dextrose agar, Candida tropicalis colonies are cream-colored with a slightly mycelial border. They produce a thin surface film and bubbles when grown in Sabourauds broth (17)(19).

Microscopic morphology of Candida tropicalis

On cornmeal tween 80 agar and at 25°C after 72 hours, it produces oval blastospores which are located along the long pseudohyphae. The blastospores may appear singly or in clusters. The pseudohyphae branch abundantly. Candida tropicalis may also produce true hyphae (17)(19).

Commensals in the ear

The commensals residing in the ear of a normal individual are the Staphylococcus epidermidis, Corynebacterium spp, Bacillus spp, Gram-positive cocci (Staphylococcus aureus. Streptococcus spp, non-pathogenic micrococci), Gram negative bacilli (Pseudomonas aeruginosa, Escherichia coli, Haemophilus influenza and Moraxella cararralis) coli, Haemophilus influenzae, Moraxella cararralis) and mycelial fungi of the Aspergillus genus or yeast-like fungi, particularly Candida spp. The pathology sets in once there is disharmony among these organisms(34).

Otomycosis

Definition: Otomycosis is a superficial, sub-acute or chronic infection of the outer ear canal, usually unilateral and characterized by inflammation, pruritus, pain and scaling(35).

Andral and Gavarret in 1843 and Mayer in 1844 first described fungal infections of the external auditory canal. Virchow suggested the term ‘otomycosis’ (3)

Gregson and La Touche stated that fungi were secondary invaders and that bacterial infection paved the way for fungus infection by providing a favorable degree of humidity. Their study showed that candida caused the disease in half their patients (36). Yet in another study by Ismail (1962) Kinery (1965), Mac Gonigle and Jillson, aspergillus was the predominant fungi grown.

There has been an increase in the prevalence of otomycosis in the recent years much blamed to the usage of antibiotic ear drops. Quinolones especially appears to have

increased the risk of otomycosis (7). Persistent otorrhoea in spite of topical antibiotic therapy should raise a suspicion of otomycosis.

The prevalence of otomycosis has been reported to be as low as 9% of cases of otitis externa, and as high as 30.4% in patients presenting with symptoms of otitis or inflammatory conditions of the ear(5). It is seen more frequently in adults than in children (37).It has been estimated that cases of otitis externa make up between 5 and 20% of all otological consultations; the etiology of the majority is bacterial, only 15-20% is attributed to fungi (9). Mixed infections are generally scarce as fungal flora tends to inhibit the bacterial kind. The high incidence of Aspergillus niger and flavus to occur alone is because of their ability to produce local antibiotic (proved in vitro) (23).

Otomycosis or fungal otitis externa is classified into:

a) Acute b) Sub-acute c) Chronic

Pathophysiology of fungal infection

Natural barrier

The skin helps prevent otomycosis by providing an intact mucosal surface and by production of secretions from sweat, sebaceous and ceruminous glands. These secretions provide an acidic pH, which are bacteriostatic and fungistatic. Various predisposing factors include humid climate, instrumentation, immunocompromised host, recently used antibiotic or steroid ear drops (5). The constant lateral migration is a way of defense by removal of residing microbes. The external auditory meatus has a lining of skin similar to that of other parts of the body.

However, there are dissimilarities:

1) The external auditory canal resembles a skin lined culture tube where it is exposed to the atmosphere by only a small inlet. This may provide optimum conditions for growth of fungi and bacteria.
2) The skin is closely applied to the perichondrium and periosteum, so there is little room for lateral expansion and hence edema is accompanied by intense pain.
3) The hair follicles sweat, ceruminous and sebaceous glands are confined entirely to the outer third of the ear canal. Ceruminous glands are modified sweat glands filled with fat droplets and brown pigment granules which form ear wax and hence differ from an apocrine gland. Sweat contains acid sodium phosphate which renders it an acidic pH of 4.7 to 7.5 (West and Todd, 1961) that hinders fungal growth. However this becomes alkaline in the presence of excessive sweating (Macleod and Muende, 1946) thus explaining the reason why tropical ear wax fails to provide the protective sleeve normally attributed to it in temperate conditions(38)

In addition, irrigation easily removes the oliferous form of wax, which is associated with swimming and diving (38).

Otomycosis has close relation to the histology and the physiology of the EAC. The canal is lined with a stratified keratinized squamous epithelium that continues along the external face of the tympanic membrane. The interior tympanic recess, medial to the isthmus, tends to accumulate remains of keratin and cerumen and is a difficult area to clean. This could probably be why this disease recurs. The skin is the thickest in the cartilaginous canal (0.5 to 1 mm) and very thin (30 to 50 microns) in the bony canal (the

internal third). It is more adherent in the external segment which in turn is hairy and has numerous sebaceous and ceruminous glands.

The glandular secretions and the flaked cellular epithelial elements form an acidic ceruminous substance which is impermeable to water and protects the skin of the canal.

Predisposing factors (39)

Trauma

Relative high degree of humidity

Epithelial debris in various stages of breakdown

High temperature nearing the human body temperature

Pregnancy

Use of systemic steroids

Presence of open mastoid cavities

Hearing aids with occlusive moulds (7).

The recurrences

When fungus is present, it is temporarily overgrown by bacteria, and is often left untouched by the drops used and hence needs only a sufficient lapse of time to develop further to recommence the cycle.

The "recurrences" are due to the sub-epithelial mycotic spores mainly left in the fissures of the ear canal which remains untouched and therefore, unattacked, and grow to produce the clinical condition repeatedly. This in turn, due to epithelial maceration and desquamation, predisposes to repeated bacterial invasion. The otalgia usually brings the patient back for treatment. These observations make it necessary to tackle this condition in two phases

a) The secondary acute external otitis and its complications
b) The underlying mycosis.

Meticulous cleansing of the ear canal is an absolute prerequisite in both the phases. It is certain that no medication introduced into the canal will be efficacious if exudate, epithelial scales, and debris remain. It has been observed consistently that the lack of complete cleansing has made the difference between success and failure in treating this problem. "Fungi grow in the presence of moisture." Hence there was fear in using water to irrigate the ear but studies have shown that there is absolutely no danger in this procedure(38)(37). Successful treatment outcome was defined as resolution of all evidence of fungal infection on physical examination. Residual disease was defined as a condition that failed to respond to the initial choice of treatment. Recurrent disease was defined as a condition that occurred in patients who had resolution of disease after initial treatment but recurred in the same ear at a later date.

Clinical presentation of otomycosis

Patients may present with either one or more of the symptoms and signs below(Table 1):

Symptoms (2)(5)	Signs
Pruritus	Tragal tenderness
Otalgia	Canal wall edema and erythema
Ear fullness	Tympanic membrane perforation
Ear discharge	Otorrhoea
Tinnitus	Fungal debris in the canal (Pic.7.)
Hearing loss	

Tab.1.

Otomycosis is confirmed by the presence of aseptate mycelium, septate mycelium, aspergillus conidia, fruiting bodies, yeast and pseudohyphae. The presence of fungal elements in stained smears is confirmed by fungal colonies in culture (37)

Treatment of otomycosis

Treatment is mainly directed to the proper debridement and cleaning of the ear canal and the application of ototopical antifungal agents (40). The first fungicidal to be used was formaldehyde (3). Invitro studies using Merthiolate (Thiomersal), Burow's solution (Aluminium Acetate) (2%), VoSol HC(Hydrocortisone+Acetic acid), VoSol plain, Cortisporin (Polymixin+neomycin) suspension, clotrimazole 1%, Mycostatin, amphotericin B, ethanol 95%, miconazole, tolnaftate 1%, natamycin, and flucytosine have been tried. Inhibition of yeast and most of the fungi with clotrimazole was noted

though Merthiolate was most effective (41). It however contains mercury which is ototoxic.

The other medications used were acetic acid (42)(43)(44), cresylate otic ear drops (5), boric acid ear drops (42) locacorten-vioform (clioquinol and flumethasone)(44) which are proven ototoxic medications.

Certain studies also advocate the use of systemic antifungals in addition to thorough and regular cleaning of the external auditory canal (45).

Common topical antifungals used in otomycosis

At present, there are 3 main drugs for the treatment of otomycosis - Triazoles, polyenes, nucleoside analogues and echinocandins (not used in otomycosis) (7). Two topical azole antifungal agents, miconazole and clotrimazole, were introduced in 1969; and was followed by the introduction of econazole in 1974 and a parenteral formulation of miconazole in the late 1970s. Today, these three agents remain the mainstay of topical therapy for many dermatophytoses (7).

The triazoles

The triazoles, better called azoles comprise of clotrimazole, fluconazole and miconazole. Azoles are a class of five membered nitrogen heterocyclic ring compounds containing at least one other non-carbon atom that is nitrogen, sulphur or oxygen.

Mechanism of action (46)

Azoles bind to ergosterol and create polarity in the fungal membrane causing ions predominantly potassium, hydrogen and other molecules to leak out of the cell, leading to the death of the cell. Azole antifungal agents prevent the synthesis of ergosterol, a major component of fungal plasma membranes, by inhibiting the cytochrome P-450-dependent enzyme lanosterol demethylase (also referred to as 14a-sterol demethylase or P-450DM)). This enzyme also plays an important role in cholesterol synthesis in mammals. When azoles are present in therapeutic concentrations, their antifungal efficacy is attributed to their greater affinity for fungal P-450DM than for the mammalian enzyme. Exposure of fungi to an azole causes depletion of ergosterol and accumulation of 14a methylated sterol. This interferes with the "bulk" functions of ergosterol in fungal membranes and disrupts both the structure of the membrane and several of its functions such as nutrient transport and chitin synthesis (34). Many authors believe that appropriate treatment is begun only on identification of the offending organism, whereas others are of the opinion that specific treatment is based on the efficacy of the drug regardless of the causal agent. Clotrimazole is the widely used azole. Clotrimazole appears to be the most effective agent for the management of otomycosis with a reported rate of effectiveness that varies from 95-100 percent with only one retrospective study showing a low efficacy of 50% by Jackman et al. Its antibacterial action on the other hand helps in treating infections of mixed origin (7)

The mechanism of resistance to azoles

Resistance to the azole group is not reported; however strains can become resistant by the following mechanisms(46).

Alteration in drug target-a demethylase.

Alteration in sterol biosynthesis.

Reduction in intracellular concentration of target enzyme.

Over expression of antifungal drug target.

Polyenes (7) (46) (47)

Until the discovery of azoles, the polyenes have been used in the treatment of both systemic and local fungal infections. The polyenes exert the antifungal action by binding to the sterol present in the fungal wall membrane. Sensitive species of fungi must contain sterol in the outer cell wall. Amphotericin B represents the standard therapy for systemic fungal infections.

Mechanism of action

The drug interacts with the cell wall and creates aqueous pores in the cell leading to the loss of cell components and eventually death of the organism (7).

The nystatin preparation is the most commonly used preparation in topical ear drops.

Mechanism of resistance

Decrease in the total ergosterol content.

Replacement of some or all of the polyene-binding sterol.

Masking or re- orientation of existing ergosterol.

The nucleoside analogues (7)

They act by interfering with nucleotide synthesis, which is a major step in cell energy production, metabolism and signaling.

The echinocandins (47)

It was discovered in 1970 that echinocandins were active against the candida species. They were produced as a byproduct of fermentation of fungi. The earliest one to be used was Cilofungin but was withdrawn because of its toxicity. The clinically accepted drug is the Caspofungin and the emerging ones are the anidulafungin and micafungin.

Mechanism of action

The drug is directed against formation of beta (1, 3) D-glucan

Susceptible fungi- Candida and Aspergillus

These drugs are used in systemic fungal infections not in use for otomycosis. They interfere with the cell biosynthesis production.

Clotrimazole

History of clotrimazole

After the World II, fungal infections began to rise and and multiple attempts have been made to counteract this threat. The first achievement was in the early 1960s when a researcher Prof. Karl Heinz Büchel discoverd clotrimazole, the earliet of the azoles.

Pharmacology of clotrimazole

The antifungal properties of azoles were first described in the 1960s(46). Azoles are divided broadly into 2 groups - the imidazoles and the triazoles. Clotrimazole, an imidazole has been used as a topical antifungal and is available in the form of creams, ear drops, lotions, powders, vaginal tablets and trouches(47). It has been used in combination with steroids, local anesthetics such as lignocaine with antibacterial drugs.Though being an antifungal it has attributed antibacterial properties(7). Resistance to clotrimazole has been reported(46).

Chemistry of clotrimazole

Clotrimazole is produced by alkylating imidazole with o-chlorotrityl chloride in acetone, with triethylamine as the base.(Pic.8.) It is an odorless crystalline powder insoluble in water.

Mechanism of action

It acts on the cell wall of the fungus and also prevents the formation of ergosterol.

Ergosterol is a major component in the fungal cell wall membrane vital for maintaining membrane integrity and fluidity of the fungal cell. It is derived from an organic compound squalene.

Squalene is converted to lanosterol by squalene epoxidase. Lanosterol is convertered to ergosterol by following either of the 2 pathways, the zymosterol pathway and the obtusifoliol pathway (47).

The primary target of the azole is the heme protein which cocatalyses the cytochrome P-450–dependent 14 a-demethylation of lanosterol (48). There is accumulation of lanosterol in the cell membrane leading to its instability and leakage of the cell components.

Clotrimazole when topically administered causes an increase in the permeability of the cell membrane leading to a loss of ions predominantly K+ and H+ resulting in cell death.

The mammalian cell wall contains ergosterol, clotrimazole at therapeutic concentrations act selectively on the fungal ergosterol and hence poses less toxicity to the mammalian cell.

Pharmacokinetics

The absorption of the drug is less than 0.5 percent when applied topically on the intact skin. About 3-10 percent is absorbed from the vagina.

The absorbed drug is metabolized in the liver and excreted in the bile. When administered orally at 200 mg, an initial rise in plasma concentration of 0.2 to 0.35 mg/ml is noted, followed by a progressive decline.

Adverse reactions

On topical application, it may cause stinging, erythema, edema, vesication, desquamation, urticaria and pruritus.

When applied to the vagina, patients may complain of a burning sensation, increase in urinary frequency or skin rash.

Oral administration may cause gastrointestinal irritation.

Therapeutic Uses (47)

Clotrimazole cures dermatophytic infections in about 60 to 100% of the cases. In cutaneous candidiasis, it achieves a cure rate of 60 percent to 100%. Recurrences are reportedly common after therapeutic regimes.

Clotrimazole in otomycosis

Clotrimazole is used either as a 1% cream in combination with antibiotics and steroids for fungal skin infections. It can be used in combination with 2% lignocaine in a propyl glycerol base as topical ear drops. Multi centric studies have been done on clotrimazole in comparison with many other antifungals and it was found to be effective and well tolerated.

Povidone iodine

History

A Dijon chemist Bernard Courtois discovered iodine, a natural element in 1811 (49). It is derived from the Greek word Ioeides meaning violet because of its intense violet vapors. It was used in the early Napoleon era where wounded soldiers were treated with seaweeds rich in iodine. It has been used as an antibacterial and this property was first described by Davaine in 1880(49). Hence for over 150 years, iodine has been used in the prevention of infections and treatment of wounds.

Iodine in the form of iodophor was found to be extremely aggressive on the mucous membrane and on the skin and only after Shelanski and Shelanski (49) detoxified iodine by binding it to larger molecules did they overcome this adverse reaction. The iodophor commonly used is polyvinylpyrrolidone and has been in use for the past 20 years.

Chemistry of polyvinylpyrrolidone

PVP-1 has a very complex structure and in a water soluble compound, iodine is linked by hydrogen bonds to the synthetic polymer polyvinylpyrrolidone, a neutral, amphipathic organic compound. Its molecular formula is C6H9I2NO (Pic 9&10). Molecular iodine in the form of I_3^- is physically intercalated with PVP-I helix (Bound Iodine) via hydrogen bonds and is in a chemical equilibrium with I_2 free iodine in the solution. The equilibrium is depicted in the following equation

$$(PVPH^+)I^3 <=> (PVPH^+)\ I^- + I_2$$

In the aqueous medium, when equilibrium is achieved, only one in thousand part of the iodine is released, the rest of the complex acts as a reservoir for protracted delivery (50). Povidone- iodine essentially retains the broad spectrum activity of iodine, yet is virtually free from the undesirable feature associated with tincture of iodine and Lugol's solution.

Published data show that stability of PVP-iodine solutions are vastly superior to that of iodine tincture or Lugol's solution. Iodine is bactericidal, sporicidal, fungicidal, protozoacidal, cysticidal and virucidal. Both gram-positive and gram-negative bacteria are equally affected. PVP-iodine was tested for its ability to inactivate HIV virus in cell culture system. All products had completely inactivated the virus at PVP iodine concentration greater than 0.5% (8). A slow release of iodine from the polymer contributes to its long lasting action and a low irritant profile. A concentration range of PVP-1 between 3.75 -2500 ppm kill candida strains between 10-120 seconds (8). Povidone (PVP-1) has been extensively used over the past 30 years for various clinical purposes on the skin and the mucosa without any serious local and systemic effects. In contrast to other antiseptics such as chlorhexidene and benzalkonium chloride, no resistance has been detected yet .Experimental studies have proved that PVP-1 aqueous solution shows no ototoxicity. In our hospital the use of BIPPS (bismuth iodoform paraffin paste) for over the past 30 years has shown no ototoxicity (51). The advantages of povidone iodine include (52)

I. Formation of a stable complex
II. Film forming capacity
III. Prolonged germicidal action
IV. Adherence to surface and non-irritating to skin and mucus membrane
V. Water solubility and hence easy formulation

Cellular targets of povidone PVP-1

PVP-1 exerts strong oxidizing action on amino acids (NH^-), Thiol (SH^-), hydroxyl group of amino acids and nucleotides. The iodine acts on the cell wall and cell organelle membranes by strongly interacting with the double bonds of unsaturated fatty acids(50).

PVP-1 is known to kill bacteria very rapidly; the damage caused being attributed to inactivation of bacterial enzymes and loss of nucleotides through transient or permanent pores in the bacterial cell wall. An electron microscopic study on the clinically relevant gram positive and gram negative bacteria was made which showed that they exhibited rapid partitioning and coagulation of the nuclear material in the presence of PVP-1. Ecoli and staphylococcus aureus showed no major structural change on exposure to PVP-1.

Fungi such as Candida albicans exhibited loosening of the cell wall in a rapid dose dependent manner. However the cells remained intact without lysis or rupture. The microscopic and the biochemical observations support that PVP-1 reacts with the cell wall of microorganism to cause transient or permanent damage to the cell wall.

Studies (53) show a profound interaction of PVP-1 with human inflammatory and effector cells and mediators. The biological effector molecules mediate the tissue destruction and the facilitation of invasion of the microbes; PVP-1 interferes with this process and hence is supportive of wound healing and repair (53). It has been shown that a diluted PVP-1 solution has more bactericidal activity than a full strength 10 percent solution. This phenomenon is difficult to explain. Trueman stated that dilution of the iodophor results in less linking of free iodine to the bound iodophor hence making free iodine available for action. The amount of iodine released follows a bell shaped curve reaching a maximum level at 7 mg/ml solution.

The spectrum of Povidone iodine

Iodine is a topical germicidal agent effective against a wide spectrum of organisms including bacteria, viruses, fungi (esp. Candida and Aspergillus) and protozoa. It is available as a solution and an alcoholic tincture (54). The microbicidal activity of povidone iodine is broad.-even after short onset times. Unlike local antibiotics or other antiseptics no resistance develops (55). To counter the severe hypersensitivity reactions and systemic absorption of iodine, the compound iodophor was formulated (54). Iodophors are compounds of iodine linked to surfactants that act as carriers and solubilizing agents for iodine (54). The most extensively used iodophor is the complex of polyvinylpyrrolidone and iodine.

Jayaraja Kumar K. et al in his paper on *application of broad spectrum antiseptic povidone iodine as powerful action: a review* has shown the activity against the commonly encountered organisms especially fungi (8)

Activity of PVP iodine Vs organisms (No. Strains)	**Range of PVP iodine in ppm available iodine**	**Contact of kill time in sec.**
Proteus(41)	100-2500	15-180
Staphylococcus(36)	66-2500	15-180
Pseudomonas(36)	25-2500	15-900
Streptococcus(25)	200-2500	15-30
Escherichia(23)	200-2500	30-120
Candida(8)	3.75-2500	10-120
Spores,baccillus;clostridium(6)	10,000	2.5hours
Enterobacter(4)	1000-2500	60
Klebsiella(4)	500-2500	60

Activity of PVP iodine Vs organisms (No. Strains)	Range of PVP iodine in ppm available iodine	Contact of kill time in sec.
Clostridium(4)	1000	30-60
Shigella(3)	1000-2500	60
Corynebacterium(3)	2500	60
Diplococcus(3)	1000-2500	60
Mycobacterium(3)	1000-2500	60-120
Bacillus(3)	7.5-1000	10-30
Aspergillus(2)	1000	30

Tab.2.

Resistance to povidone iodine

Antibiotic resistance is an omnipresent problem and in the present age, heavy growth of resistant strains demands antibiotic and disinfectant strategies in hospitals. When compared to antiseptics like chlorhexidene gluconate and benzalkonium chloride, PVP-1 had highest activity in test strains of MRSA (methicillin resistant staphylococcus aureus), S.marcescens, and pseudomonas aeruginosa and bacillus cepacia.

Lanker Klossner et al(56) had reported no resistance in coagulase negative staphylococcus in patients with long term peritoneal dialysis.

These organisms, though showed cross resistance to all antiseptics did not develop resistance to povidone iodine.(57) Schaffer in his study had proved that povidone iodine at dilutions of up to 1/100 and with a 30 second exposure destroyed various isolates of methicillin resistant staphylococcus aureus and highly resistant strains of enterococcus faecium.

Effect of organic substance on the activity of povidone iodine

There was no reducible cell count or no activity when 0.05 percent of the PVP-1 was used in the presence of serum, but at concentrations of 0.2 to 0.5 percent showed bactericidal activities even after the addition of serum to final concentrations of 5 to 10 percent respectively.

The local tolerance of povidone iodine

Povidone iodine does cause irritation or damage to the oral mucosa even after prolonged rinsing for a period of 8-10 weeks. Use of povidone iodine reduced mucositis during antineoplastic radiation therapy in head and neck cancers.(58)

Povidone iodine does not affect epithelial growth; this has been demonstrated by E Pels et al on decontamination of the human donor eye using povidone iodine. Decontaminating procedures with PVP-1 solutions of 5-100 mg/ml for 2-5 minutes can be applied without affecting the subsequent epithelial regrowth during organ culture of the corneoscleral button (59).

It is a presumed fact that antiseptics with a good antimicrobial efficacy possess cytotoxic activity. Examples are the triphenylmethane dyes such as the gentian violet and brilliant green, which hinders wound healing, so also does chlorhexidene but effects do not occur with chloramine T, silver nitrate and povidone iodine.(60) Povidone iodine if used appropriately at a concentration of 10 percent does not cause cell damage. If combined with detergents, it may produce cytotoxic effects. These effects do not occur on intact skin, and hence widely used as a surgical disinfectant for hands.

Considering sensitivity of povidone-iodine, out of 6,050 individuals who underwent a routine patch test, only 0.73% showed an epicutaneous sensitization against povidone-iodine and the allergy was attributed to the iodine component (60).

The adverse effects of povidone-iodine

Absorption of iodine from povidone application is enhanced when the compound is applied to denuded surfaces, mucosal surfaces with highly absorptive capacity or extensive areas of intact skin(54).

The compound can cause local toxicity when applied to fresh surgical wounds and the toxicity is directly proportional to the concentration of the solution used.

Allergic reactions

When applied to the intact skin in normal individuals, the incidence of contact dermatitis is very low, that is about 2 in 5000 applications (61).

Mutagenicity

Mutagenicity in mice and hamsters caused by povidone-iodine was tested by the micronucleus test or the dominant lethal assay test and none of them showed any evidence of mutagenic effect (62).

Thyroid dysfunction

Excessive incorporation of iodine can occur in individuals treated with povidone-iodine leading to thyroid dysfunction. Predisposed individuals include individuals with Hashimotos disease, goiter and newborns (63).

However a number of clinical trials exist on the repeated use of povidone iodine in the disinfection of hands and skin, mucosal antiseptics, burns and chronic wounds, eye infections etc.(49)

The toxicity of iodine has been detected in very few cases. No ototoxicity was noted in vivo studies when used in chronic otitis media with central perforation(51), though a study done in guinea pigs in 1982 by Aursnes J showed a slight damage to the basal part of the organ of Corti in ears exposed to Iodophor or Iodine for 60 minutes(63). A study was done by Perez et al in 2000 which compared povidone-iodine, chlorhexidene and alcohol on the vestibular and cochlear function of sand rats inner ear, which showed povidone-iodine to have no effect on the vestibular and auditory evoked potentials as compared to chlorhexidene and alcohol. Iodine has been used in the form (BIPP), bismuth iodophorm paste for packing of the mastoid cavities for many years and no ototoxicity has been observed till date, however a clinical trial is yet to be done. Thus considering the above facts, we felt it reasonable to use this drops in otomycosis with an intact drum where the chances of systemic absorption will be almost negligible.

MATERIALS AND METHODS

The purpose of the study is to know if povidone-iodine is effective in treating clinically diagnosed fungal otitis externa of the ear.

Type of study

Pilot study - Single blinded prospective randomized case control study.

Period of study - 2 years

Subjects

All patients with clinically diagnosed otomycosis, who satisfied the following inclusion and exclusion criteria.

Inclusion Criteria:

Age group- individuals from age 15-70 years

Exclusion Criteria:

1) Age group – less than 15 years and more than 70 years
2) Chronic suppurative otitis media
3) Postoperative mastoidectomy cases
4) Malignant otitis externa
5) Uncontrolled Diabetics
6) Patients with hearing aids
7) Patients receiving chemotherapy and post chemotherapy

Target sample size and rationale:

A sample size of 270 was calculated. Sample size calculations were based on the fact that the primary outcome for this study was improvement in symptoms and cure. It was estimated that 90% in the clotrimazole group will improve compared to 75% in the povidone-iodine group. To find a 15% difference in the outcome, assuming the power to 80% and level of significance to be 5%, sample size was calculated as 135 in each arm (total sample size = 270).

For two groups with percentages (cure rate), clotrimazole (p1) = 90% and proposed cure rate of povidone iodine is (p2) =75%, sample size is calculated by

Sample size(n)=(Z@+Z1-b)22PQ/d2

Where P=(p1+p2)/2=(90+75)/2

Z@=type 1 error=1.96

Z1-b=type 2 error=1.28

d = difference in outcome=15

Q=100%-P=100-82.5=17.5

Therefore n=10.4x2x82x17.5/225=134.7=135 patients in each arm

Since this is the first study using povidone in clinically diagnosed case of otomycosis, we planned to do a pilot study.

Method of allocation concealment:

Each of the drugs were concealed in containers covered externally.

Blinding and masking: The drugs were given in an open method. The drug was dispensed by a trained staff nurse. The principal investigator, staff nurse and the patient were unaware of the drug being administered.

The setting, location and the methodology of the study:

The study was done in the ENT department at our tertiary hospital. All patients who presented in the outpatient department with symptoms of pruritus of the ear, ear ache, ear discharge, blocked sensation in the ear, tinnitus or hard of hearing, were evaluated. The ear was inspected with an otoscope and a clinical diagnosis of otomycosis was made based on the history and presence of matted hyphae, spores or curdy precipitate in the external auditory canal. The patients who fulfilled the inclusion and exclusion criteria were referred to the principal investigator.

The principal investigator re-examined these patients, visualized the ear under the microscope (Karl Zeiss) with a 250 mm objective lens and noted the findings (Pic. 11).

Position of the otomycotic debris in the ear canal was noted as lying in the isthmus, in the bony canal or in the cartilaginous canal. The presence of any erythema over the cartilaginous canal and bony canal were noted and the status of the tympanic membrane whether congested or perforated was noted .The presence of tragal tenderness or mastoid tenderness was looked for.

Otomycotic debris was scooped out with a sterile swab and put in a sterile test tube containing 2 ml normal saline .The sample was immediately sent for a fungal smear. Rest of the fungal debris was removed using a sterile suction tip.

Fungal debris were teased onto a slide and stained with gram stain. Presence of fungi and bacteria were looked for.

The ear swabs for this study were inoculated onto Blood agar (BA), Sabouraud's dextrose agar (SAB) with antibiotics & thioglycolate broth. BA was incubated at 37^{o}C in CO2 atmosphere and SAB & thioglycolate broth at 37^{o}C for 18 hours. If there was a suspicion of fungal growth at the point of inoculation, the plates were incubated for a further 24 to 48 hours till sporulation occurred in order to facilitate identification. Fungal growth was identified by doing Lacto Phenol Cotton Blue (LPCB) preparation.(Pic.12 & 13)

After thorough toileting of the ear, the patient was sent to the ENT treatment room for administration of the study drug or the control drug by the sister in charge. At the beginning of the study itself, the drugs were serialed according to the randomization order generated by a computer and the sister in charge was given sealed envelopes which contained the drug to be administered to the patient in a serial order. In case of bilateral otomycosis, the more severely affected ear was taken as the test ear. The patient was advised to put 3 drops of the drug into the affected ear once a day. The patient was advised to clean his/her hands or the helper's hands prior to the instillation. The instillation was done with the patient lying on his non- affected side or the side with fewer symptoms. The affected ear was placed upright and the pinna pulled upwards, backwards and outwards to straighten the canal. The drops were instilled and the patient asked to remain in that position for about 10 minutes.

He /She was asked to repeat this step every day for the next 13 consecutive days.

At the end of the 2 weeks the patient was reviewed in the OPD, questioned regarding relief, persistence or worsening of any symptoms or appearance of any new symptoms. The ear was re-examined under the microscope and the findings were noted and the repeat culture was taken from the ear. If there was no debris noted, a smear from the canal wall was taken.

Outcome

A favourable outcome was said to be achieved if the patient had no symptoms, external auditory canal was free of debris and the post treatment smear showed a normal flora or no growth.

RESULTS

Statistical analysis - all statistical analysis were performed using statistical package for social science version 16.0 (SPSS Inc, Chicago ,IL)

Demographic details

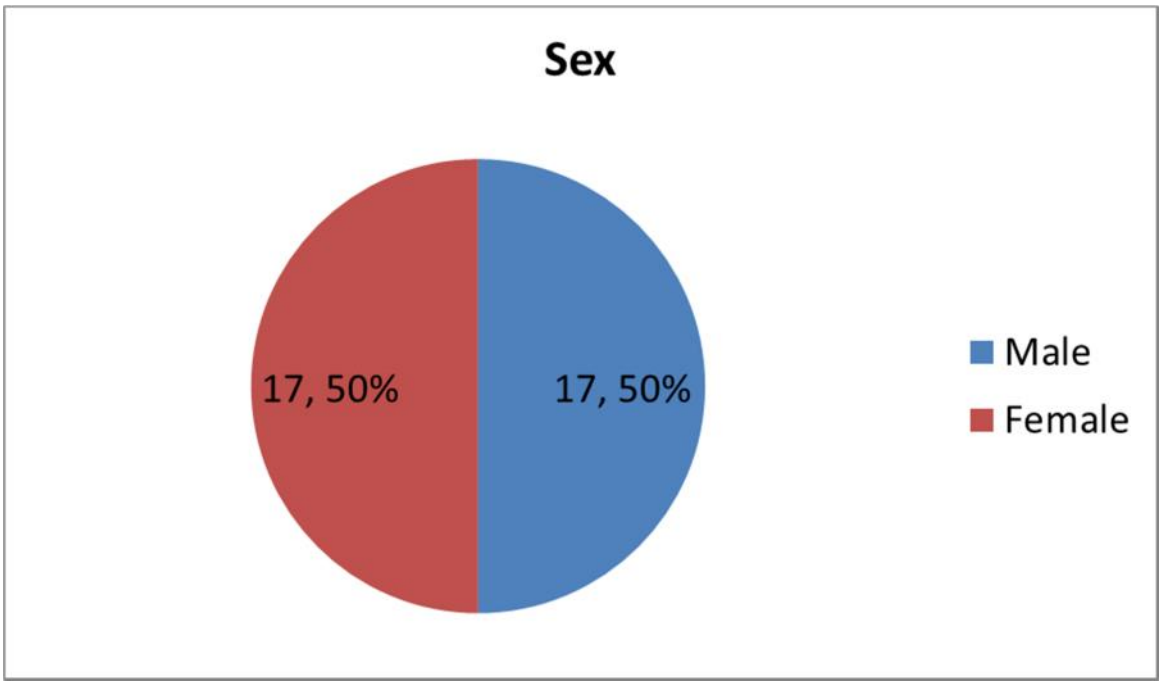


Fig.1

Our study showed an equal predilection in both the genders (Fig 1).

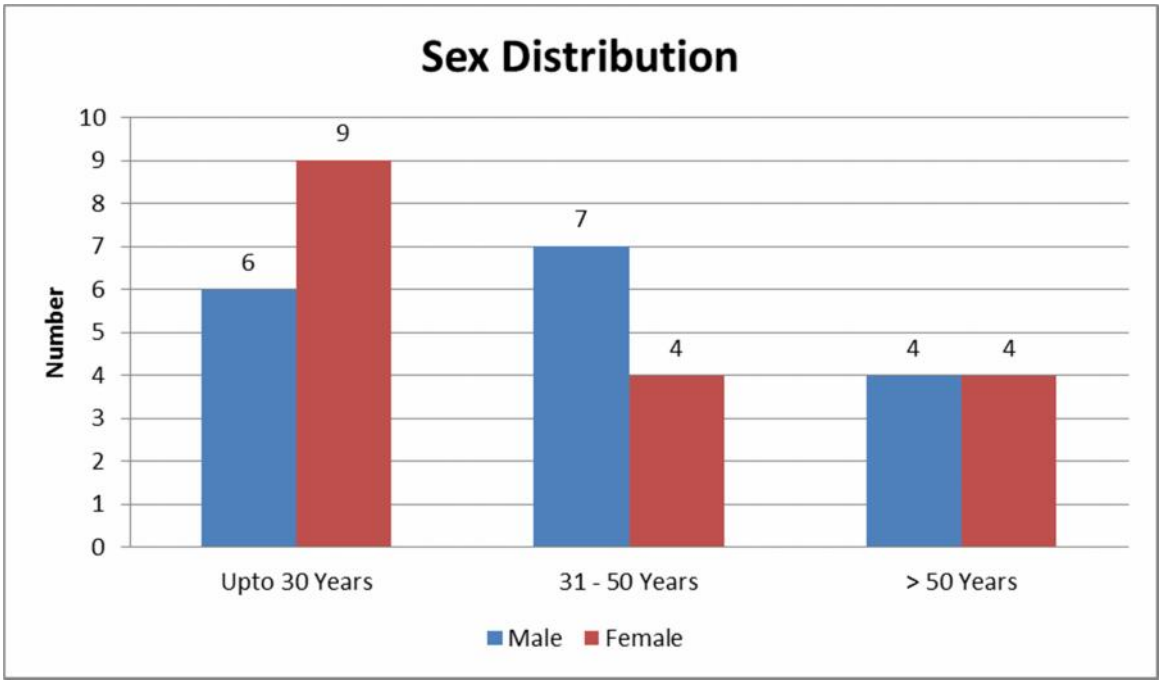


Fig.2.

The number of males and females in the three age groups were compared and it was found that there is a female predominance in the first age group, a male predominance in the second age group and equal predominance of both the genders in the third age group. The 'p' value was 0.524. Since there is no significant difference between the sexes in each age group (p value>0.05), the groups are comparable (Fig.2).

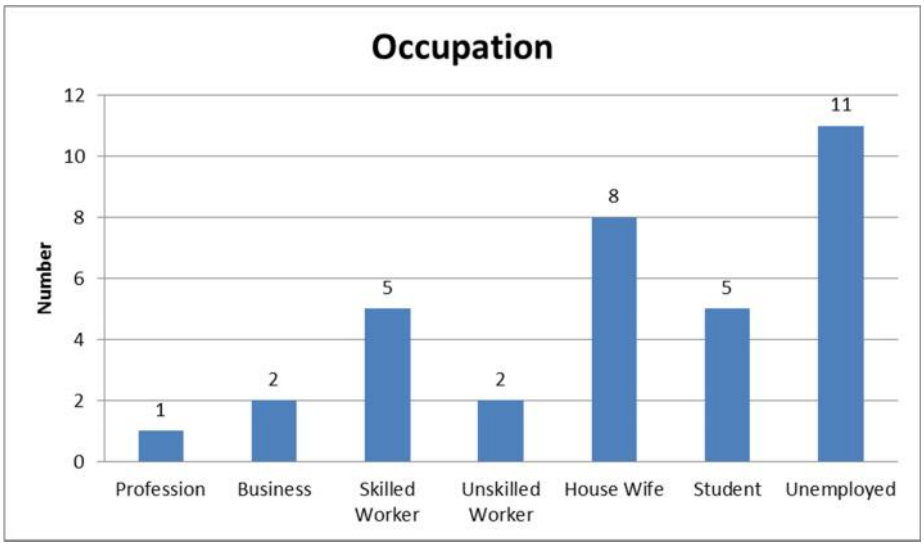


Fig.3.

Unemployed individuals accounted for the maximum number of cases, with housewives comprising the second most affected individuals (Fig 3).

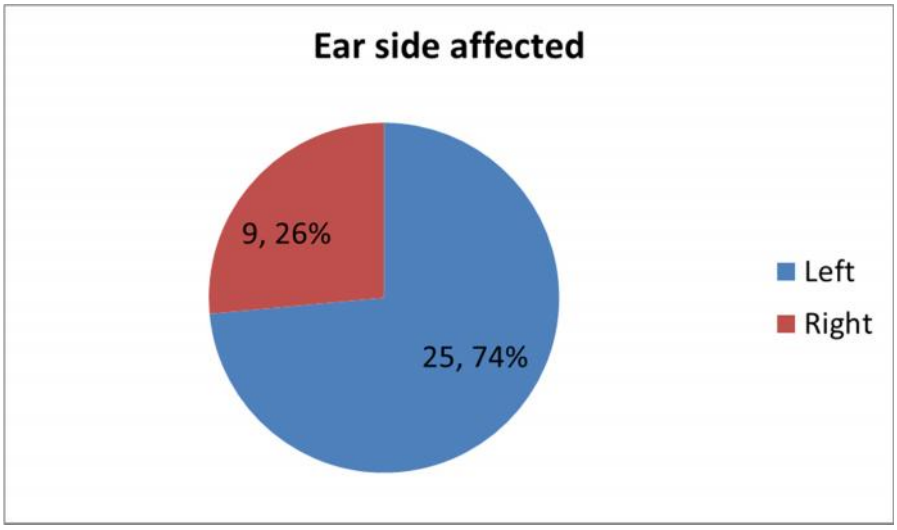


Fig.4

74% of the individuals had involvement of the left ear, with the remaining 26% having involvement of the right ear (Fig 4).

Symptoms- Pre- treatment:

Variables	Number of patients	Percentage
Pruritus		
Yes	26	76.5
No	8	23.5
Ear Discharge		
Yes	19	55.9
No	15	44.1
Otalgia		
Yes	18	52.9
No	16	47.1
Tinnitus		
Yes	10	29.4
No	24	70.6
Deafness		
Yes	7	20.6
No	27	79.4

Tab.3

Pruritus was the most common symptom seen in 76.5% of the study followed by ear discharge, ear fullness, otalgia, tinnitus and deafness in a descending order (Tab.3.).

Signs- Pre-treatment

Variables	Number	Percentage
Tragal Tenderness		
Yes	15	44.1
No	19	55.9
Cartilaginous canal wall erythema		
Yes	16	47.1
No	18	52.9
Cartilaginous canal wall edema		
Yes	12	36.4
No	21	63.6
Bony Canal wall erythema		
Yes	20	58.8
No	14	41.2
Bony Canal wall edema		
Yes	10	29.4
No	24	70.6
Ear discharge in the canal		
Yes	12	35.3
No	22	64.7
Tympanic membrane congestion		
Yes	23	67.6
No	11	32.4

Tab.4.

Tympanic membrane congestion was found in 67.6% of the individuals, followed by bony canal wall erythema, cartilaginous canal wall erythema, tragal tenderness, cartilaginous canal wall edema, ear discharge in the canal, bony canal wall edema in the descending order(Tab.4.).

Self -cleaning and the presence of wax

Variables	Number	Percentage
Self-Cleaning		
Yes	24	70.6
No	10	29.4
Wax		
Yes	10	29.4
No	24	70.6

Tab.5.

Out of 34 individuals, 24 had history of self-cleaning and 24 had no wax in the ears. This probably explains that wax has antifungal properties (Tab.5.).

Microbiology – Pre treatment

Variables	Number	Percentage
Ear Swab Bacterial – Pre treatment		
Non fermenting GNB	1	2.9
Staphylococcus aureus	3	8.8
Enterococcus	-	-
Pseudomonas aeruginosa	-	-
Klebsiella	2	5.9
Enterobacter species	1	2.9
Gram negative bacilli	-	-
Occasional gram positive cocci	1	2.9
Escherichia coli	1	2.9
Citrobacter diversus	-	-
Proteus mirabilis	-	-
Group A streptococci	1	2.9
Non fermenting GNB + Staphylococcus aureus + Enterococcus	1	2.9
Non fermenting GNB + pseudomonas aeruginosa	4	11.8
Staphylococcus aureus + pseudomonas aeruginosa + enterobacter species + escherichia coli	1	2.9
Pseudomonas aeruginosa + klebsiella	2	5.9
Pseudomonas aeruginosa + enterobacter species	3	8.8
Gram negative bacilli + enterobacter species	1	2.9
Ear Swab Fungal – Pre treatment		
No growth	1	2.9
candida tropicalis	-	-
aspergillus niger	8	23.5
aspergillus flavus	8	23.5
yeast	-	-
candida glabrata	-	-
candida tropicalis + aspergillus niger	1	2.9
aspergillus niger + Yeast	4	11.7
aspergillus niger + candida glabrata	1	2.9

Tab.6.

PRE-TREATMENT SWAB BACTERIAL FLORA

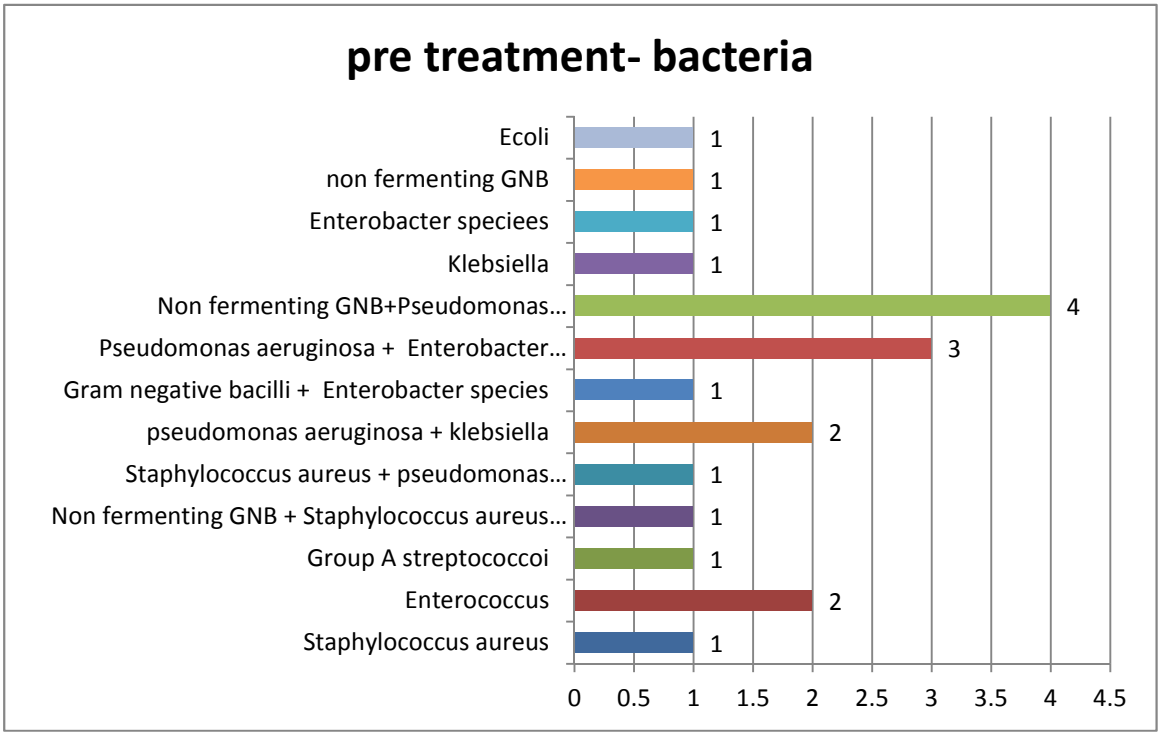


Fig.5.

In pre-treatment ear swabs, (non fermenting GNB + pseudomonas aeruginosa) accounted for 11.8% of the cases and (pseudomonas aeruginosa + enterobacter) species and staphylococcus aureus formed 8.8% of the cases.

Among the fungi, aspergillus niger and aspergillus flavus was most commonly isolated (23.5%) and (aspergillus niger with yeast) formed 11.7% of the cases (Fig.19.).

Aspergillus niger was the most common fungi isolated, forming 60.86% of the isolates either in association with other fungi or in isolation and hence was the most commonly isolated species in our institution.

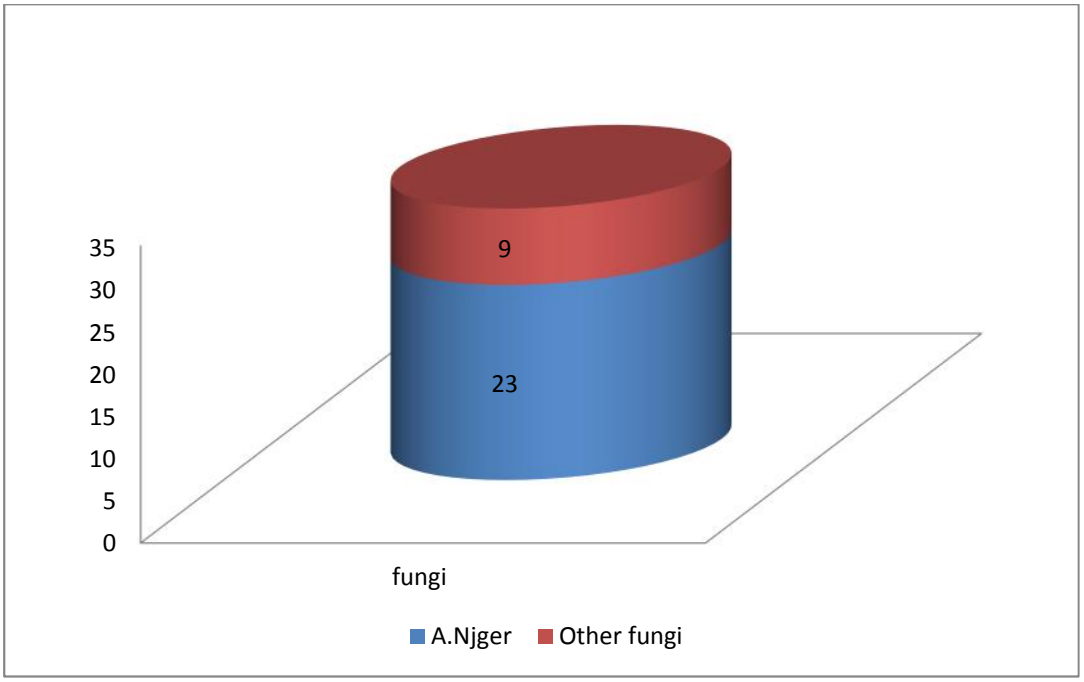


Fig.6.

Number of individuals with pure fungal infection was 32.3%.

Number of individuals with pure bacterial infection was 32.3%

Mixed infection were seen in 35.4 percent of the individuals (Fig. 6.)

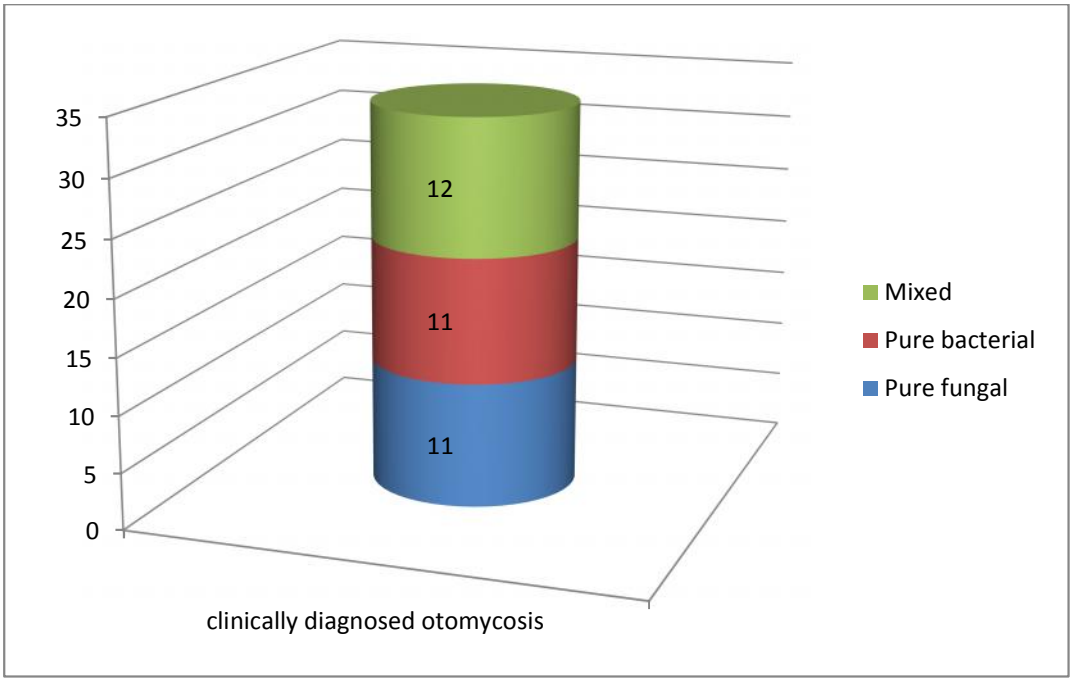

35
30
25
20
15
10
5
0
12
11
11
clinically diagnosed otomycosis
Mixed
Pure bacterial
Pure fungal

Fig.7.

Microbiology – Post treatment

Variables	Number	Percentage
Ear Swab Bacterial – Post treatment		
No growth	14	41.2
Non fermenting GNB	-	-
Staphylococcus aureus	1	2.9
Enterococcus	-	-
Pseudomonas aeruginosa	1	2.9
Klebsiella	-	-
Enterobacter species	-	-
Gram negative bacilli	-	-
Occasional gram positive cocci	-	-
Escheria coli	-	-
Citrobacter diversus	-	-
Proteus mirabilis	1	2.9
Group A streptococci	-	-
Non fermenting GNB + Pseudomonas aeruginosa	2	5.9
Non fermenting GNB + pseudomonas aeruginosa + enterobacter species	1	2.9
Citrobacter diversus + non fermenting GNB	1	2.9
Pseudomonas aeruginosa + klebsiella	1	2.9
Pseudomonas aeruginosa + enterobacter species	3	8.8
Klebsiella + enterobacter species + Enterococcus	1	2.9
Lost to follow-up	8	23.5
Ear Swab Fungal – Post treatment		
No growth	23	67.6
Candida tropicalis	-	-
Aspergillus niger	1	2.9
Aspergillus flavus	2	5.9
Yeast	-	-
Candida glabrata	-	-
Lost to follow-up	8	23.5

Tab.7. Post –treatment bacterial swab (Tab .7.)

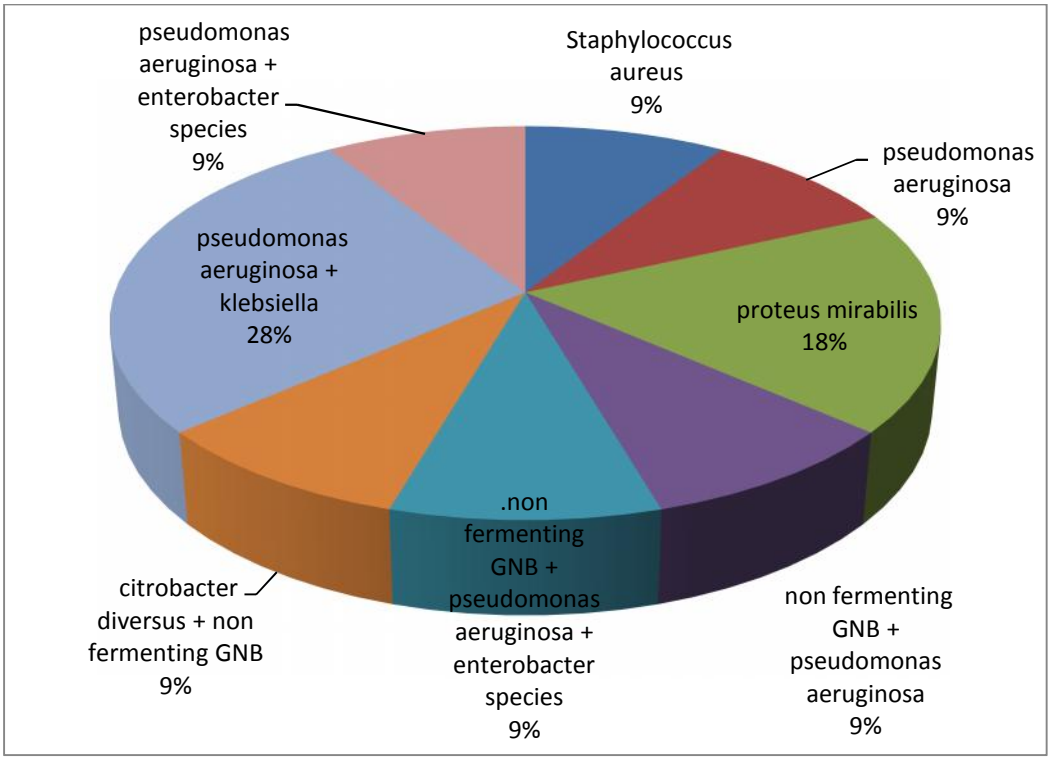


Fig.8 .

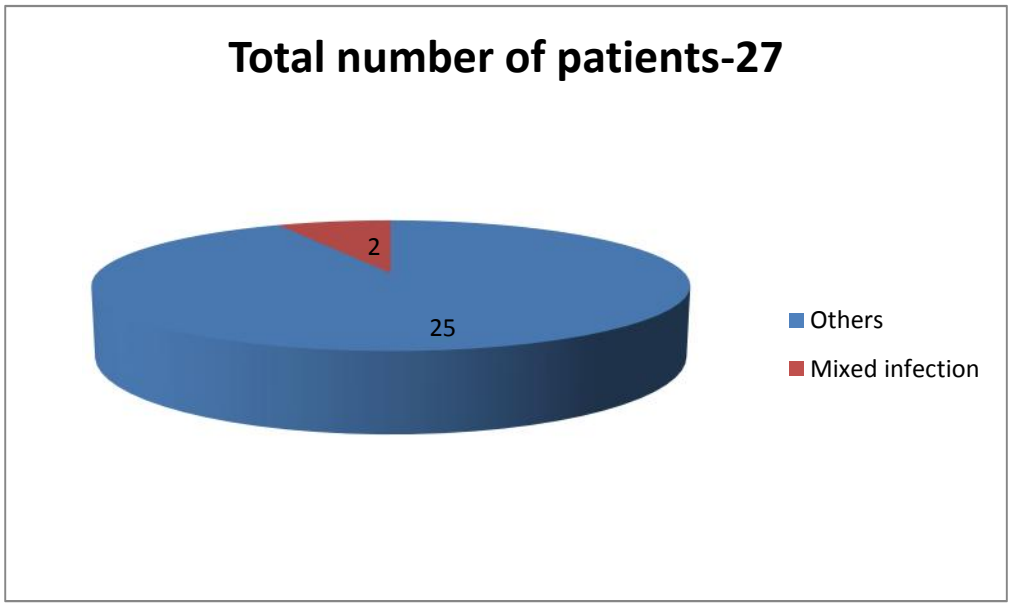


Fig.9.

Patients with mixed infection comprised 7.4% (Fig.9.)

Number of patients who received candid ear drops and povidone-iodine ear drops (fig.10.)

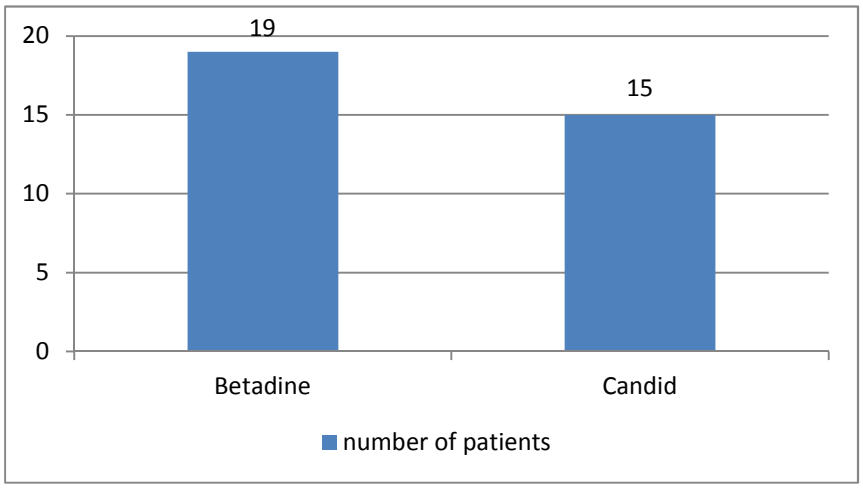


Fig.10.

Number of patients with residual disease – fungus

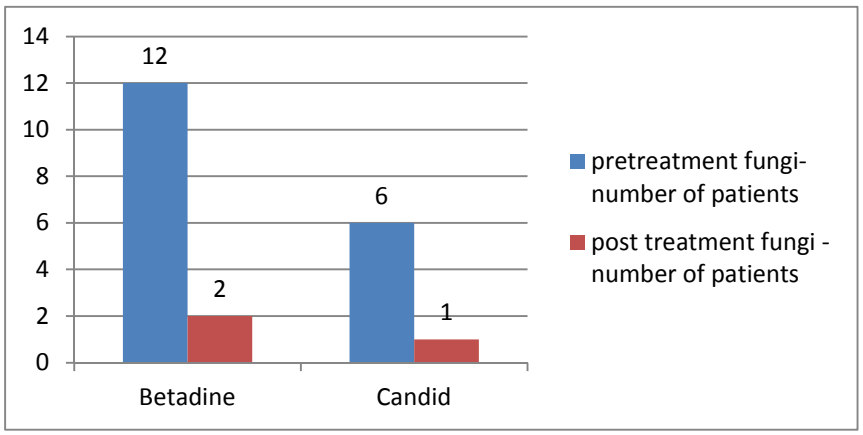


Fig.11.

After treatment with povidone-iodine nine of the smears grew bacteria, pseudomonas aeruginosa was the most common isolate followed by enterobacter.

After treatment with clotrimazole and lignocaine, 3 had grown bacteria, with pseudomonas aeruginosa forming the most common isolate followed by non-fermenting gram negative bacilli.

Considering fungal infections,

Post treatment 23 of the patients had no fungal growth, 8 were lost to follow up and 3 had residual fungal infection out of which 2 belonged to the povidone- iodine group and 1 in the clotrimazole group (Fig.24.).

No of individuals who received povidone-iodine and clotrimazole with lignocaine ear drops in each symptom profile (Tab.8.)

Variables	Drug				p – Value
	Clotrimazole+ Lignocaine		Povidone-iodine		
	n	%	n	%	
Pruritus					
Yes	11	73.3	15	78.9	1.000
No	4	26.7	4	21.1	
Ear Discharge					
Yes	5	33.3	14	73.7	0.036
No	10	66.7	5	26.3	
Ear Fullness					
Yes	10	66.7	9	47.4	0.314
No	5	33.3	10	52.6	
Otalgia					
Yes	5	33.3	13	68.4	0.082
No	10	66.7	6	31.6	
Tinnitus					
Yes	4	26.7	6	31.6	1.000
No	11	73.3	13	68.4	
Deafness					
Yes	3	20.0	4	21.1	1.000
No	12	80.0	15	78.9	

Tab.8.

Post-treatment symptoms with levels of significance between the 2 groups (Tab.9.)

Variables	Drug				p – Value
	Clotrimazole+ lignocaine		Povidone -iodine		
	n	%	n	%	
Pruritus					
Yes	2	16.7	1	6.7	0.569
No	10	83.3	14	93.3	
Ear Discharge					
Yes	1	8.3	1	6.7	1.000
No	11	91.7	14	93.3	
Ear Fullness					
Yes	2	16.7	1	6.7	0.569
No	10	83.3	14	93.3	
Otalgia					
Yes	-	-	2	13.3	0.487
No	12	100.0	13	86.7	
Tinnitus					
Yes	1	8.3	-	-	0.444
No	11	91.7	15	100.0	
Deafness					
Yes	1	8.3	-	-	0.444
No	11	91.7	15	100.0	

Tab.9.

In the symptom profile the clotrimazole group showed a resolution of symptoms in pruritus, ear discharge, fullness, tinnitus and deafness of 83.3%, 91.7%, 83.3%, 91.7% and 91.7% respectively. However there was a 100% resolution of otalgia.

In the povidone-iodine group, there was complete resolution of deafness and tinnitus, whereas pruritus, ear discharge and ear fullness had 93.3% resolution. However, the otalgia resolved only in 86.7% of the cases.

Considering the number of individuals who received the drops in each sign profile (Tab.10.)

Variables	Drug			
	Clotrimazole+Lignocaine		Povidone-iodine	
	n	%	n	%
Tragal Tenderness				
Yes	7	46.7	8	42.1
No	8	53.3	11	57.9
Cartilaginous canal wall erythema				
Yes	8	53.3	8	42.1
No	7	46.7	11	57.9
Cartilaginous canal wall edema				
Yes	6	42.9	6	31.6
No	8	57.1	13	68.4
Bony Canal wall erythema				
Yes	9	60.0	11	57.9
No	6	40.0	8	42.1
Bony Canal wall edema				
Yes	3	20.0	7	36.8
No	12	80.0	12	63.2
Ear discharge in the canal				
Yes	5	33.3	7	36.8
No	10	66.7	12	63.2
Tympanic membrane congestion				
Yes	9	60.0	14	73.7
No	6	40.0	5	26.3

Tab.10.

Post –treatment signs with levels of significance (Tab.11.)

Variables	Drug				p – Value
	Clotrimazole + Lignocaine		Povidone - iodine		
	n	%	n	%	
Tragal Tenderness					
Yes	-	-	-	-	-
No	12	100.0	15	100.0	
Cartilaginous canal wall erythema					
Yes	2	16.7	-	-	0.188
No	10	83.3	15	100.0	
Cartilaginous canal wall edema					
Yes	1	8.3	-	-	0.444
No	11	91.7	15	100.0	
Bony Canal wall erythema					
Yes	1	8.3	1	6.7	1.000
No	11	91.7	14	93.3	
Bony Canal wall edema					
Yes	-	-	1	6.7	1.000
No	12	100.0	14	93.3	
Ear discharge in the canal					
Yes	-	-	-	-	-
No	12	100.0	15	100.0	
Tympanic membrane congestion					
Yes	-	-	2	13.3	0.487
No	12	100.0	13	86.7	

Tab.11.

Considering tragal tenderness, 100% had relief of the symptom using both the ear drops. There was no statistical significance between the 2 groups (p value>0.05), hence the groups are only comparable.

Povidone-iodine had shown 100% resolution of both the cartilaginous wall erythema and the edema whereas the clotrimazole group showed a favorable response of 83.3% and 91.7% respectively. There was no statistical difference between the groups (p value>0.05), hence the groups are comparable.

Bony canal erythema had resolved in 91.7% and 93.3 % of the cases respectively which was not statistically significant (p value>0.05) and hence the two groups were comparable.

Clotrimazole showed a 100 % resolution in the bony wall edema, ear discharge and tympanic membrane congestion whereas povidone-iodine showed a resolution of 93%, 100% and 86.7 % respectively. Both drugs had a 100 percent cure in regard to bony wall edema. It was no statistically significant (p>0.05) and hence the two groups were comparable.

In view of the above findings, it can be stated that both drugs were equally efficacious in resolving the above symptoms and signs. But this could not be established as the statistical value was insignificant. Hence we recommend a study with larger sample size in order to gather further information.

DISCUSSION

Otomycosis, a common condition encountered in any ENT practice, can often be a challenging and frustrating entity for both patients and treating otolaryngologists. Though complications are infrequent and rarely life threatening, it often recurs and may require prolonged treatment and follow-up. The aim of treatment is not only to cure the infection, but also to alleviate the symptoms and signs caused by this condition. The high recurrence is attributed to the persistence of spores.

Chronic suppurative otitis media, post-operative mastoidectomy cavities and immunocompromised individuals are well documented predisposing factors for this condition. Hence in our study we had excluded the above conditions and tried to analyze if there are any other factors for otomycosis. For complete disease clearance, management should address the underlying factors.

The basic principles of management of fungal otitis externa include effective aural toilet, identifying the causative organism and eliminating it using the appropriate antifungal agent. Though systemic antifungals have been attempted in otomycosis, topical preparations are commonly used as these fungi cause superficial infections only. Frequent relapses of otomycosis have been encountered due to the persistence of spores. Studies have shown that sub epithelial spores persist in spite of using topical antifungal eardrops and hence stressed the importance of longer duration of treatment and follow up (6). However in our study, on examination after 2 weeks of treatment, no spores were encountered. Hence we emphasize on meticulous aural toileting, especially in the region of the isthmus and the anterior recess.

A number of ototopical antifungal treatments have been tried in the past, these include application of antiseptics such as gentian violet, boric acid, cresylate and aluminium acetate (Burrows Solution) but these drugs fell out of favor in view of their ototoxicity, when the condition was associated with a perforation.

Clotrimazole is a common antifungal of the azole group used in the treatment of otomycosis. It is used most commonly in combination with either topical antibiotics or steroid preparations. The drug was found to be effective in most other studies, achieving a cure rate of 95 % (7).

We planned to look at the efficacy of 7.5 % of povidone iodine solution in the management of otomycosis. 1% clotrimazole with 2% lignocaine in propyl glycerol base was used as the control drug. Our primary aim was to find an alternative to clotrimazole in the treatment of otomycosis.

We selected povidone- iodine as it is easily available and has been proven to be effective in chronic suppurative otitis media which is one of the predisposing factors of otomycosis. It is chemically stable, inexpensive and resistance in bacteria and fungi is yet to be reported.

Excessive and indiscrete use of any topical antibiotic and antimicrobials may lead to the emergence of resistant organisms. Povidone iodine overcomes this problem as there are no studies to date showing development of resistance, which is an increasing cause of concern in this antibiotic resistance era.

In developing countries like India and the third world countries, where a cheaper and effective form of medication without ototoxicity is a requisite, povidone iodine forms a better choice.

We removed confounding factors such as immunocompromised individuals, patients with hearing aids and tympanic membrane perforations as they would need a longer duration of therapy as 2 weeks of treatment may not have sufficed.

In view of the demographic details of otomycosis, a retrospective study done in Shanghai in 2010(64), concluded that females were more affected with a female: male ratio of 2:1. A similar result was seen in a study in northern Iraq(65). However in our study we found an equal preponderance in both the sexes. Yet another retrospective study by P. Hueso Gutiérrez et al (34) and a study in Nigeria gave a higher male predominance to this condition. Hence we conclude that there is no sex preponderance to this disease though a larger sample size may be required.

Very few studies have described the sex and age distribution, and the affected individuals mainly belonged to the 30-40 years age groups (2)(37) In our study, a larger number of individuals belonged to the age group 15-30 with a female preponderance. This was however not statistically significant. Unemployed individuals were seen more affected with the disease followed by house wives.

The various factors taken in comparison of the drugs such as the patient's symptoms and signs were compared with the pre-treatment and post-treatment and tabulated. This is the first study in literature where we have graded signs and noted the resolution of signs after the treatment and hence can propose grading of otomycosis based on the signs. The signs

and symptoms in this study to each drug was later Chi squared and found to be insignificant (p value>0.05) and so the groups were comparable.

Majority of our patients presented with pruritus followed by otorrhoea, ear fullness, otalgia, tinnitus and deafness when compared with other studies such as that of Tang Ho (5) in which otalgia was the major symptom followed by otorrhoea and hearing loss. Pruritus would have instigated the individual to self–clean his ear, traumatizing the epithelium leading to maceration and causing the introduction of fungal and bacterial organisms thus leading to infection.

In our study, repeated self-cleaning seemed to have a close relation to the absence of wax. Majority of the patients had their left ear affected. This probably would have related to the handedness of the general population. The general population comprises of mostly right handed individuals. Use of the non-dominant hand would have caused more epithelial damage and hence infection. Further studies can be done including the handedness of the individual and ear side affected.

Looking at the microbial floral growth, studies have shown that mixed infections are quite rare as the fungi generally tend to inhibit bacterial flora (36).In our study of clinically diagnosed cases of otomycosis, infection due to the mixed flora topped the list and we propose it may be due to formation of bio-films which are known to be quite resistant to the topical agents commonly used. This may also explain the recurrent nature of otomycosis. Further research will be necessary to confirm this.

The commensals residing in the ear of a normal individual are the Staphylococcus epidermidis, Corynebacterium spp, Bacillus spp, Gram-positive cocci (Staphylococcus aureus. Streptococcus spp, non-pathogenic micrococci), Gram negative bacilli

(Pseudomonas aeruginosa, Escherichia coli, Haemophilus influenza and Moraxella cararrhalis) and mycelial fungi of the Aspergillus genus or yeast-like fungi, particularly Candida spp.

Our pretreatment smears had a predominance of Non fermenting GNB and Pseudomonas aeruginosa, and 75% of this group had association with fungus. Our studies tallied with most of the others in isolating aspergillus niger as the most common species. When a person developed symptoms it often denoted a dis-harmony between the pathogens and the onset of infection.

Presence of enterococcus and enterobacter in our study suggests a faeco-aural transmission of the bacteria.

Though both clotrimazole and povidone-iodine groups had improvement in the post-treatment symptoms and signs, the clotrimazole and povidone – iodine group had a residual fungal disease of 16.6 percent and hence povidone iodine had a cure rate as equal to clotrimazole.

Povidone – iodine has shown to kill most of the bacteria in a biofilm if not all as proved in invitro studies. However it is less effective than hydrogen peroxide in biofilms. Hydrogen peroxide is irritative to the skin and its application to an already erythematous ear canal may cause the patient more discomfort(66). It causes effervescence and must be only used under supervision. Alcohol rapidly destroyed biofilms of staphylococcus epidermidis. Candida has known to form biofilms especially in in dwelling catheters and studies are now suggesting biofilm formation of aspergillus species with bacteria (67)(68)(69).There has been no literature showing biofilms as a cause for recurrent external auditory canal infection, hence we strongly suggest that recurrence and

persistence of disease is not just as a result of spores, but probably due to biofilm formation.

Oral antibiotics are indicated when co existing bacterial infection results in incomplete resolution of the canal infection or when cellulitis of the external auditory canal sets in.

Unlike other studies which compared only the symptoms and the culture, we categorized the signs as confined to various parts of the ear canal, and the tympanic membrane and concluded that most of the patients had tympanic membrane congestion followed by bony and cartilaginous wall erythema.

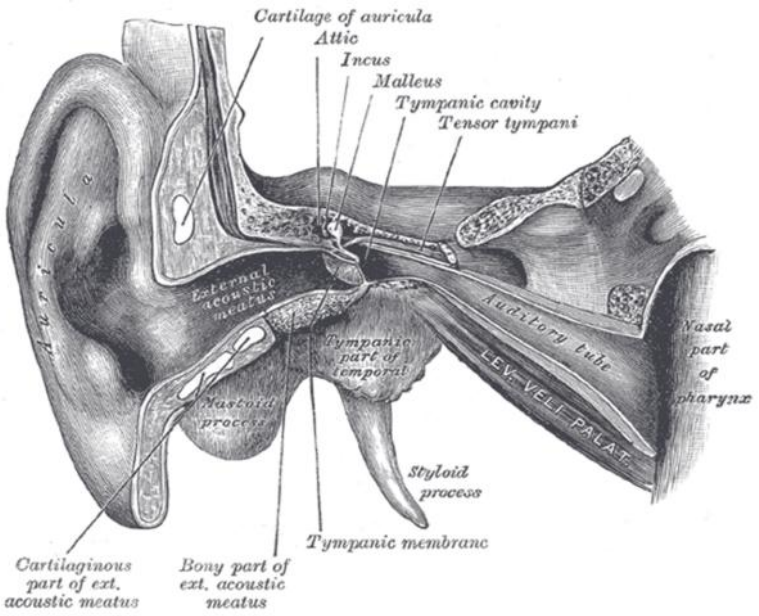
Fungal debris was most commonly noted in the bony cartilaginous isthmus, suggesting a defective epithelial migration and failure of normal lateral excursion in removal of the offending organism, thus forming a nidus for fungi to thrive on.

A once a day application of the ear drops was done based on the study done earlier by Nong et al , which showed a cure rate of 95% (7). As povidone-iodine results were comparable with the clotrimazole group, povidone may also be applied once a day hence increasing the patient compliance.

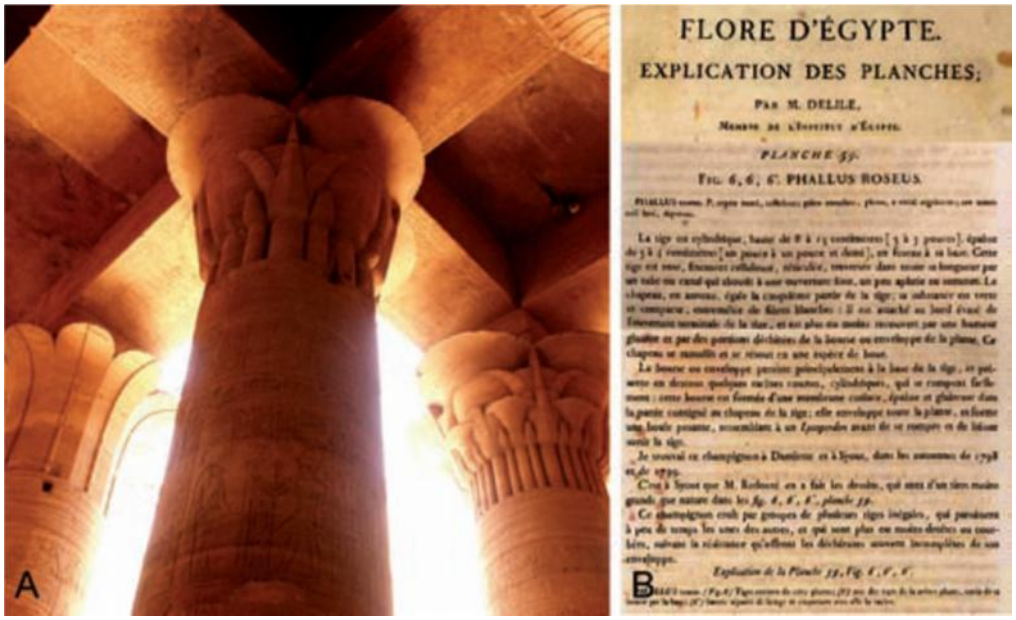
None of our patients developed any symptoms and signs of allergic contact dermatitis.

CONCLUSIONS

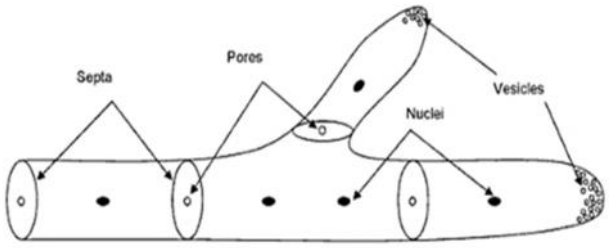
The result of this study supports the use of Povidone-iodine in the treatment of otomycosis, thus avoiding emergence of resistant organisms. Future studies in larger groups of patients are necessary to see which is more effective. This study has opened a window in the application of povidone –iodine in clinically diagnosed case of otomycosis in humans in addition to the management of chronic suppurative otitis media.



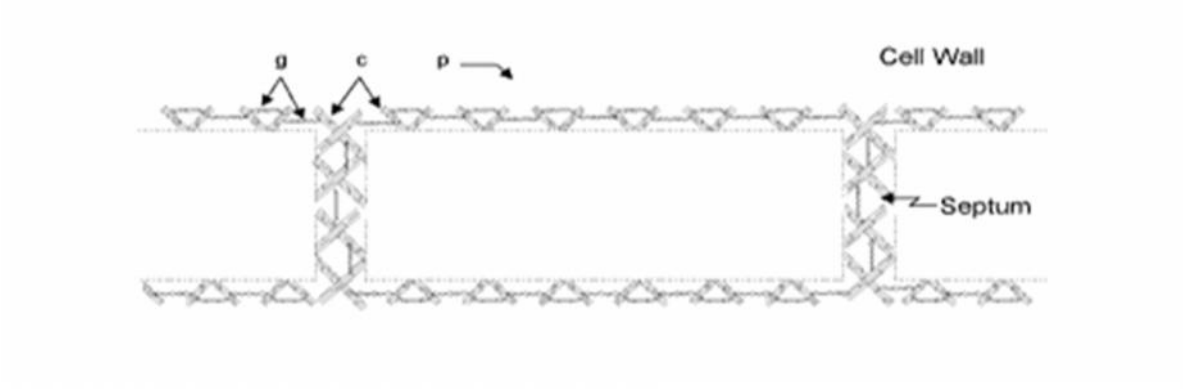
Pic.1.Anatomy of the ear (Adapted from the Gray`s Anatomy of the Human body.)



Pic.2. Adapted from IMA Fungus volume 1 The history, fungal biodiversity, conservation, and future perspectives for mycology in Egypt

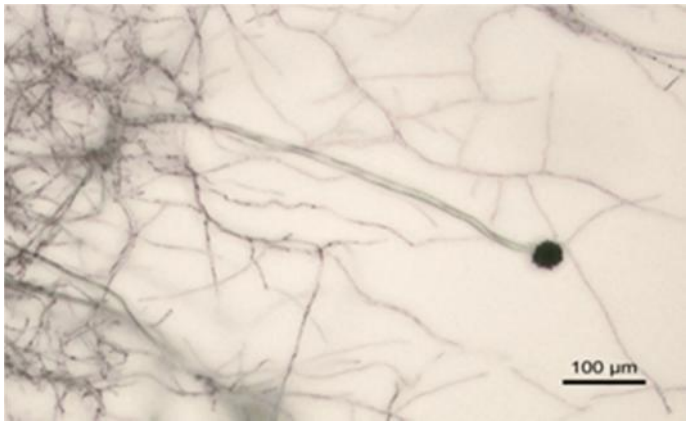


Pic.3.The structure of aspergillus hyphae Adapted from "Surface structures and mechanical properties of model fungus Aspergillus nidulans"

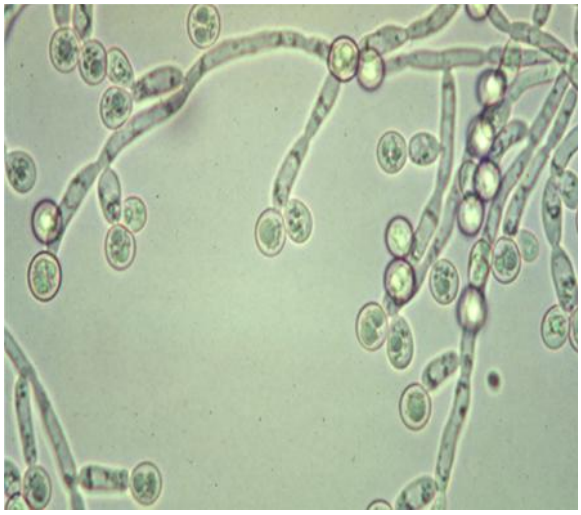


Pic.4.Schematic diagram of cell wall components Adapted from "Surface structures and mechanical properties of model fungus Aspergillus nidulans"

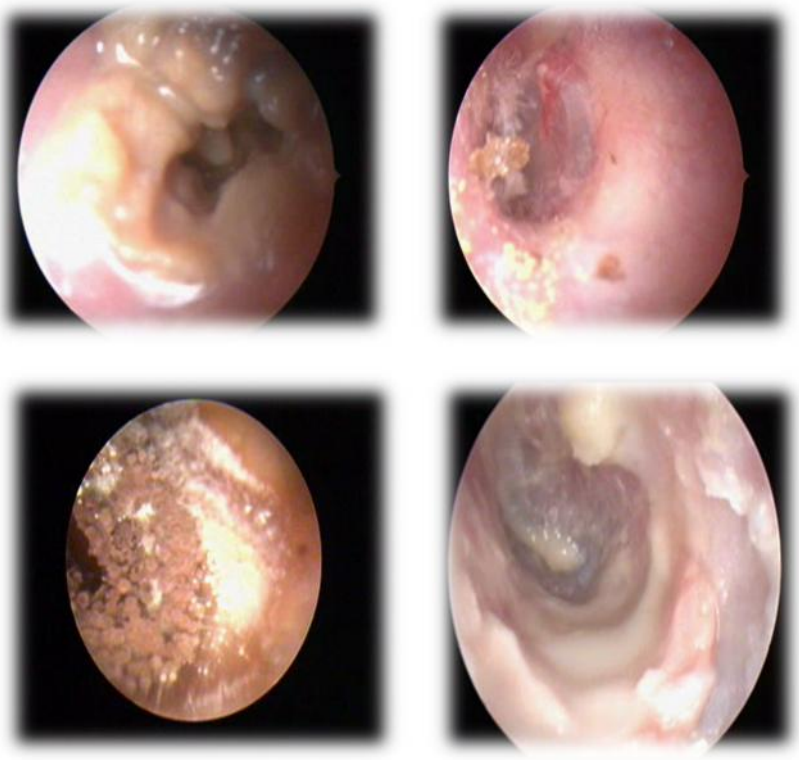
Glycoproteins-p, chitin-c, glucan-g



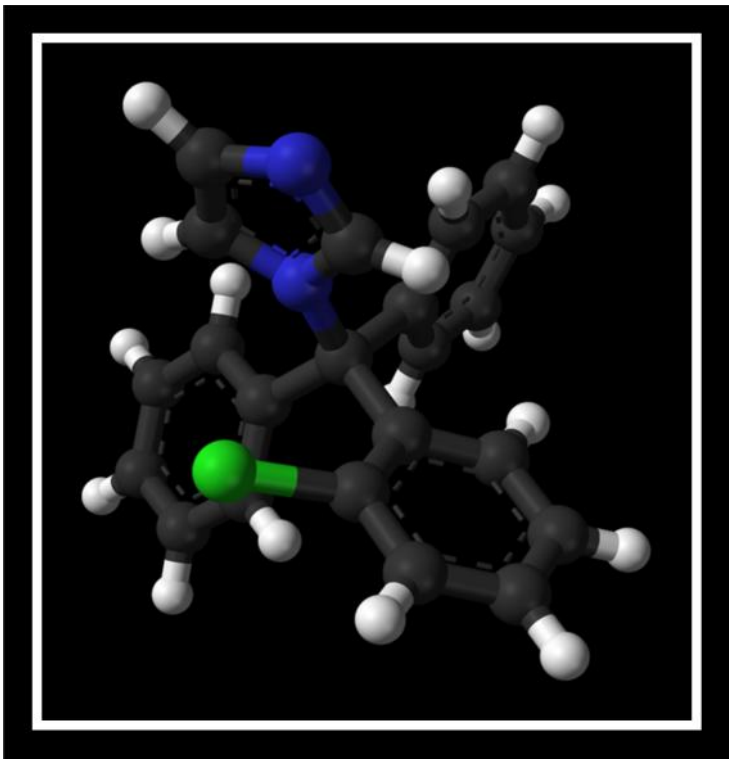
Pic.5. Microscopic image (100-fold magnification) of Aspergillus niger, grown on Sabourauds agar medium

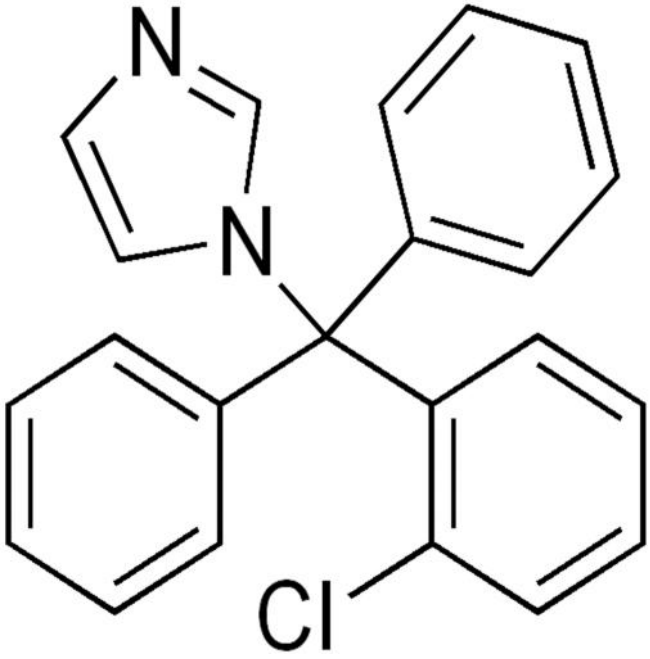


Pic.6.Candida albicans grown on cornmeal agar

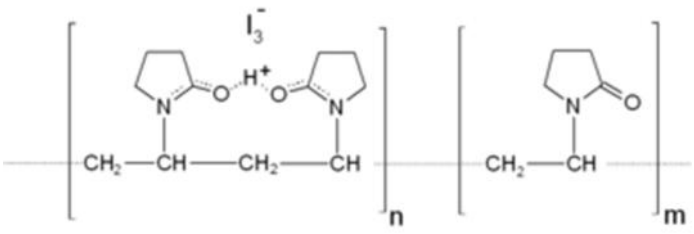


Pic.7. Endoscopic view of otomycosis and spores



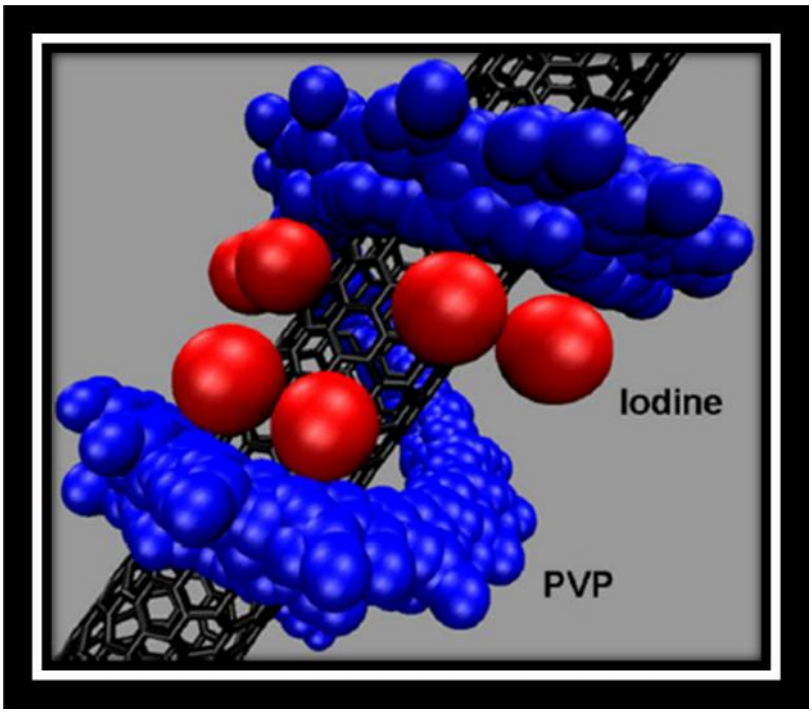


Pic.8. Structure of the clotrimazole molecule



1nm to 18 m

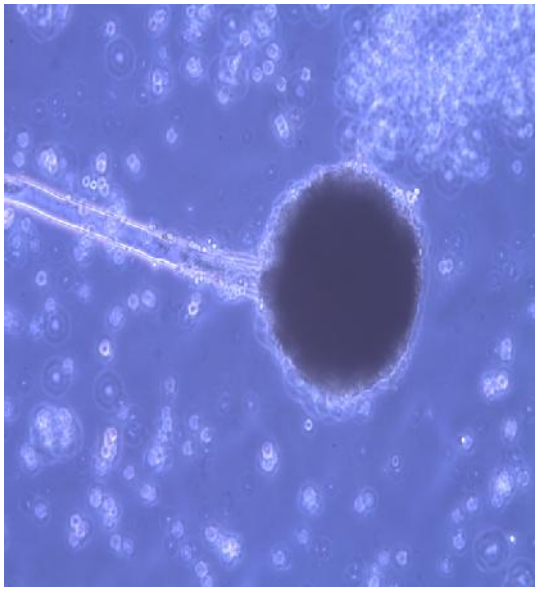
Pic. 9. The Poly (1-vinyl-2-pyrrolidone)-iodine complex



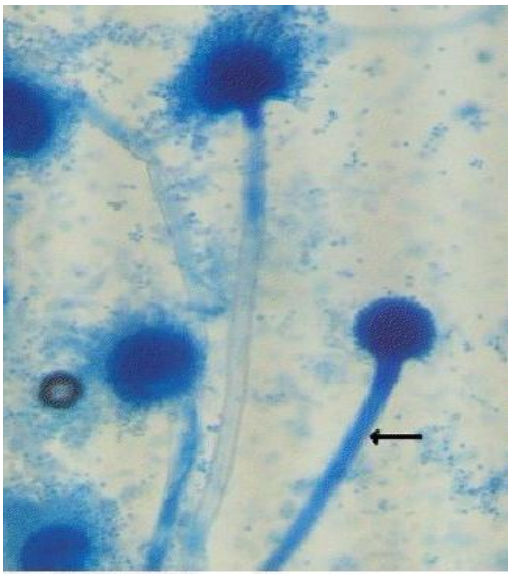
Pic.10. The Image of PVP-I wrapping a single wall carbon nanotube (black in color)

Adopted from Dr Trevor .J. Simmons

Pic. 11. Examination of the ear under the microscope and collection of samples



Pic.12. Aspergillus niger in LPCB



Pic.13.Aspergillus flavus in LPCB

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PATIENT INFORMATION SHEET

You are invited to participate in the research project that is explained below.

Thank you for taking time to read this information. Please make sure you have read all the papers.

What is this research about?

This research is carried out with a purpose of finding an alternative cheaper treatment for the treatment of fungal infection of the ear. Fungal infection is very common in this part of our country and in this study we compare the effectiveness of povidone iodine ear drops to 1% clotrimazole ear drops in the management of clinically proven case of fungal infection of the ear, hence to establish an alternative cheaper treatment to otomycosis.

Who are the researchers?

The researchers will include the doctor who will attend you and the group of doctors that are interested in this study. The principal investigator is the doctor who will be questioning you regarding the complaints and will examine you to see if you fall in the criteria for the study. The principal investigator is the person you will be able to approach in case of any queries before during or after the study.

What are the questions I will probably be asked before being enrolled for the study?

I will be questioned regarding

1. Itching, pain, ear discharge, fullness, tinnitus in the ear
2. If the symptoms are present in one or both the ears
3. The duration of symptoms
4. My occupation
5. Whether I have been treated for the similar complaints previously and if yes if I knew what medications
6. If I constantly self-clean my ear
7. Have I undergone any previous surgeries?
8. Am I suffering from diabetes and if yes what medications am I on and what is my recent blood sugars like the last time it was checked
9. Whether I have undergone any chemotherapy/radiation therapy in the past
10. If I am pregnant.

11. Do I have any known allergies to any drugs, oral or topical, if so I may be asked to specify

12. If I use hearing aids

13. Whether I suffer from recurrent ear discharges especially when I catch recurrent colds and if I am in the habit of using ear drops constantly.

Why am I chosen for the study?

You are chosen as you have fulfilled the criteria for being enrolled in the study.

Can I leave the trial when I like?

Yes, you are entitled to leave the trial if you find it inconvenient .Do bring it to the attention of the principal investigator while doing so.

How will this trial be conducted .What is expected of me?

Once you are selected for the above study, you will be subjected to examination of both the ears under microscope. Any debris will be sent by sterile technique for examination of fungal elements and for culture. You ears will be cleaned .You will also be explained as what you are to do orally .If you are suffering from diabetes, a blood test will be done to see if your blood sugar is under good control. I will be asked to use an ear drop selected randomly .This ear medications will be one of the two drugs in the study, one of which will be an established cure for the disease and the other the drug under experimentation. You are required to instill in this ear 3 drops once a day with the affected ear facing upward for a period of 10 minutes. This will be continued for the next two weeks.

You will be expected to come after 2 weeks to the OPD where you will be re-examined.

What is the duration of the trial? Am I supposed to be hospitalized?

The total duration of the trial is a period of 2 weeks. In the two weeks I am to visit the principal investigator freely if I have any queries or any reactions to the drug.

If you give us consent by signing on the consent form we plan to publish the result.

What happens to my treatment when the trial is over?

Once the trial is over, if you have found to be benefited from the medication you may continue the treatment, but if the disease still persists you will be put on an alternative proven therapy for otomycosis

Informed Consent form to participate in a clinical trial

Study Title: Effectiveness of 7.5% povidone iodine ear drops as compared to 1 %clotrimazole ear drops in the treatment of otomycosis.

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

PROFORMA Study number

Name Age Sex Hospital number

.

Address . Phone Number- Study ear-

Presenting complaints

Symptoms	**Pre treatment** **Yes-1 No-0**	**Post treatment** **Yes-1 No-0**
Itching		
Pain		
Ear discharge		
Fullness		
Tinnitus		
Hearing loss		

Past medical history
Past surgical history
Personal history
Self-cleaning/socioeconomic status

ENT EXAMINATION

Signs	**Pre treatment** **Yes-1 No-0**	**Post treatment** **Yes-1 No-0**
Tragal tenderness		
Cartilaginous wall erythema		
Cartilaginous edema		
Bony canal wall erythema		
Bony canal wall edema		
Ear discharge		
Fungal debris in the canal		
Tympanic membrane congestion		
Tympanic membrane - Perforation		

Final diagnosis-
Adverse effects-

Ear-Swab culture- pre and post treatment

Pre-treatment ear swab	Post-treatment ear swab
Fungi Bacteria	Fungi Bacteria

S NO	H NO	OCPN	AGE	SEX	E_S	ITCH	PN	ED	EF	TN	DF	SE_CLN	TRG_T	CCW_R
1	514260A	Clinical virologist	25	F	1	1	1	0	1	0	0	0	0	0
2	878329D	Business man	45	M	0	1	0	1	1	1	1	1	0	0
3	711159D	Housewife	57	F	1	1	0	1	1	1	1	1	0	1
4	771117C	Housewife	36	F	1	1	1	1	1	0	1	0	0	0
5	105225D	Business man	30	M	1	1	0	1	1	0	0	1	0	0
6	812850d	Housewife	75	F	0	1	1	1	1	0	0	1	1	1
7	830958D	Housewife	24	F	0	1	1	1	0	0	0	1	1	1
8	377998D	Driver	43	M	0	1	0	1	0	0	0	1	0	0
9	402773B	Driver	37	M	0	1	1	1	1	1	1	1	1	1
10	922773O	Attender	24	M	0	1	0	0	1	0	0	1	1	1
11	088778b	Retired	50	M	1	1	1	1	1	0	0	1	1	1
12	909480D	Housewife	27	F	0	0	1	1	0	0	0	1	0	1
13	247117D	Driver	47	M	0	1	1	0	1	1	0	1	1	0
14	911123D	Student	23	F	0	1	0	1	0	1	0	1	0	0
15	209306B	Student	17	M	1	1	0	1	1	0	0	1	1	1
16	328625C	Student	22	M	0	1	0	0	1	0	0	0	0	0
17	363675B	Student	15	F	1	0	1	1	0	0	0	0	1	1
18	978308A	Unemployed	53	M	0	1	0	0	0	0	1	1	0	0
19	462975d	Unemployed	39	F	0	1	0	0	1	0	0	1	0	1
20	543253d	Unemployed	39	F	0	0	1	0	0	0	0	1	0	0
21	708649c	Unemployed	23	F	0	1	0	0	0	0	0	0	0	0
22	946504d	Unemployed	36	F	0	1	1	1	0	0	0	1	1	1
23	242414C	Unemployed	29	M	1	1	1	0	0	0	0	1	0	0
24	267243D	Housewife	29	F	0	1	1	0	1	1	0	1	1	1
25	052487A	Retired	60	F	1	1	1	1	1	1	0	0	1	1
26	315555a	Farmer	70	M	0	1	1	0	1	1	0	1	1	0
27	974855d	Housewife	20	F	0	0	0	1	1	0	0	1	1	0
28	976867d	Mill worker	52	M	0	0	0	0	0	1	0	1	1	1
29	986498D	Housewife	56	F	0	1	0	1	1	1	1	1	0	0
30	971827d	Self employed	33	M	0	0	1	0	1	0	0	0	1	1
31	005446F	Student	21	F	0	0	0	1	0	0	0	1	0	0
32	858508B	Unemployed	40	M	0	0	1	0	0	0	0	0	0	0

33	015505F	Unemployed	65	M	0	1	1	1	0	0	1	0	0	1
34	017101f	Unemployed	27	M	0	1	0	0	0	0	0	0	0	0

S NO	H NO	CCW_E	F_DBR	WAX	BC_R	BC_E	DSCRG	TMC	ESS_F	PPN
1	514260A	0	1	0	1	0	0	1		0
2	878329D	0	1	0	0	0	1	1	4,2	0
3	711159D	1	1	0	1	0	1	1	1,2	0
4	771117C	0	1-bony canal	0	1	1	0	1	2	1
5	105225D	0	0	0	1	0	1	1		0
6	812850d	1	1-otomycotic debris in bony cartilaginous junction	1	1	1	1	1	2	0
7	830958D	1	1-black colonies in bony canal cartilaginous junction	0	1	1	1	1	2	
8	377998D	0	1-fungal debris	0	0	0	0	0		0
9	402773B	1	1-black colonies adjacent to tm	0	0	0	1	1	3	0
10	922773O	1	1-black colonies	0	1	0	1	0		0
11	088778b	0	1-black colonies	1	0	0	1	1	2	
12	909480D	0	1-whitish debris at isthmus	0	1	0	0	1		
13	247117D	0	1-black colonies-adjacent to tm	1	1	1	0	1	2	0
14	911123D	0	1-whitish debris at isthmus	1	1	1	0	1	3	0
15	209306B	1	1-curdy white ppt	0	1	1	1	1		0
16	328625C	0	1-curdy white ppt	0	1	1	0	1		0
17	363675B	1	1-whitish debris at the isthmus	0	0	0	0	0	3	
18	978308A	0	1-wax with black and white colonies	1	1	0	0	1	2,4	0
19	462975d	0	1-white debris in bony cartilaginous junction	0	0	0	0	0		0
20	543253d	0	1-bony canal	0	0	0	0	0	3	
21	708649c	0		0	0	0	0	0		
22	946504d	1	1-black colonies	0	0	0	1	1	5,2	0
23	242414C	0	1	0	0	0	0	1	3	0
24	267243D	1	1-black colonies	0	1	1	1	1	2	0
25	052487A	1	1-whitish curdy ppt	1	0	0	0	0		0
26	315555a	0	1-white colonies in bony canal wall	0	1	0	0	1	3	0
27	974855d	0	1-white and black colonies in bony canal	0	1	0	1	1		
28	976867d	1	1	1	1	1	0	1	3	0
29	986498D	0	1	1	1	1	0	1	0	0
30	971827d	0	1-debri-black in deep bony canal	1	0	0	0	0	2	0
31	005446F	0	1-white debris in bony cartilaginous junction	0	0	0	0	0	4,2	1
32	858508B	0	1-debri-black in deep bony canal	0	0	0	0	0	4,2	0

33	015505F	1	1-black colonies in bony canal wall	1	1	0	0	0	3	0
34	017101f	0	1	0	1	0	0	1	2	0

S NO	H NO	PPN	PED	PEF	PTN	PDF	PTRG_T	PCCW_R	PCCW_E	PBC_R	PBC_E	PF_DBR	PDSCRG	P_TMC	P_TMP
1	514260A	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	878329D	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	711159D	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	771117C	1	0	0	0	0	0	0	0	0	0	0	0	0	0
5	105225D	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	812850d	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	830958D														
8	377998D	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	402773B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	922773O	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	088778b														
12	909480D														
13	247117D	0	0	0	0	0	0	0	0	0	0	0	0	1	0
14	911123D	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	209306B	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	328625C	0	0	1	0	1	0	1	0	0	0	0	0	0	0
17	363675B														
18	978308A	0	1	0	0	0	0	0	0	1	0	0	0	0	0
19	462975d	0	0	0	1	0	0	0	0	0	0	1	0	0	0
20	543253d														
21	708649c														
22	946504d	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	242414C	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	267243D	0	0	0	0	0	0	0	0	1	1	1	0	1	0
25	052487A	0	0	1	0	0	0	1	1	0	0	0	0	0	0
26	315555a	0	0	1	0	0	0	0	0	0	0	0	0	0	0
27	974855d														
28	976867d	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	986498D	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	971827d	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	005446F	1	1	0	0	0	0	0	0	0	0	0	0	0	0
32	858508B	0	0	0	0	0	0	0	0	0	0	0	0	0	0

33	015505F	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	017101f	0	0	0	0	0	0	0	0	0	0	0	0	0	0

S NO	H NO	PESS_F	PESS_B	Drug
1	514260A	0		1
2	878329D		5,6,3	2
3	711159D	0		1
4	771117C		4,6	2
5	105225D	0		2
6	812850d		4,5	2
7	830958D			2
8	377998D			2
9	402773B	0		1
10	922773O	3		1
11	088778b			2
12	909480D			2
13	247117D		2+	2
14	911123D		4,6	2
15	209306B		1,4	1
16	328625C			1
17	363675B			2
18	978308A		10, 1	1
19	462975d		6, 4	1
20	543253d			1
21	708649c			1
22	946504d			2
23	242414C	0		2
24	267243D	2	4	2
25	052487A		1,4	1
26	315555a	3	1,4, 6	2
27	974855d			1
28	976867d	0		1
29	986498D	0		2
30	971827d	0		1
31	005446F		11	2
32	858508B			2

33 34	015505F 017101f	0 0		2 1