



MODERN APPROACHES TO THE TREATMENT OF OTOMYCOSIS IN CHILDREN: ANTIFUNGAL THERAPY, OZONE THERAPY AND IMMUNOCORRECTION (LITERATURE REVIEW)

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<https://doi.org/10.5281/zenodo.23340751>

Abstract. The review analyses clinical studies and meta-analyses on the efficacy and safety of otomycosis treatments, together with the pathogenetic rationale for ozone therapy and immunocorrection. Topical azoles (clotrimazole, miconazole, sertaconazole, luliconazole) combined with meticulous aural toilet are first-line therapy; antiseptic solutions are an inexpensive alternative but require caution in tympanic membrane perforation because of ototoxicity. Recurrence after conventional treatment reaches 15–30%, which drives the search for new approaches. Besides a direct fungicidal effect through oxidation of the fungal cell wall and membrane, medical ozone has antihypoxic, regenerative and immunomodulatory properties, and ozonated oils have proven effective in skin and nail mycoses. Antifungal defence relies on the Th17/IL-17 axis, natural killer cells and IL-10-mediated regulatory mechanisms, and their disturbance leads to chronic and recurrent disease. Combining topical antifungal therapy with ozone therapy and immunocorrection is a promising direction for treating otomycosis in children.

Keywords: otomycosis, children, clotrimazole, fluconazole, ozone therapy, immunocorrection, IL-17, recurrence.

Annotatsiya. Sharhda otomikozni davolash usullarining samaradorligi va xavfsizligi bo'yicha klinik tadqiqotlar, meta-tahlillar hamda ozonoterapiya va immunokorreksiyaning patogenetik asoslari tahlil qilingan. Mahalliy azol preparatlari (klotrimazol, mikonazol, sertakonazol, lulikonazol) eshituv yo'lini puxta tozalash bilan birgalikda birinchi qator davo hisoblanadi; antiseptik eritmalar arzon alternativ bo'lsa-da, nog'ora parda perforatsiyasida ototoksiklik xavfi tufayli ehtiyotkorlikni talab qiladi. An'anaviy davodan keyin qaytalanishlar 15–30% ga yetadi, bu esa yangi yondashuvlarni izlashni taqozo etadi. Tibbiy ozon zamburug' hujayra devori va membranasini oksidlovchi to'g'ridan-to'g'ri fungitsid ta'sir bilan bir qatorda antigipoksik, regenerativ va immunomodulyator xususiyatlarga ega; ozonlangan moylar teri va tirnoq mikozlarida samarali ekanligi isbotlangan. Zamburug'larga qarshi himoyada Th17/IL-17 o'qi, tabiiy killerlar va IL-10 vositachiligidagi regulyator mexanizmlar asosiy rol o'ynaydi, ularning buzilishi surunkali va qaytalanuvchi kechishga sabab bo'ladi. Mahalliy antimikotik terapiyani ozonoterapiya va immunokorreksiya bilan uyg'unlashtirish bolalarda otomikozni davolashning istiqbolli yo'nalishi hisoblanadi.

Kalit so'zlar: otomikoz, bolalar, klotrimazol, flukonazol, ozonoterapiya, immunokorreksiya, IL-17, qaytalanish.

Аннотация. В обзоре проанализированы клинические исследования и метаанализы, посвящённые эффективности и безопасности методов лечения отомикоза, а также патогенетические основы озонотерапии и иммунокоррекции. Местные азоловые препараты (клотримазол, миконазол, сертаконазол, луликоназол) в сочетании с тщательным туалетом слухового прохода являются средствами первой

линии; антисептические растворы — недорогая альтернатива, но при перфорации барабанной перепонки требуют осторожности из-за риска ототоксичности. После традиционной терапии рецидивы достигают 15–30%, что обуславливает поиск новых подходов. Медицинский озон, наряду с прямым фунгицидным действием за счёт окисления клеточной стенки и мембраны гриба, обладает антигипоксическим, регенеративным и иммуномодулирующим эффектами; эффективность озонированных масел доказана при микозах кожи и ногтей. В противогрибковой защите ключевую роль играют ось Th17/IL-17, естественные киллеры и регуляторные механизмы, опосредованные IL-10, нарушение которых приводит к хроническому и рецидивирующему течению. Сочетание местной антимикотической терапии с озонотерапией и иммунокоррекцией является перспективным направлением лечения отомикоза у детей.

Ключевые слова: отомикоз, дети, клотримазол, флуконазол, озонотерапия, иммунокоррекция, IL-17, рецидив.

Introduction

The treatment of otomycosis remains one of the unresolved problems of otorhinolaryngology. To date, there is no single international clinical protocol for the management of this disease, and dozens of antifungal and antiseptic agents are used in practice [1, 2]. On the one hand, the abundance of available drugs indicates the absence of a single effective agent; on the other hand, it shows that treatment outcomes depend not only on the choice of drug, but also on the quality of aural toilet, the elimination of predisposing factors and the patient's immune status [3].

The treatment of otomycosis in children imposes additional requirements: the drug should be safe, painless, non-ototoxic, convenient to use and effective within a short course. From this standpoint, the limitations of conventional antifungal agents and the high recurrence rate have increased interest in alternative and adjunctive treatment modalities such as ozone therapy and immunomodulation.

The aim of the review is to analyse the effectiveness of modern methods of otomycosis treatment and the pathogenetic rationale for ozone therapy and immunocorrection, and to substantiate a comprehensive treatment approach in children.

Materials and Methods

Randomised controlled trials, meta-analyses, reviews and experimental studies published in 2000–2024 were searched in the PubMed/MEDLINE, Scopus, Cochrane Library, Google Scholar and eLIBRARY.RU databases using the keywords “otomycosis treatment”, “clotrimazole”, “antifungal”, “ozone therapy”, “ozonated oil”, “IL-17 antifungal immunity”, “отомикоз лечение” (otomycosis treatment) and “озонотерапия” (ozone therapy). A total of 38 sources were included in the analysis.

Principles of Local Treatment and Aural Toilet

The fundamental prerequisite for treating otomycosis is meticulous cleaning of the external auditory canal from fungal masses, discharge and epidermal debris. Accumulations of fungal mycelium and spores prevent the drug from reaching the skin and serve as a source of recurrence [1, 4]. Cleaning is performed under microscopic or endoscopic control by suction, atraumatic instruments or irrigation. In children, it is important that this procedure be painless

and atraumatic, since additional injury to the canal skin creates conditions for deeper spread of the infection.

During treatment, it is recommended to discontinue topical antibacterial and corticosteroid drops, prevent water from entering the ear, prohibit self-cleaning of the ear and correct concomitant diseases [2, 5].

Topical Antifungal Agents

Azole derivatives. Clotrimazole is the most extensively studied and widely used drug for otomycosis: it has a broad spectrum of activity against *Aspergillus* and *Candida* species, is non-ototoxic and inexpensive [6]. In the systematic review and meta-analysis by Wu S. et al., antifungal drugs (mainly azoles) showed higher clinical efficacy than traditional antiseptics [7]. In the randomised trial by Jimenez-Garcia L. et al., clotrimazole was more effective than tolnaftate [8]. Dundar R. and İynen İ., as well as Chavan R.P. et al., demonstrated that even a single application of clotrimazole cream is highly effective provided the ear canal has been thoroughly cleaned, which is particularly convenient in paediatric practice [9, 10]. Antunes J. et al. noted that the efficacy of clotrimazole depends on the fungal species isolated [11].

Sertaconazole, miconazole, econazole and luliconazole have also shown high efficacy: in the placebo-controlled trial by Nemati S. et al., sertaconazole produced results comparable to those of clotrimazole and miconazole [12], while luliconazole demonstrated very high in vitro activity against *A. flavus* strains [13]. Fluconazole is effective mainly in *Candida* otomycosis and has intrinsically low activity against *Aspergillus* species; its use as monotherapy for *Aspergillus* infection is therefore limited [6, 14].

Allylamines. Terbinafine exerts a fungicidal effect against moulds. Yang T.H. and Young Y.H. demonstrated, both experimentally and clinically, the effectiveness of terbinafine solution in eradicating otomycosis [15]. The results of a metagenomic study also indicated that terbinafine may be a rational option for otomycosis [16].

Polyene antibiotics. Nystatin and amphotericin B are highly active against yeasts but relatively less active against moulds, and *A. terreus* is intrinsically resistant to amphotericin B [6, 14].

Antiseptic and Acidifying Agents

Agents such as alcoholic boric acid solution, acetic acid, povidone-iodine, gentian violet, Castellani's paint and nitrofungin have been used for many years. They are inexpensive, have a broad spectrum and do not induce resistance in fungi [17]. The review by Yassin Z. et al. showed that acidifying agents in some cases are nearly as effective as clotrimazole, although the results are heterogeneous [17]. Mofatteh M.R. et al. compared clotrimazole and iodine tincture and found both methods to be effective [18]. However, alcohol- and iodine-based solutions cause burning and pain when applied to inflamed skin, and in the presence of tympanic membrane perforation their introduction into the middle ear is not recommended because of the risk of ototoxicity [2, 19].

Nitrofungin (active ingredient 2-chloro-4-nitrophenol) is widely used to treat otomycosis in Central Asia and the CIS countries. Although inexpensive and effective, its alcohol base causes unpleasant sensations in children, and the course of treatment often extends to 2–3 weeks [20, 21].

Management of Patients with Tympanic Membrane Perforation

Treatment becomes more complicated in middle ear otomycosis and in mycosis of the postoperative cavity, because penetration of the drug into the tympanic cavity carries a risk of ototoxicity. Dyckhoff G. et al. studied the safety of antifungal therapy in patients with tympanic membrane defects and recommended clotrimazole as a reliable agent [22]. Görür K. et al. showed that the use of a paper patch facilitates treatment in perforated ears [23]. Clinical observations of successful topical voriconazole application in resistant cases have also been described [24]. Novel agents such as nanocrystalline silver preparations are also showing promising results [25].

Recurrence and Its Prevention

The recurrence rate of otomycosis after conventional treatment is estimated at 15–30% in various sources [26, 27]. The main causes of recurrence are inadequate cleaning of the ear canal, premature discontinuation of treatment, persistence of predisposing factors, fungal resistance and weakened local immune defence. Kiakojuri K. et al. showed that a prophylactic course of clotrimazole after treatment reduces recurrences [27]. Russian authors also recommend applying an antifungal agent once or twice a week for several weeks after treatment to prevent recurrence [21].

Mechanisms of the Therapeutic Action of Ozone Therapy

Medical ozone is a gas mixture consisting of 0.05–5% ozone and 95–99.95% oxygen; in clinical practice it is used as a gas, ozonated distilled water, ozonated saline and ozonated oils [28, 29]. Since ozone is an unstable molecule, it is generated immediately before use; when dissolved in water and oils, its activity is preserved for a certain period.

Antimicrobial effect. As a powerful oxidant, ozone oxidises the lipid and lipoprotein components of the microbial cell wall and cytoplasmic membrane, disrupts membrane permeability and inactivates intracellular enzymes [28, 30]. In fungi, ozone acts on the glycoprotein and lipid components of the cell wall, suppressing their growth and sporulation. Ouf S.A. et al. confirmed the fungicidal potential of ozone against dermatophytes in vitro [31]. Importantly, because the mechanism of action of ozone is non-specific, resistance to it does not develop, and it is active against strains resistant to antibiotics and antifungals [29, 32].

Clinical efficacy. In a controlled clinical trial of ozonated sunflower oil (Oleozone) in the treatment of tinea pedis, it showed high clinical and mycological efficacy compared with ketoconazole [33]. Ozone therapy is also widely used in the treatment of infectious and inflammatory skin diseases [30]. However, controlled studies on the efficacy of ozone therapy in otorhinolaryngology, and in otomycosis in particular, are very scarce, and in children they are virtually non-existent.

Immunomodulatory and regenerative effect. At low therapeutic doses, ozone induces “mild oxidative stress”, which activates the Nrf2 signalling pathway and enhances the synthesis of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) [32, 34]. Ozone increases the phagocytic activity of macrophages and neutrophils, modulates cytokine production, improves tissue oxygenation and microcirculation, and accelerates epithelialisation [29, 34]. These properties contribute to the restoration of the ear canal skin and the normalisation of local defence.

Table 1

Main effects of medical ozone relevant to the treatment of otomycosis

Effect	Mechanism	Clinical significance
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Fungicidal and bactericidal	Oxidation of cell wall and membrane lipids and proteins	Eradication of fungal and mixed flora
Overcoming resistance	Non-specific oxidative action	Activity against antifungal-resistant strains
Immunomodulatory	Modulation of phagocytosis and cytokine synthesis	Restoration of local defence
Antihypoxic	Improved tissue oxygen utilisation	Reduction of inflammation and oedema
Regenerative	Activation of the antioxidant system, epithelialisation	Rapid restoration of ear canal skin

Immune Defence and Immunocorrection in Otomycosis

Antifungal defence relies on the coordinated action of innate and adaptive immunity. β -glucans, mannans and chitin of the fungal cell wall are recognised by Dectin-1, Toll-like receptors and other pattern recognition receptors on epithelial cells, macrophages and dendritic cells [35, 36]. This triggers activation of neutrophils and macrophages, phagocytosis and the oxidative burst, as well as T-helper cell differentiation.

Th17 cells and the IL-17 they produce are of decisive importance in defence against mucosal and cutaneous fungal infections: IL-17 stimulates the synthesis of antimicrobial peptides (β -defensins) by epithelial cells and the recruitment of neutrophils; congenital or acquired defects in IL-17 signalling lead to chronic candidiasis [37]. At the same time, excessive IL-17 production aggravates inflammatory tissue damage. IL-10, in turn, is the principal anti-inflammatory regulatory cytokine, and its overexpression may favour fungal persistence and chronicity of the infection [35, 36]. Natural killer cells (CD16+/CD56+) are also described as cells that act directly against fungi and amplify the immune response through cytokines.

Data on the immune status of patients with otomycosis are limited. Viswanatha B. et al. showed that otomycosis runs a more severe course in immunodeficiency [38]. However, cellular immunity, the cytokine profile and their dynamics during treatment in children with otomycosis have hardly been studied. Domestic and foreign authors focus mainly on antifungal therapy, leaving the assessment and correction of immune status aside. Meanwhile, immunomodulatory therapy aimed at restoring the balance of T-helper subpopulations and regulatory cytokines may be a pathogenetically justified way to reduce recurrences.

Discussion

The data analysed allow several key principles of otomycosis treatment to be identified. First, meticulous mechanical cleaning of the ear canal is an essential prerequisite for any drug therapy. Second, topical azoles, especially clotrimazole, have the largest evidence base in terms of efficacy and safety, although their effect depends on the causative species. Third, although antiseptic agents are inexpensive, their use in children is limited by pain and the risk of ototoxicity.

The main drawbacks of conventional treatment methods are the duration of the treatment course (up to 2–3 weeks) and the high recurrence rate. This necessitates the search for additional treatment components. Ozone therapy is capable of simultaneously acting on several pathogenetic links of otomycosis: fungal and bacterial flora, local hypoxia and inflammation,

the epithelial barrier and local immunity. Irrigation of the ear canal with an ozonated solution, combined with mechanical cleaning, provides an antimicrobial effect, is painless and is convenient for use in children.

From an immunological standpoint, the chronic and recurrent course of otomycosis may be associated with impaired cellular immunity and a disturbed Th17/IL-10 regulatory balance. Therefore, incorporating immunomodulatory agents into comprehensive treatment and evaluating immunological parameters as criteria of treatment effectiveness is a promising direction. However, the efficacy and safety of such a comprehensive approach in children must be proven in prospective comparative studies.

Conclusions

1. Meticulous aural toilet and topical azoles constitute first-line treatment of otomycosis; the choice of drug should take into account the causative species and the condition of the tympanic membrane.

2. Conventional treatment methods are characterised by a long treatment course and recurrence rates of up to 15–30%, which calls for the development of new comprehensive approaches.

3. Medical ozone has fungicidal, bactericidal, antihypoxic, regenerative and immunomodulatory effects, and no resistance develops to it; this forms the pathogenetic basis for using ozone therapy in the treatment of otomycosis.

4. The Th17/IL-17 axis, natural killer cells and the IL-10 regulatory system play an important role in antifungal defence; combining antifungal therapy, ozone therapy and immunocorrection is a promising direction in the treatment of otomycosis in children.

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