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# IMPROVEMENT OF DIAGNOSIS AND TREATMENT OF EXUDATIVE OTITIS IN PATIENTS WITH BENIGN NEOPLASMS OF THE NOSE, PARANASAL SINUSES, AND NASOPHARYNX

## MONOGRAPH

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*До настоящего времени диагностика и лечение ЭСО при новообразованиях носа, околоносовых пазух и носоглотки мало изучены. Не учитывается взаимосвязь между заболеваниями, в частности между воспалительными в слуховой трубе и опухолевыми процесссами, их коморбидность. В данной монографии приведены результаты совершенствования методов диагностики и повышение эффективности лечения экссудативного среднего отита у больных с доброкачественными новообразованиями носа, околоносовых пазух и носоглотки путем применения в комплексной терапии локальной иммунокоррекции.*

*Bugungi kunga qadar burun, burun yondosh bo‘shliqlari va burun-halqum o‘smalarida ekssudativ o’rta otitni tashxislash va uni davolash juda kam o'rganilgan. Komorbid holatlar, xususan, eshitish naychasidagi yallig'lanish jarayoni va o'smalar o'rtasidagi bog’liqlik ko’p holatlarda hisobga olinmaydi. Ushbu monografiyada kompleks terapiyada mahalliy immunokorrektsiya orqali burun, burun yondosh bo‘shliqlari va burun-halqumning xavfsiz o'smalari bilan kasallangan bemorlarda diagnostika usullarini takomillashtirish va ekssudativ otitni davolash samaradorligini oshirish natijalari keltirilgan.*

*To date, the diagnosis and treatment of exudative otitis media (EOM) associated with tumors of the nose, paranasal sinuses, and nasopharynx have been poorly studied. The relationship between diseases, particularly between inflammatory conditions in the Eustachian tube and tumor processes, as well as their comorbidity, is not taken into account. This monograph presents the results of improving diagnostic methods and enhancing the effectiveness of treatment for exudative otitis media in patients with benign tumors of the nose, paranasal sinuses, and nasopharynx through the use of local immunocorrection in comprehensive therapy.*

# INTRODUCTION

Exudative Otitis Media (EOM) is a common inflammatory condition of the middle ear characterized by the accumulation of serous-mucous fluid in the cavity behind the eardrum [4; 7; 13]. According to the literature, EOM is most frequently observed in children [2; 25; 37]. However, recent data indicate a rise in the incidence of EOM within the structure of adult otolaryngological pathology [5; 51; 74].

A considerable number of contemporary studies and scientific papers have been dedicated to the issue of EOM among the pediatric population. In many of these studies, the authors agree on the etiology and pathogenesis of the disease, as well as on diagnostic methods and approaches to the treatment and rehabilitation of patients with EOM [15; 37; 45]. In contrast, clinical and epidemiological data regarding EOM in the adult population are rather contradictory, and there is no consensus on the causes of this condition.

Initially, age-related features were not taken into account in the etiology and pathogenesis of EOM. It was believed that the etiology of the disease did not depend on age-related characteristics. This led to the widely accepted view that tubal dysfunction played a primary role among the established causes [4; 12; 13; 38]. The clinical presentation of EOM in adults is ambiguous, treatment outcomes are often unsatisfactory, and the recurrence rate is very high, necessitating deeper investigations into the etiology of this condition.

Recent studies have identified several potential factors contributing to the development of EOM and variations in the clinical course of the disease, depending on the combination and prevalence of these factors [3; 13; 24; 42; 53]. For instance, modern research has significantly broadened the understanding of tubal dysfunction and its importance in relation to the development of this disease. Previously, studies considered only the ventilation function of the Eustachian tube, but several investigations conducted in recent years have provided precise data on the frequency of impaired drainage function [60; 63; 65; 71].

In the pathogenesis of Exudative Otitis Media (EOM), many researchers believe that a combination of inflammatory processes and prolonged tubal dysfunction plays a central role. Analyzing the data presented in the literature, all these etiological factors can be grouped into corresponding categories. For example, certain anatomical features such as nasal architecture (54%) and the structure of the tympanic cavity (53%), as well as a less developed function of the Eustachian tube in dolichocephalics and the wider tube of the left ear compared to the right, are common otological anatomical characteristics in patients with EOM [54; 58; 62; 75; 83].

According to some authors, hyperplasia of lymphoid tissue in the lower poles of the tubal tonsils, the posterior wall of the pharynx, and the root of the tongue can lead to prolonged but often asymptomatic tubal dysfunction. In contrast, hyperplasia of lymphoid tissue in the upper poles of the tonsils is associated with more severe tubal dysfunction and results in a much faster development of EOM [60]. The formation of effusion is caused by lymphostasis in the mucosa of the nose and Eustachian tubes, triggered by a local reaction of the autonomic sections of the pterygopalatine plexus [67].

Some authors argue that the failure of the walls to close and open, as well as the loss of elasticity in the cartilaginous part or excessive dilation of the Eustachian tubes, are primary causes of EOM development as a result of a "lymphoid block" in the retropharyngeal and peritubal spaces [59; 60].

A number of researchers have also examined factors influencing the inflammatory process. According to these studies, the likelihood of developing EOM increases with the severity of general intoxication [64; 65]. Furthermore, the transition from acute otitis media to chronic has been linked to dysfunctions in both systemic and local immunity [2; 26; 28; 47]. Additionally, antibacterial therapy may support chronic inflammation by increasing the resistance of microorganisms to treatment [7; 15; 17; 43].

Research findings regarding the role of allergic factors in the development of EOM are mixed. There is credible evidence supporting the role of inhalant allergens in the development of EOM [59; 67; 76; 80; 76]. However, several studies completely refute such factors. H.A. Preobrazhensky posits that the ear acts as a "shock organ" and that typical exudative otitis media develops in the context of allergies, with allergic edema serving as a cause of effusion formation in the tympanic cavity due to Eustachian tube obstruction [34; 35].

According to many authors, the specificity of the immune response in patients with EOM may influence the inflammatory process [23; 28]. Despite numerous studies on both systemic and local immunity in this patient group, no definitive results have been obtained. These studies not only failed to identify systematic changes but often yielded contradictory and mutually exclusive results, which can be attributed to discrepancies in the research and analysis methods used [73; 86; 98].

### *Immunopathogenesis and Pathophysiology of Exudative Otitis Media*

For decades, numerous studies have focused on describing the mechanisms behind the development of Exudative Otitis Media (EOM). One of the earliest theories was proposed by A. Politzer in 1878, known as "hydrops ex vacuo," which posited that the cause of EOM is linked to factors leading to negative pressure in the middle ear [79]. Additionally, the secretion formation in the tympanic cavity is a consequence of inflammatory processes in the mucous membrane of the middle ear, triggered by various factors [19; 52]. These theories reflect certain links in the unified pathological process underlying chronic middle ear inflammation [8; 25; 59].

The transition of the inflammatory process from the nasopharynx to the pharyngeal opening is accompanied by the spread of inflammation and the development of Eustachian tube dysfunction, leading to impaired drainage from the middle ear [4; 6; 9]. This results in negative pressure and an increase in carbon dioxide concentration in the tympanic cavity [72; 77; 80; 93]. Consequently, an effusion forms in the tympanic cavity, followed by the colonization of bacteria from the nasopharynx. Furthermore, the invasion of microorganisms into the tympanic cavity is also facilitated by impaired ventilation and drainage function of the Eustachian tube, caused by an imbalance between the mechanisms of opening and closing the tube [73; 86; 98].

Increased exudation leads to heightened blood flow intensity, compression of veins, and impaired drainage. The exudate, as a component of the inflammatory response, reduces the concentration of toxins, while antibodies from the serum facilitate phagocytosis, which is supported by the inflammatory reaction and stimulation of leukocyte release at the site of inflammation [34; 35; 59]. In a healthy mucous layer of the middle ear, basal cells predominately exist, alongside non-ciliated secretory cells and, to a lesser extent, ciliated cells with and without secretory granules. The primary role in the nonspecific defense of the middle ear cavity belongs to the Eustachian tube. The mucus produced and the movement of cilia facilitate mucociliary transport, which serves as an effective mechanism for protecting the middle ear cavity [2; 59; 96].

In Exudative Otitis Media (EOM), the inflammatory process in the middle ear typically does not extend to the mucous membrane. The characteristic pathological picture is expressed through edema, hyperemia of capillaries, and leukocyte infiltration of the mucous membrane. Additionally, there is a slightly increased number of goblet cells in the epithelial layer, resulting in the exudate containing a certain amount of mucus. Researchers believe that the combination of these changes leads to significant hyperplasia of the middle ear mucosa. The auditory ossicles lose their mobility due to the accumulated exudate, which, together with the inflammatory changes, leads to a substantial impairment of hearing function. Perforation and the development of transmeatal otorrhea are the results of an increased volume of exudate in the middle ear. This causes increased pressure on the tympanic membrane, which can disrupt microcirculation, leading to trophic and necrotic changes [2; 59; 75; 85; 176].

The immunological element in the study of middle ear diseases, particularly EOM, is central as it is a crucial component. The immune response is a synergistic interaction between the humoral and cellular responses of the immune system to antigenic stimulation. Immunoglobulins of various classes produced by immune-competent B lymphocytes are characteristic features of the humoral response.

In cellular immunity, T lymphocytes play a decisive role. Their subpopulations, such as killer cells, helper cells, and memory cells, are categorized based on their mechanisms of action and participation in immunity. Cytotoxic T lymphocytes can induce lysis of the membranes of target cells. Under the influence of T helpers, B lymphocytes participate in proliferation and differentiation when activated by antigens [86; 96].

"Local immunity" refers to a set of protective adaptations that safeguard the body from the external environment and is specific to the mucous membranes and skin. This complex also includes nonspecific defense mechanisms, such as the mucociliary system and the synthesis of active proteins like properdin and interferon [2; 86; 98]. Modern immunology typically defines this type of local immunity as special reactions involving local lymphoid tissue, such as infiltrates of lymphoid and plasma cells, and localized aggregates of varying density in the mucous tissue [96].

Studies of the morphology, histology, and immunomorphology of the middle ear mucosa have supported and refined the concept of immune protection in the middle ear, which was initially based on the detection of exudates in various forms of otitis media. The mucociliary system of the middle ear mucosa is viewed as one manifestation of the synergy between specialized and nonspecific protective mechanisms [86; 94].

To describe the immunopathogenesis of Exudative Otitis Media (EOM), it is currently proposed to categorize immune damage based on four types of immunopathological reactions. If there is an elevated concentration of IgE in the middle ear secretions, this suggests immediate-type hypersensitivity, also known as Type I. Cytotoxic reactions can be observed in patients with tympanosclerosis (Type II). The presence of immune complexes in the exudate of secretory otitis media indicates that these complexes were synthesized in the presence of complement of Type III. A significant number of T cells in the mucoid exudate indicates delayed-type hypersensitivity (Type IV) [95; 97].

According to this interpretation, the hypersensitivity hypothesis distinguishes between a specific immune stage and a nonspecific inflammatory stage of immune inflammation. The development of the immune response occurs simultaneously with the action of tissue resistance mechanisms, which are not specific to the given tissue. This particular form of immune response is associated with the production of secretory antibodies, which are responsible for the protective action of epithelial secretions [94]. Laboratory analyses of exudate from the middle ear in cases of EOM have shown the presence of secretory immunoglobulins. The identification of antibody-producing cells in the lymphoid-plasmatic infiltrate [94; 95] supports the hypothesis that the mucous membrane of the middle ear is responsible for the local production of immunoglobulins.

It is well known that inflammatory diseases occurring in the middle ear are characterized by the accumulation of exudate composed of soluble and insoluble components. Soluble components are similar to those found in blood serum, while insoluble components consist of carbohydrate glycoproteins associated with proteins, akin to mucins. The exudate may also contain various inflammatory cells involved in the immune defense of the middle ear against infection. These cells include leukocytes, lymphocytes, and monocytes, as well as various oxidative and hydrolytic enzymes of lysosomal origin, complement and its fractions, inflammatory mediators, protease inhibitors, and antibacterial and antiviral antibodies—immunoglobulins [40].

Neutrophils, monocytes, macrophages, and lymphocytes are the most common types of inflammatory cells found in the exudate of patients diagnosed with EOM [94]. Eosinophilic leukocytes are less frequently observed in individuals with EOM. The variations in the cellular composition indicate that EOM is an active process, characterized by changes in the cellular makeup of the exudate that vary depending on the phase of inflammation. The presence of exudate suggests either a proliferative phase or chronic progression of the disease. Changes in the proportions of inflammatory cells present in the exudate associated with EOM have been linked to immunological processes that affect the nature and progression of the inflammatory response [98; 99].

All of this information points to an increase in both specific and nonspecific resistance of the mucous membrane and its epithelial covering in the middle ear and Eustachian tube. As a result of EOM, there is a marked increase in the number of secretory cells in the epithelial lining, an expanded capillary network, and heightened enzymatic and immunological activity of the covering epithelium and lymphoid cells, along with a significant increase in cell proliferation in the subepithelial layer [50; 100].

The presence of immunoglobulins in the exudate of the middle ear, with concentrations significantly higher than those in blood serum, is another indicator of the proper functioning of the local immune system. The concentration of immunoglobulins in the middle ear exudate is notably higher than in serum. In patients with EOM, the level of specific immunoglobulins, particularly IgA, increases, while levels of IgM and IgE remain stable. The duration of the disease correlates with an increased likelihood of detecting IgA in the middle ear exudate. Additionally, there is a correlation between increased secretion viscosity and the frequency of IgA presence [97; 98].

Studies on the morphology, histochemistry, and immunology of the middle ear mucosa confirm the existence of immune protection mechanisms in this area. The mucociliary system of the middle ear mucosa serves as the site for both specific and nonspecific protective mechanisms responsible for local immune responses [86; 94; 95].

According to a review of the relevant literature, the immunopathogenesis of EOM remains incompletely understood and requires further investigation. To address this issue, studies of local immunopathological processes occurring at the level of the middle ear mucosa are necessary.

## *Classification and Clinical Characteristics*

As of today, exudative otitis media (EOM) is classified based on the duration of the disease into three periods: acute (up to 3 weeks), subacute (from 3 to 8 weeks), and chronic (over 8 weeks) [57].

There are numerous classifications for the stages of EOM development that take into account the pathogenesis of the disease. According to Tos M. (1980), EOM is divided into primary, secretory, and degenerative stages. Additionally, there are classification variants that are based on similar principles, with differences mainly in establishing treatment strategies for patients according to the disease stage [7; 8; 15]. In this classification, four stages are distinguished: catarrhal (lasting up to 1 month), secretory (from 1 to 12 months), mucoid (from 12 to 24 months), and fibrous stages (over 24 months).

In contrast to the previous classification, the one proposed by Stratieva O.V. et al. distinguishes between the initial exudative stage, pronounced secretory stage, productive secretory stage, and degenerative-secretory stages. It should be noted that the clinical picture of EOM largely depends on the intensity of the inflammatory process and the specific pathological manifestations, which also divide the disease into three clinical stages [14].

In the first, brief stage, there is transudation and the migration of a small number of neutrophils and leukocytes, along with the death of some epithelial cells; secretory cells show readiness to secrete mucus. Clinical symptoms are mild: the ear feels slightly blocked, the eardrum appears thin and gray with injected vessels, and bubbles of air are occasionally seen in the tympanic cavity. The transition from the tubal stage to the secretory stage occurs with the appearance of liquid contents in the tympanic cavity.

The second, secretory stage is characterized by mucus secretion and accumulation, along with the development of mucosal hyperplasia. Clinically, it presents with feelings of fullness and pressure in the ear, dizziness, occasional tinnitus, and slight hearing loss. The eardrum appears grayish, thickened, and retracted, and there may be persistent hyperemia of the skin in the ear canal around the fibrous ring. Tubal function is impaired. This stage gradually progresses to the terminal, or degenerative stage [14; 55].

During this stage, mucus accumulation in the middle ear decreases due to impaired mucociliary function of the epithelial mucosa. The number of goblet cells decreases, and the inflammatory process subsides. Following the resolution of tubal dysfunction, the middle ear gradually clears of mucus. By the end of the sixth month, spontaneous recovery occurs in approximately 70% of patients with untreated EOM [31; 52; 78]. In about one in ten patients with untreated secretory otitis media, the disease may transition into a chronic condition. In cases of tubal dysfunction, any infection may lead to the formation of a perforation in the eardrum [45; 46].

The clinical history of EOM is also characterized by a prolonged course of the disease and frequent exacerbations of the inflammatory process, during which mucous or mucopurulent discharge occurs. Both of these characteristics are associated with the long duration of the condition. However, during such exacerbations, most patients do not experience any discomfort in the ear or any systemic reactions. Gradually, patients begin to develop hearing loss, characterized by fluctuations that depend on the accumulation of exudate in the labyrinth and the functional state of the Eustachian tube. This occurs despite an overall benign background. EOM is associated with a significant degree of hearing loss when the disease is prolonged [16; 19; 20].

Conductive hearing loss is characterized by a reduction in sound conduction due to negative pressure, thickening of the eardrum, perforation of the tympanic membrane, accumulation of mucus, or fibrous fixation of the auditory ossicles. Sensorineural hearing loss in EOM is primarily caused by toxic products of inflammation and microbial decay entering the inner ear through the secondary membrane, hypoxia of the cochlea, effects on cochlear microcirculation, and ototoxic medications [59; 101].

With the prolonged course of otitis media, fibrosis and destruction of the ossicular chain occur, leading to obliteration of the tympanic cavity, irreversible cochlear anomalies, and the development of cholesteatoma. The longer EOM persists, the more severe the consequences related to fibrosis become [5; 7; 8; 10].

Thus, EOM has several stages of development, and fibrosis, proliferation, and inflammatory exudation are subsequent stages in the progression of this pathology.

### *Modern Treatment Methods for Exudative Otitis Media (EOM)*

Currently, the primary approach to treating individuals with EOM is to eliminate the causes of Eustachian tube dysfunction. This method is often combined with additional treatments aimed at restoring hearing and preventing long-term changes in the structure of the middle ear. The main objectives of treatment for uncomplicated EOM should be the removal of exudate, restoration of hearing, and disease prevention [7; 25; 29]. Early treatment of EOM is a crucial factor determining its effectiveness. Depending on the type of pathogen, therapies such as desensitization or antibacterial treatment may be prescribed. Concurrently, patients are given procedures aimed at restoring aeration of the tympanic cavity, improving Eustachian tube function, and removing pathological material from the middle ear spaces. Depending on the stage and type of the disease, either conservative or surgical therapy may be appropriate [31; 52; 69].

Conservative treatment methods are often quite successful for patients in the first stage (catarrhal stage) of exudative otitis media. Upper respiratory tract sanitation is one method that can be used during the first stage of EOM. If surgical intervention is necessary, audiometry and tympanometry are performed one month after the procedure. If hearing loss persists and a type C tympanogram is obtained, measures are taken to address Eustachian tube dysfunction. With timely initiation of treatment in the catarrhal stage, quick recovery is possible. The procedure continues into subsequent stages, even if therapy is not conducted [14; 31].

In the second stage, known as the secretory stage, in addition to non-invasive treatments such as antibiotics and steroids (if they have not been previously used), surgical procedures are employed, including tympanocentesis, myringotomy with tympanostomy, and upper respiratory tract sanitation. The stage of exudative otitis media is clarified intraoperatively [14; 31].

In the third (mucous) and fourth (fibrous) stages, conservative therapy is generally ineffective; moreover, myringotomy does not always successfully remove thick exudate. Treatment methods include tympanostomy in the anterior sections of the tympanic membrane, insertion of ventilation tubes, simultaneous sanitation of the upper respiratory tract along with tympanostomy, irrigation and removal of exudate from all sections of the tympanic cavity, tympanotomy with revision of the tympanic cavity, and tympanostomy with revision of the tympanic membrane. Thick exudate cannot be effectively removed with tympanostomy alone, necessitating a one-step tympanotomy. In the fourth stage, the tympanic cavity is re-examined, and tympanosclerosis foci are removed [31; 52].

Non-medication treatments for EOM include Eustachian tube inflation, also known as Politzer inflation, Eustachian tube catheterization, and the Valsalva maneuver [56]. This can create a massage effect on the tympanic membrane by inflating the middle ear [7]. Contributors to the International Practical Guidelines [71; 86], maintain that self-inflation should be prescribed in addition to other available options. Internal electrophoresis as part of physiotherapy, combined with steroid hormones and proteolytic enzymes, may also be beneficial [73; 89]. Additionally, electrical stimulation of the muscles of the Eustachian tube can positively affect EOM treatment by stimulating the evacuation of secretions, thereby restoring Eustachian tube function.

Medication is also recommended in the treatment of exudative otitis media. There are circumstances in which the use of antibiotics is warranted. Inflammation of the middle ear associated with EOM is sterile in more than half of cases, while in others, various microorganisms are isolated from the exudate. The same sequence of antibiotics is used for treating both chronic and acute otitis media. Antibiotics remain a controversial topic in the treatment of EOM, with their effectiveness reported at only 15%. Adding glucocorticoids to the treatment regimen (for 7-14 days) improves therapeutic outcomes by just 25% [73]. However, the vast majority of researchers in other countries agree on the appropriateness of using antibiotics.

Before starting conservative treatment for EOM, it is essential to assess the need for immediate therapy and to conduct a follow-up evaluation after one month. This is a prerequisite for treatment. To achieve this goal, threshold audiometry and acoustic impedance audiometry are used [20; 21].

Immunomodulators, such as Imudon, Polyoxidonium, and IRS-19, are beneficial in the early stages of the disease [31]. Research has shown that Betaleukin is effective in treating individuals with chronic otitis media. According to studies, Betaleukin is an active immunomodulator that has a positive effect on improving immunological parameters and stimulating the immune system of the mucosa. However, it does not possess high antibacterial effectiveness and does not influence the microflora of the middle ear [6; 70; 71].

Due to a lack of reliable clinical studies worldwide on the relative effectiveness of various treatment methods, the question of effective therapy for exudative otitis media remains contentious.

The effectiveness of using immune-active and immune-modulating agents, according to conducted research, remains promising [94]. This underscores the importance of investigating the processes of local immune response in the middle ear. Treatment for exudative otitis media should focus not only on eradicating identified microflora but also on restoring the mucosa. Therefore, we believe that a combined approach utilizing foundational therapy alongside immunocorrective agents represents the best treatment method.

Any disease inevitably leads to an imbalance in the functioning of the immune system [15; 26; 28]. Various ENT disorders are associated with immunological deviations that require correction, including allergic conditions, tumor processes, and both chronic and acute inflammatory pathologies. In the practice of otorhinolaryngologists, immunological issues are also recognized in chronic and acute inflammatory diseases, which arise against a backdrop of weakened local anti-infective defenses [68; 99]. From an immunological perspective, almost all ENT organs share a similar level of specificity. As these organs interact with the surrounding environment, they primarily serve two significant roles: that of an informant and a barrier [57]. Pathogenic material on the surface of the epithelial layer must first be neutralized and then removed for the barrier function to be successfully completed. When a foreign substance penetrates the epithelium and reaches the subepithelial space, processes are initiated that isolate this area and lead to its destruction.

Several key components contribute to the protective role of the mucous membranes lining the respiratory system. The first mechanism is mechanical, preventing the entry of pathogenic elements into the subepithelial layer of epithelial cells that are not yet damaged. Secondly, epithelial cells are part of the mucociliary system, which, when functioning properly, directs the removal of harmful factors from the surface of the mucous membranes, primarily toward the nasopharynx [59; 60]. Goblet cells produce mucus, synthesizing substrates that envelop foreign particles, allowing them to be trapped within the mucus. The cilia of columnar epithelial cells are responsible for directing the mucus flow appropriately. Thirdly, damaged epithelial cells, upon completing their biological role, are shed, carrying foreign substances with them. Lastly, epithelial cells play a direct role in the development of local immunity, containing a secretory component of immunoglobulin A (IgA). These cells act as sites for the fixation of the secretory component of the antibody after its production, slowing the degradation of antibodies on the mucosal surface, thus creating a more effective antiviral barrier [69; 78].

Mucous membranes are significantly protected by colonization immunity, which plays a crucial role in this process. Normal flora residing on the surfaces of mucous membranes competes with pathogenic bacteria, constantly activating local immunity through the enzymes they produce and the use of fragments from destroyed cells, effectively acting as natural stimulators [26].

There are protective elements that have both humoral and cellular characteristics. Up to 80% of the total cell count in the blood comprises cellular components that contribute to the innate immune response. These primarily include segmented neutrophils, eosinophils, and basophils, as well as monocytes and CD16+, CD56+ natural killer cells. They provide the first line of defense at the mucosal surfaces along with secretory IgA and other humoral components, such as the complement system and acute-phase inflammatory proteins [86; 87; 94]

Despite reliable mucosal protection reducing the risk of disease, immunological issues are the most common cause of recurrent acute inflammation and the progression of disease to a chronic form.

Noticeable local immune responses can occur even in healthy individuals, as the mucosa of the upper respiratory tract constantly reacts to changes in the environment. It is reasonable to assume that adaptive activation, adaptation stages, and pre-morbid de-adaptation are linked to the function of local immune defense factors[84; 94]. Research findings indicate that secondary immunodeficiency states predominantly occur locally in viral and inflammatory diseases of the ENT organs [27; 28; 87].

Changes in the numbers of neutrophils, macrophages, and eosinophils are external manifestations of a unique pre-morbid adaptation triggered by imbalances in the local immune system. This response is characterized by decreased functional qualities of phagocytes, specifically a reduction in the phagocytosis of auto-flora, and an increase in damaged phagocytes with incomplete phagocytosis. Lower levels of antibodies and decreased complement concentrations in the secretions are signs of a condition known as humoral deficiency. This state of inactivity is often accompanied by a deficiency in the production of pro-inflammatory cytokines, which is one of the factors contributing to the chronic nature of the disease [94; 82].

All of this explains the necessity of justifying a logical medication strategy aimed not only at eradicating the microbe causing the disease but also at restoring the immune system to its baseline state.

The effects of locally applied immunomodulators such as prodigiosan, pentoxyl, levamisole, diucifon, autoserum, and methyluracil are well documented [18; 29; 32]. Research on local immunomodulatory drugs has been ongoing for quite some time. Physical elements, such as magnetic fields and ultrasound, are part of a separate set of local effects that, among other things, help stimulate antibody production and activate protective cellular mechanisms [68].

In this context, it is important to note a study conducted on the use of topical immunomodulatory therapy in acute cases of middle ear inflammation [56]. The use of a mucosal vaccine (IRS-19) led to an increase in both natural specific immunity and nonspecific mucosal responses, stimulating the production of secretory IgA in the nasal cavity and nasopharyngeal mucosa, enhancing the phagocytic activity of macrophages, and increasing levels of endogenous interferon and lysozyme. All these benefits can be attributed to the mucosal vaccine. After therapy with IRS-19, patients no longer exhibited clinical signs of acute otitis media, and the impaired function of the Eustachian tube was restored much more quickly. Endonasal administration of IRS-19 had an immunomodulatory effect specifically on the mucous membranes of the upper respiratory tract [53]. Essentially, this method can be conditionally termed topical immunotherapy, as the immunomodulatory effect of IRS-19 was limited to the mucous membranes of the upper respiratory tract.

It is known that in 86% of cases, adenoids are the cause of exudative otitis media in children, while in adults, the predominant factors include nasal breathing disorders, hypertrophy of the tubal cushions, immunological disorders, and tumors of the nasopharynx and paranasal sinuses [11; 14; 33; 36; 86; 88].

Surgical correction of conditions causing obstruction of the pharyngeal orifice of the Eustachian tube is often a straightforward process. On the other hand, the more complex aspects of treating exudative otitis media in adults are related to immune system diseases [23; 28; 86; 87; 94; 96].

Based on the findings of the conducted study, it can be concluded that improving both general and local immunity—critical components in the pathogenesis of exudative otitis media in adults—will enhance the effectiveness of therapy for this condition.

Immunotropic drugs are those whose therapeutic effect results primarily from their selective action on the immune system [57; 81; 87].

The impact of immunotropic drugs on various components of the immunological and nonspecific defense system allows them to be categorized into three distinct groups: stimulating, inhibiting, or compensating the immune system. Immunotropic drugs can be either biogenic or chemically synthesized, depending on the method of production. Biogenic immunotropic drugs may also be chemically synthesized.

Immunomodulatory drugs are designed to restore the levels of physiologically active substances that have been depleted in the body (e.g., interferons, cytokines, and antibodies). According to recommendations, this medication should be administered no earlier than three days after the onset of the disease, as it does not affect the natural immune response process. Immunosuppression is advised not only in the early stages of the disease, particularly in allergic (atopic) variants, but also in later stages of autoimmune processes to stabilize and prolong the remission period. This is due to the fact that immunosuppression suppresses the immune system's ability to respond. Immunostimulation is conducted later, once the immune system has regained its ability to react to further stimulation and has had sufficient time to recover [73; 90].

The second category of drugs that provide stimulating or, rather, immunomodulatory effects—normalizing the markers of immune defense—is of particular interest to otolaryngologists [23; 28; 87; 94; 96]. These drugs specifically stimulate the immune system. It is widely accepted that immunomodulators are drugs with immunotropic action that, when taken in therapeutic doses, help restore immune system function. Secondary immunodeficiency states caused by viral and inflammatory diseases can be treated with these drugs, which can be used as corrective measures. The application of immunotropic drugs requires a clear and reliable immunological examination during the ongoing therapy. This examination should clearly and reliably demonstrate the presence of immunodeficiency [91; 92].

Given the significant prevalence of secondary immunodeficiencies in ENT diseases, it is evident that their complex treatment will necessitate immunocorrection. As an example of immunocorrection in the treatment of otitis media, it is worth mentioning the study of the clinical-immunological effectiveness of sodium nucleate in patients with secretory otitis media. It has been established that the use of sodium nucleate at the systemic level contributes to the correction of immunological disorders and the achievement of clinical remission [86; 96].

In patients with chronic purulent otitis media, the combination of leukinferon and myelopid administered in the postoperative period can effectively eliminate the initial defects in the T and B cell immune response, leading to improved clinical outcomes and a reduction in hospital stays [86; 87].

Thus, immunopathological processes play a significant role in the pathogenesis of exudative otitis media (EOM), and the application of immunotropic interventions targeting key components of EOM pathogenesis is justified. However, published studies in recent decades lack sufficient data on the effectiveness of local immunocorrective therapy for EOM.

# METHODS FOR RESEARCHING PATIENTS WITH EXUDATIVE OTITIS MEDIA

## *General Characteristics of Patients with Exudative Otitis Media*

This study is based on the results of examinations and comprehensive treatment of 103 patients with exudative otitis media (EOM), aged from 11 to 82 years, who sought care at the Otolaryngology Department of the 1st Clinic of Samarkand State Medical Institute from 2018 to 2021, along with 20 healthy individuals.

The patients were divided into three groups: 55 patients with EOM associated with benign neoplasms of the nose, paranasal sinuses, and nasopharynx formed the first main group; 48 patients with EOM associated with chronic rhinosinusitis formed the second comparison group; and 20 healthy individuals made up the control group.

The following selection criteria were used for the patients in our study:

1. Clinical Data: Complaints of hearing loss, tinnitus, a sensation of ear fullness, a feeling of "liquid sloshing" in the ear, and autophony.
2. Otoscopy Data: Changes in the color of the tympanic membrane, opacity, retraction or bulging, presence of fluid levels, and air bubbles in the tympanic cavity.
3. Hearing Impairment: Diagnosed through pure tone audiometry.
4. Pathological Tympanogram Type: Type B.

## *Methods for Investigating Patients with Exudative Otitis Media*

All patients in the aforementioned groups underwent audiological, otolaryngological, and laboratory investigations.

The comprehensive otolaryngological examination included: a classic ENT examination, detailed collection of complaints and medical history, otomicroscopy, evaluation of Eustachian tube function, and tuning fork tests.

Traditional otoscopy does not allow for a detailed examination of the tympanic membrane [57]. In our study, we utilized endoscopic examination with a Suntem (China) ENT apparatus, as well as rigid endoscopes with diameters of 4.0 mm and 2.7 mm with a 0° angle of view (Delon, Germany) to study the fine features and details of the anatomical structure of the tympanic membrane in both normal and pathological conditions, as well as to perform mobility tests. After connecting the endoscope, an enlarged image of the tympanic membrane was displayed on the monitor. The LED 300 computer system (Delon, Germany) was used for archiving photo and video data ( Fig. 1).

**Figure 1. ENT Combination Unit by Suntem (China) with LED 300 Computer System (Delon, Germany)**

In classical methodology, the evaluation of Eustachian tube function is conducted through a series of inflation tests, followed by listening to the sounds of passing air. Each of the five methods is performed sequentially:

1. First Degree of Eustachian Tube Patency: Test with an empty swallow (if the Eustachian tubes are patent, a "crackling" sensation is felt in the ears).
2. Second Degree: Known as the Toynbee maneuver: the patient swallows while pinching their nostrils. The patient applies pressure on the nasal septum with their nostrils and swallows (if the Eustachian tubes are well-patent, a "crackling" sensation is felt).
3. Third Degree: Valsalva maneuver: the patient bears down while pinching their nostrils. The patient takes a deep breath, closes their nose and mouth, then forcefully exhales, sending air into the Eustachian tubes. A "crackling" sensation is felt if they are well-patent.
4. Fourth Degree: Politzer method, using a Politzer bag, which is a rubber bulb (300-500 ml) with a tube. The nozzle is inserted into the nostril, and the other wing is pressed against the septum. While pronouncing certain words (like "train" or "peek-a-boo"), the bulb is squeezed vigorously, allowing air to enter the Eustachian tubes and nasopharynx.
5. Fifth Degree: In this method, the Eustachian tubes are inflated using an ear catheter.

In clinical practice, five degrees of Eustachian tube patency are utilized and assessed using the aforementioned methods. Patency is rated as the first degree if all tests are passed. The tubes are considered obstructed at the fifth degree if positive results are only obtained through catheterization. The main drawbacks of this method are its subjectivity and the inability to provide quantitative data on tube patency changes. However, due to its accessibility and ease of execution, it is widely used in practice to assess the functional and physiological state of the Eustachian tubes [11].

In the classical methodology, tuning fork tests are conducted using a standard set of tuning forks: C – 128, C – 512, C – 2048, and C – 1024.

### *Method of Pure Tone Audiometry in Patients with Exudative Otitis Media*

The sensitivity level of the auditory analyzer is represented by an audiogram. The arrangement of the lines on the audiogram serves as the primary criterion for conducting a differential diagnosis of the type of hearing loss. A tonal audiometer, using both air and bone conduction, allows for the determination of hearing thresholds across a wider range of frequencies and with greater accuracy compared to hearing tests conducted with tuning forks. Pure tone audiometry is a method used to assess an individual's auditory perception or the faintest sound that a person can hear [57].

Pure tones, also known as sinusoidal sounds with a constant frequency, are utilized by modern audiometers to check threshold sensitivity. Depending on the manufacturer, the frequency range of these signals can vary from 125 Hz to 8000 Hz. The obtained results are recorded in the form of an audiogram, where the horizontal axis indicates the signal frequencies and the vertical axis represents the hearing thresholds.

Hearing thresholds via air conduction are first established at a frequency of 1 kHz for the better-hearing ear. Following this, thresholds are determined at higher frequencies, specifically in the range of 2 to 8 kHz, and at lower frequencies, particularly in the range of 0.5 to 0.125 kHz. The threshold for the poorer-hearing ear is then established. If necessary, the better-hearing ear is masked. Similarly, thresholds for bone conduction are determined. If the difference between the air conduction thresholds of the tested ear and the non-hearing ear is 40 dB or more, the better-hearing ear needs to be masked to accurately interpret the test results. If the difference between the hearing thresholds of the tested ear and the non-hearing ear is 5 dB or more, masking is also required for assessing the bone conduction threshold. Bone conduction testing is performed using a vibrator placed on the mastoid process across frequency ranges of 250 to 8000 Hz [59; 52].

An important test during the audiological examination is the reliability of measuring the air-bone gap, which involves clearly identifying the difference between the thresholds for air and bone conduction. The size of this gap directly influences both the treatment strategy and the prognosis of the outcome [59; 52].

In this study, pure tone audiometry was conducted using a 2-channel **audiometry device, "Neuro-Audio" (Russia) (Figure 2).**

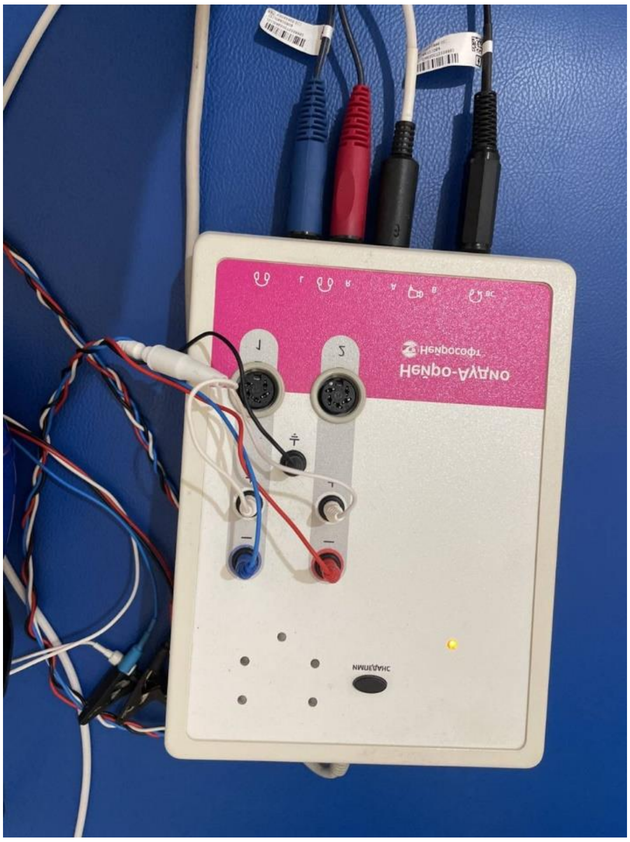


**Figure 2. Audiometer "Neuro-Audio" (Russia)**

In our study, we investigated:
- Measurement of the air-bone gap;
- Hearing thresholds measured via air and bone conduction.

For pure tones, the hearing threshold was calculated as the arithmetic mean of the air conduction thresholds at frequencies of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. The air-bone gap is computed by subtracting the arithmetic mean of the four aforementioned air conduction frequencies from the values obtained for bone conduction [125].

**Table 1.**

**Degrees of Hearing Loss According to International Classification**

| Degree of Hearing Loss | Normal | First | Second | Third | Fourth | Deafness |
|---|---|---|---|---|---|---|
| Perception Threshold (in decibels, dB) | 0-25 dB | 26-40 dB | 41-55 dB | 56-70 dB | 71-90 dB | 91 dB and above |

Table 1 presents the classification of hearing loss used in this study. This classification was created based on average sound perception threshold values [82; 122].

### *Tympanometric Studies of Patients with Exudative Otitis Media*

Tympanometry, also known as impedance audiometry, is a diagnostic method used to assess disorders of the middle ear and tympanic membrane. This method allows for the registration of changes in the conductivity of the middle ear system during an artificially created pressure difference in the external auditory canal of the patient. The device consists of a pump, a probe with amplifiers, a microphone, and a pressure sensor. Sound from the probe is continuously delivered to the ear through the probe's amplifiers, and the acoustic perception of the ear is evaluated by monitoring the sound pressure level of the probe's sound in the ear canal using the probe's microphone.

Under optimal listening conditions, a small portion of the sound energy is reflected off the tympanic membrane. However, under unfavorable conditions, a significant portion of the delivered sound is reflected back into the probe's microphone.

There are three main properties that affect the response to incoming sound: stiffness, mass, and friction. The sound frequency function is determined by the mass and stiffness components, and the higher the frequency of the sound, the greater the resistance of the mass. The vibration of the tympanic membrane occurs as a result of sound wave interactions with the membrane. Some sound waves are reflected from its surface, while others pass through the tympanic membrane. The sound waves that reflect off the tympanic membrane are phase-shifted and decrease in amplitude. The stiffness component has an inverse relationship with the frequency of the sound waves. The stiffness of the vibrational system determines the nature and magnitude of the phase shift. Information about the acoustic resistance of the tympanic membrane is obtained by measuring the intensity and phase shift of the reflected sound waves from the tympanic membrane.

The tension in the tympanic membrane, as well as in other structures of the middle ear (ligaments, ossicles, and muscles), creates overall impedance. Additionally, the tension of the fenestration membrane of the cochlea and the annular ligament of the stapes is of great significance. Acoustic resistance from the fluids and tissues of the inner ear also contributes to the overall impedance.

In this study, the analysis of tympanograms utilizes the classification by J. Jerger [105; 120] (Figure 2.3). Under normal conditions, the tympanic membrane has minimal stiffness and maximum acoustic conductance. This is due to equal atmospheric pressure and pressure within the tympanic cavity. Typically, the pressure in the external auditory canal, particularly in its occluded part, varies in the range of -400 to +400 mmHg.

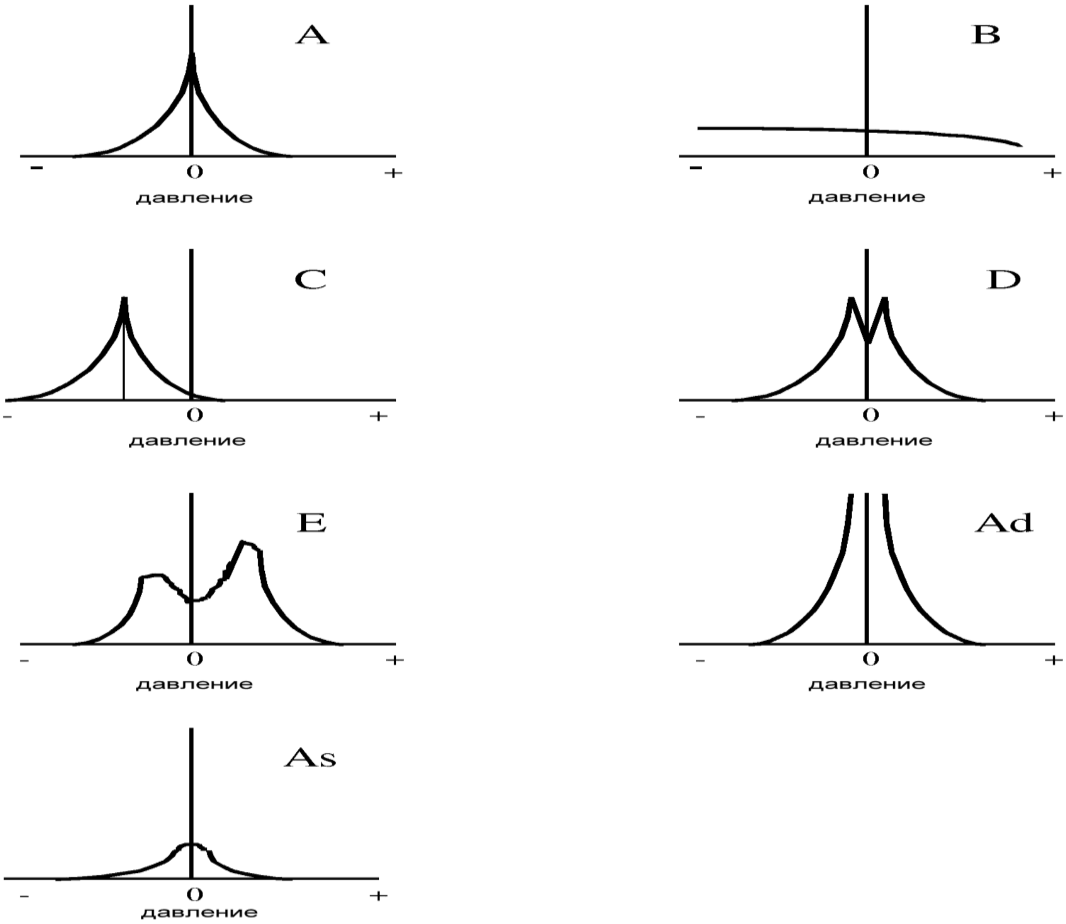



**Figure 3. Types of Tympanograms According to J. Jerger Classification**

During tympanometry, acoustic conductance decreases to levels of air acoustic conductance. This results in a symmetrical curve, with the peak corresponding to the pressure in the occluded part of the external auditory canal. According to J. Jerger's classification, this curve is labeled "A," while all other tympanogram types are considered pathological.

The tympanometric curve labeled "C" is recorded in cases of ventilation impairment in the middle ear. In this type of tympanogram, the peak shifts toward negative pressure, which is associated with minimal stiffness of the tympanic membrane and maximum acoustic conductance. The degree of negative pressure in the middle ear cavities can be determined by observing the peak's position on the tympanogram relative to the abscissa axis [108, 109].

When the middle ear cavities are filled with exudate, the tympanogram changes according to J. Jerger's classification and is designated as "B." This condition can be caused by the accumulation of fluid without pronounced inflammatory changes, as well as acute otitis media.


**Figure 4. Clinical Tympanometer "MA1CO" M1 24 (Germany)**

A horizontal tympanogram curve of type "B" is recorded when the stiffness of the tympanic membrane does not change in response to pressure variations in the occluded part of the external auditory canal. Conversely, in cases of adhesive otitis media, a type "B" curve can also be observed. In this condition, changes in the stiffness of the tympanic membrane caused by pressure changes in the occluded part of the external auditory canal cannot occur, as the tympanic membrane is pressed against the medial wall of the middle ear.

It is more likely that type "C" will be characterized by retraction of the tympanic membrane, a reduction in the light reflex, and darkening of the tympanic membrane. These three features also suggest that there may be a correlation between the tympanogram and otoscopic findings. Additionally, opacity, thickening, and cyanosis of the tympanic membrane, as well as the absence of the light reflex and transparent exudate, are associated with a type "B" tympanogram.

Tympanometry was performed using the clinical tympanometer "MA1CO" M1 24 (Germany) (Figure 4).

## *Bacteriological Methods for Investigating Patients with Exudative Otitis Media*

Isolation of a pure culture of the pathogen is conducted to determine optimal treatment or to adjust already initiated empirical therapy (19; 57). In our study, we collected samples from the posterior part of the nasal mucosa and samples obtained during tympanocentesis. The skin of the external auditory canal was always pre-treated with an antiseptic solution to avoid contamination of the swab with saprophytic microflora.

Immediately after collecting the pathological material, inoculation was performed using a bacteriological loop on dense culture media (MPA) in Petri dishes. The cultures were incubated for 24-48 hours at 37 °C in an incubator.

To count the number of colonies of each species, the grown colonies of microorganisms were examined using macroscopic and microscopic methods. At the next stage, pure cultures of microorganisms were isolated on slanted agar. Subsequently, specific diagnostic systems were used for the precise identification of the microorganism. The isolated pure cultures were then tested for antibiotic susceptibility.

### *Immunological Methods for Studying Patients with Exudative Otitis Media*

In addition to the standard clinical examination, all patients were analyzed for immunological parameters before and after treatment on day 21.

In this study, we determined the levels of certain classes of immunoglobulins in serum and lymphocyte subpopulations using the radial immunodiffusion method according to Mancini. Immunofluorescence was employed to obtain specific cell counts, including CD3+ (T-lymphocytes), CD4+ (T-helper cells), CD8+ (suppressor T-cells), and CD19+ (B-lymphocytes).

At the beginning of the test, following local anesthesia, a sample of transtympanic exudate was extracted from the patient's tympanic cavity. This study aimed to evaluate the level of local immunity. The amounts of immunoglobulin classes present in the collected sample, as well as its cellular composition and protein content, were examined. A volume of 0.5 ml of exudate was centrifuged at 4 degrees Celsius and 2000 rpm for 15 minutes. After a single thawing, aliquots of 0.2 ml were frozen at -20 degrees Celsius to determine 0.05 ml of immunoglobulins and 0.2 ml of total protein. Following the centrifugation step, the pellet was resuspended in 0.1 ml of liquid. The remaining portion of the sample, 0.05 ml, was used for the NBT test. The precipitate was used to obtain a smear, which was then examined to determine the cellular composition and the level of epithelial cell damage. Since there was no exudate in the tympanic cavity at the end of the treatment, a repeat indicator test was not performed.

For the quantitative determination of immunoglobulins, test serum extracted from the middle ear was placed into wells in an agar layer with monospecific antisera against various immunoglobulin classes. Under standard conditions, the diameter of the precipitation ring is proportional to the concentration of the immunoglobulin being tested [53].

Glass plates were coated with a mixture of monospecific antisera and an agar layer. To prepare this mixture, the specific type of antisera was mixed with 1-2% agar in Veronal-Medinah buffer at 56°C. Wells approximately 2 mm in diameter were punctured in the agar layer containing the antisera, spaced 15-25 mm apart. In the first series of wells, 2 μl of standard serum at various dilutions was added, followed by the addition of test liquids in subsequent wells.

At the end of the incubation period, the diameter of the secretion rings on the plates was measured after incubation with IgM antisera at room temperature in a humid environment for 24 or 48 hours. To determine lymphocyte subpopulations, mononuclear cells were isolated from venous blood with the addition of heparin by centrifugation in a gradient of 1.077 g/ml (Ficoll-Hypaque - Pharmacia, Sweden). They were then washed twice through single centrifugation in Medium 199, resuspended, and concentrated to 2 million/ml.

Twenty microliters of monoclonal antibodies specific for CD3+, CD4+, CD8+, and CD19+ were mixed with 20 µl of the lymphocyte suspension and incubated for 30 minutes at 37 °C. Afterward, 1 ml of Medium 199 was added to the test tube and centrifuged at room temperature for 5 minutes. The supernatant was discarded, and 20 µl of the second antibody labeled with FITC was added. This mixture was then incubated in the refrigerator for 30 minutes at 4 °C. The results were counted under a fluorescent microscope with a magnification of 90x10 after pelleting the cells by adding 20 µl of glycerol.

### *Laboratory Investigation of Middle Ear Exudate Composition in Patients with Exudative Otitis Media*

The cellular sediment used for preparing smears was obtained by centrifuging middle ear exudate at a speed of 1000 rpm for ten minutes at +4 degrees Celsius. The collected sediment was diluted with 0.1 ml of solution, a smear was prepared, air-dried, and then fixed in ethanol for 10-15 minutes. The smear was stained using the Romanowsky-Giemsa method for 15 minutes, and finally, the sediment was air-dried. For microscopy, a light microscope equipped with an immersion objective and set to a magnification of 90x10 was used. A morphological count of neutrophils, lymphocytes, monocytes, and eosinophils was performed simultaneously.

Neutrophils measured 10-15 micrometers in size and had a three to four-segmented nucleus. The chromatin exhibited a coarse granular structure and stained purple.

Lymphocytes ranged from 7 to 9 micrometers in size with a round or slightly bean-shaped nucleus. They displayed a clumped chromatin structure with a purple or dark purple color, and the cytoplasm appeared as a thin rim.

Eosinophils measured up to 15 micrometers, with a segmented nucleus consisting of 2-5 segments. Eosinophils had a coarse granular chromatin structure that stained purple, and their cytoplasm contained large granules that were pink in color.

Monocytes varied in size from 14 to 20 micrometers and had a large nucleus, often bean-shaped or round. They exhibited loose chromatin that stained light purple. Monocytes featured a wide cytoplasmic network with a smoky or grayish hue when stained using the Romanowsky-Giemsa method.

The NBT (Nitro Blue Tetrazolium) test is based on the reduction of nitro blue tetrazolium by reactive oxygen species (ROS). This test is used to assess the functional activity of neutrophilic granulocytes from the cellular exudate of the middle ear.

NBT is reduced to diformazan when in contact with activated neutrophils, resulting in the formation of large, dark blue granules within the cells.

For this test, exudate was centrifuged at 1000 rpm at +4 °C for 10 minutes. The supernatant liquid was collected in a plastic tube. The resulting sediment was then diluted in saline to a volume of 0.1 ml. Half of this volume was used to evaluate the cellular composition of the middle ear exudate. For the NBT analysis, the other half of the sediment was mixed with 0.025 ml of NBT solution and incubated for 15 minutes at +37 °C. A thick smear was prepared, air-dried, and fixed in ethanol for 10-15 minutes. The smear was then stained for 10 minutes with a 0.5% solution of safranin, followed by staining with a 1% solution of brilliant green for 1 minute. Microscopy was performed using a light microscope with an immersion objective at a magnification of 90x10.

## *Statistical Processing Methods*

The obtained results were evaluated using the method of variation statistics. The arithmetic mean and its square error were determined using the method of moments. The arithmetic mean of the sample was calculated using the following formula:

$$\overline{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

where n - is the total number of sample values used for the specific analysis ( x ).

To measure the standard deviation (sample standard deviation), the following formula was used:

$$s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

Where:

- $s$ = sample standard deviation
- $n$ = number of observations in the sample
- $x_i$ = each individual observation
- $\bar{x}$ = sample mean (average of the observations)

To test the hypothesis of normality of the random variable distribution (H0): "the random variable (X ) is normally distributed"), the Shapiro-Wilk test was used. This test is a specific case of goodness-of-fit tests that allows for the application of parametric criteria and tests.

For comparing two groups of quantitative characteristics with a normal distribution (after the Shapiro-Wilk test), Student's t-test was conducted. The t-test is applied when comparing only two groups of quantitative characteristics with a normal distribution (a specific case of analysis of variance).

To test for differences between two samples of paired or independent ordinal measurements based on a quantitative characteristic, the non-parametric Wilcoxon test (Mann-Whitney-Wilcoxon test) was used.

To assess the significance of differences between the number of outcomes or qualitative characteristics of the sample and the theoretical number expected in groups under the null hypothesis, the Pearson $\chi 2$ test was applied. The following formula was used for calculations:

$$\chi^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

X2 – is the Pearson value,

Oi – is the observed value,

Ei – is the expected value.

All data analyses were conducted using the modern statistical software R Studio version 3.6.2 for the Windows 10 operating system, with a significance level of \( p < 0.05 \). The following statistical analysis packages were used: "epiDisplay," "qwraps2," "tidyverse," "rstatix," "ggpubr," and "ggplot2."

For describing the results of the study, we used a 95% confidence interval (CI), which encompasses the measured values from the experiment corresponding to the confidence probability.

To quantitatively describe the strength of the association between two variables of interest in our statistical population, the odds ratio (OR) with a 95% confidence interval (CI) was utilized.

To predict the probability of the occurrence of an event of interest based on values of multiple known variables, logistic regression was employed.

## *Treatment Methods for Patients with Exudative Otitis Media*

The postoperative period following surgical interventions in the nasopharynx, nasal cavity, and paranasal sinuses varies considerably and often does not correlate with the extent of the surgery performed. During this period, especially in the early days, patients typically experience pain related to intraoperative trauma and nasal packing. After the removal of tampons, patients may also suffer from nasal breathing difficulties due to pronounced reactive edema of the mucous membrane or atrophic processes leading to hemorrhagic crusts in the nasal passages. In light of this, it is essential to foster the formation of compensatory-adaptive reactions in the body that expedite the reparative process; to prevent potential complications; to shorten hospitalization duration and the number of relapses; to improve patients' quality of life; and to actively promote the recovery of Eustachian tube function.

After surgical treatment, 27 patients were assigned to group IA (traditional therapy). They received vasoconstrictor drops, mucolytics, nasal irrigation of the nasopharynx and Eustachian tube orifices with a furacilin solution from days 2 to 4 after tampon removal, and local transtympanic administration of 0.5 milliliters of a 0.1% dexamethasone solution.

Patients in group IB, totaling 28 individuals (comprehensive therapy group), received traditional treatment alongside the immunomodulator "Gepone" and the nasal spray "Sinulor." The immunomodulator "Gepone" stimulates the production of alpha and beta interferons, has macrophage mobilizing activity, and inhibits the production of anti-inflammatory cytokines such as interleukins 1, 6, and 8, as well as tumor necrosis factor. Additionally, "Gepone" inhibits viral replication and stimulates the production of antibodies against various antigens. Due to these pharmacological properties, this medication enhances the body's resistance to infections caused by viruses, bacteria, and fungi. "Gepone" exerts anti-inflammatory effects within 1-2 days of application. We irrigated the nasopharyngeal mucosa and the orifices of the Eustachian tubes with 9.0 ml of a 0.02% solution of the immunomodulator "Gepone," followed by a transtympanic injection of the same medication at a dose of 0.5 ml. The treatment course for both groups included administering the medication via transtympanic injection three times, with a two-day interval between each injection.

"Sinulor" is a solution containing framicetin sulfate, an antibiotic from the aminoglycoside group known for its high bactericidal activity. This substance prevents the influx of metabolites into cells, disrupts the cytoplasmic membrane, and leads to the rapid death of microorganisms. It is effective against both gram-positive and gram-negative bacteria. In the comprehensive treatment, the nasal spray "Sinulor" was used after tampon removal: one spray in each nasal passage 3-4 times a day, over a treatment course of 5-7 days. The total duration of comprehensive treatment was 7 days.

Control audiometry and tympanometry were performed on the 21st day after treatment to evaluate the immediate results. The number of disease recurrences during the six months following treatment was considered an indicator of long-term treatment effectiveness. In this study, a recurrence was defined as an increase in the sound threshold in air by at least 20 dB and the presence of exudate in the tympanic cavity. Conversely, the absence of clinical symptoms in the ear, improvement in hearing thresholds during audiometry, normalization of the otomicroscopic picture, normalization of tympanograms, and restoration of Eustachian tube ventilation function were regarded as criteria for clinical recovery in both groups.

# COMPREHENSIVE TREATMENT OF PATIENTS WITH EXUDATIVE OTITIS MEDIA ASSOCIATED WITH BENIGN NEOPLASMS OF THE NOSE, PARANASAL SINUSES, AND NASOPHARYNX

## *Clinical Characteristics of Exudative Otitis Media*

The results of the distribution of patients by age categories are presented in Figure 4.

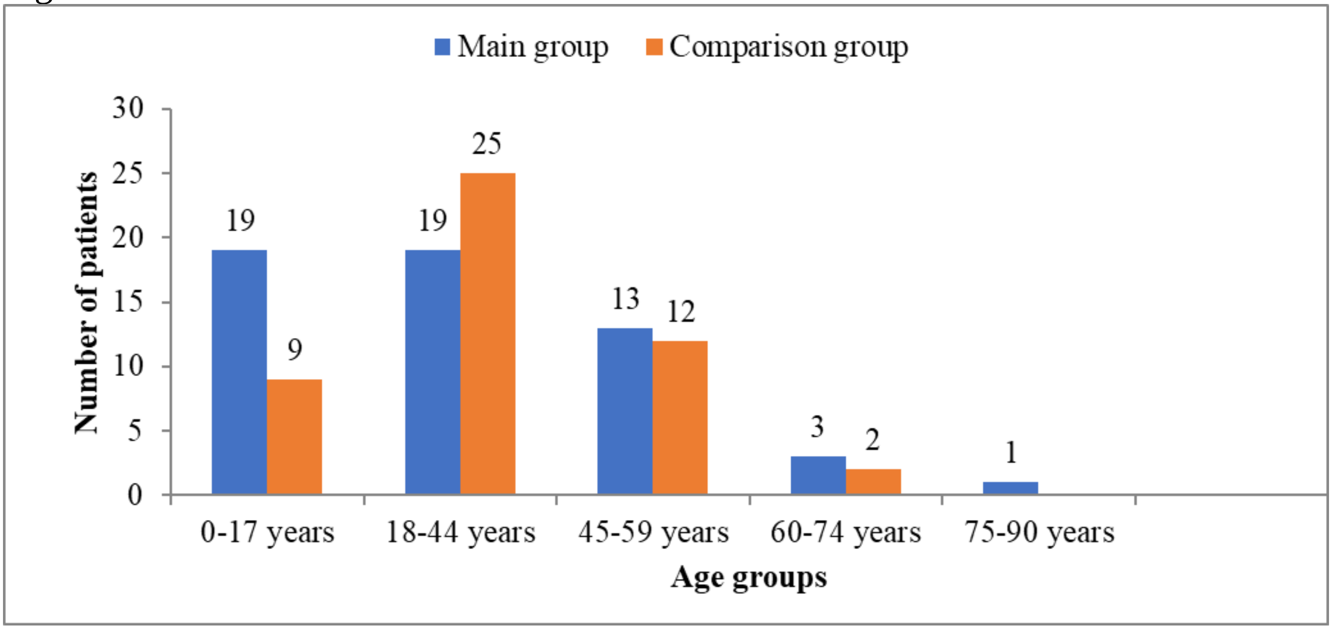



**Figure 4. Distribution of Patients by Age**

Analysis of the distribution of patients by age categories revealed that in Group I (exudative otitis media with benign neoplasms of the nose, paranasal sinuses, and nasopharynx), the highest percentage of patients was found in the adolescent age group under 17 years (34.5%) and in the young adult age group of 18-44 years (34.5%). In contrast, Group II (exudative otitis media with chronic respiratory syndrome) predominantly included young adults (52.1%) and middle-aged individuals (45-59 years) at 25%.

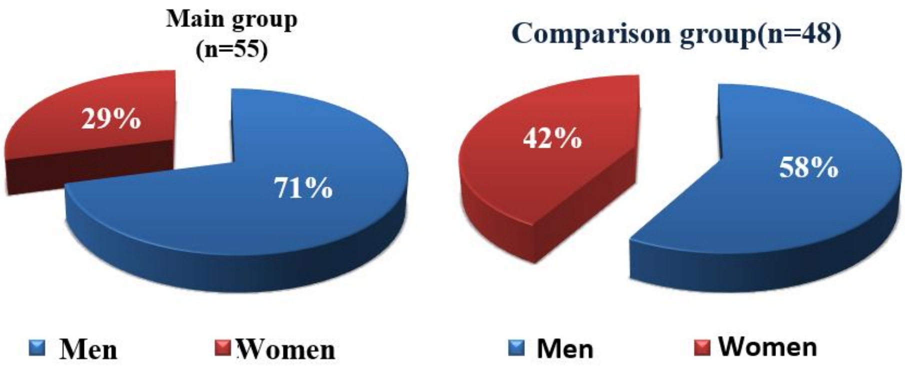



**Figure 5. Distribution of patients by gender.**

In the main group, there was a significant predominance of male patients at 71%, while the comparison group also showed a slight predominance of male patients at 58% (Figure 5).

When analyzing the patients in Group I based on the histological structure of the neoplasms (Figure 6), the largest number of patients was found to have angiofibromas (53%) and papillomas (20%). This was followed by fibromas (13%), hemangiomas (9%), and bleeding polyps (5%).

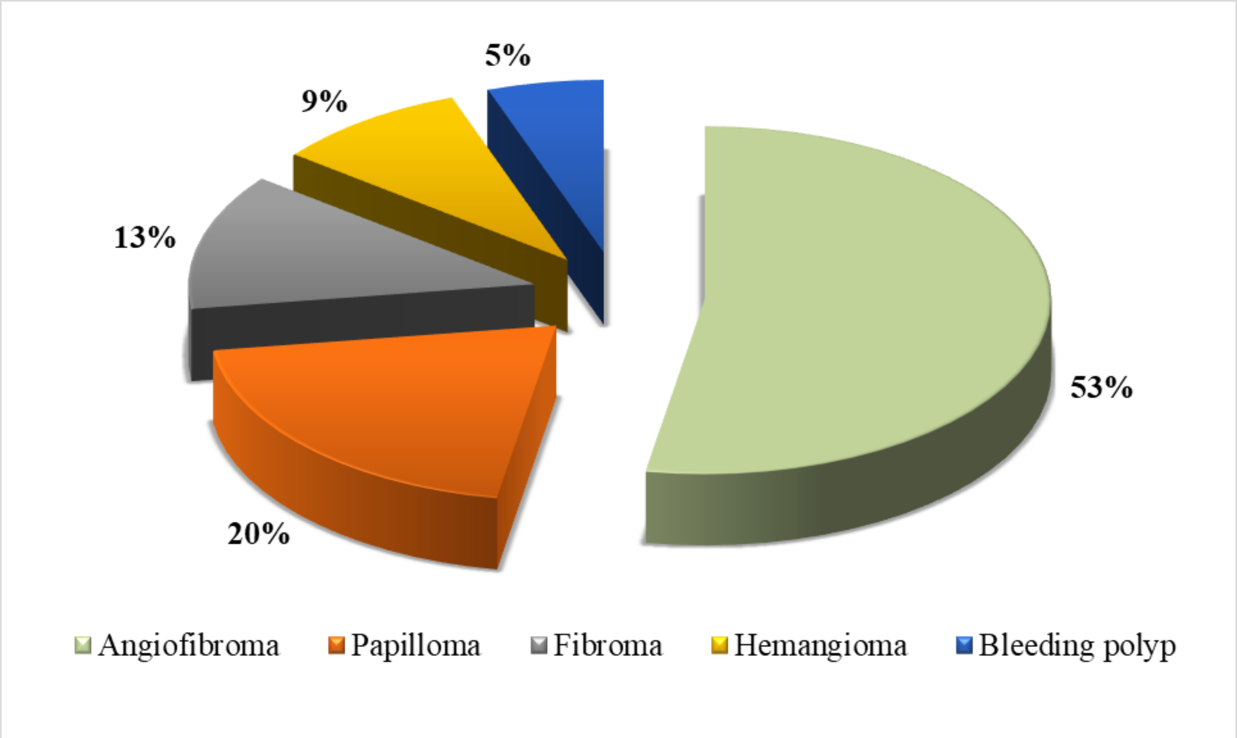
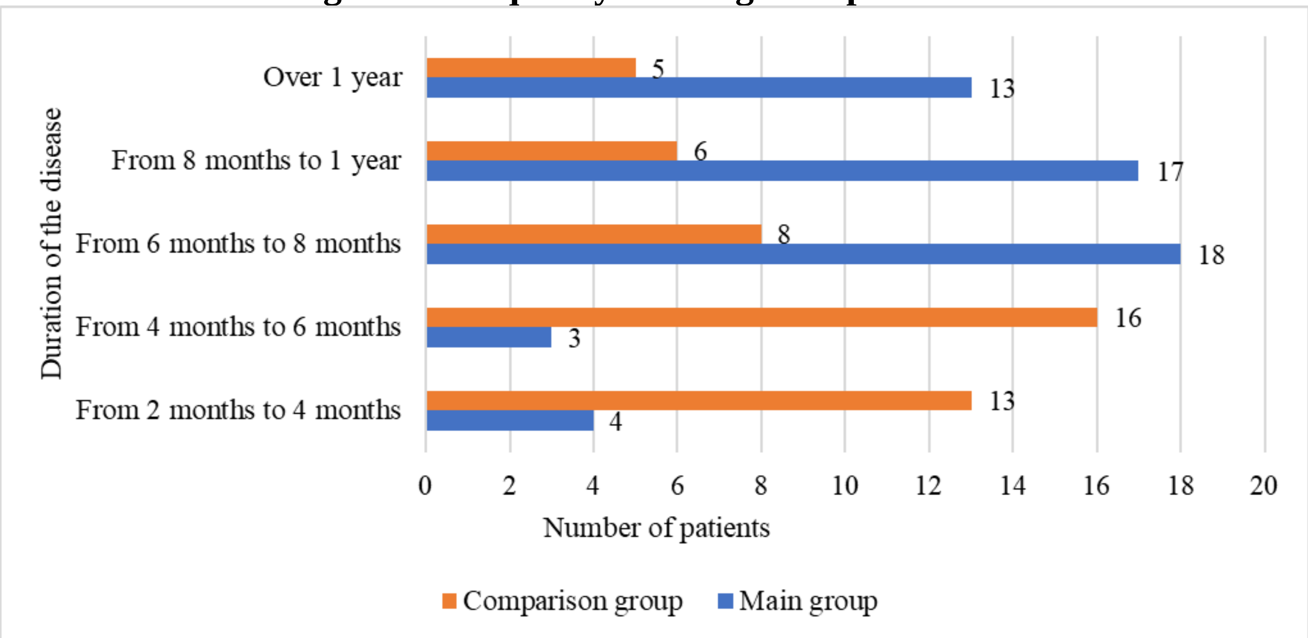



**Figure 6. Frequency of Benign Neoplasms**




The duration of the disease is presented in Figure 7.

**Figure 7. Distribution of patients by duration of the disease.**

The study of the disease history showed that patients with DNN, ONP, and NG sought medical help later, after 6 months or more (87.3%), while the majority of patients with CRS sought help within six months (60.4%).

The table indicates that the complaints of patients in both groups are similar. The largest number of patients in both groups reported difficulty in nasal breathing, with 54 patients (98.1%) in the main group and 46 (95.8%) in the control group. In the main group, the second most common symptom was the sensation of a foreign body (92.7%), while in the comparison group, the second most common symptom was nasal discharge of purulent and mucous character (93.7%). The main group also reported frequent nasal bleeding (38.1%).

**Table 2.**

**Clinical symptoms of exudative otitis media in DNN, ONP, NG, and CRS.**

| Symptoms | Absolute number of ESO in DNN, ONP, and NG (n=55) | ESO in DNN, ONP, and NG % | ESO in CRS (n=48) | Absolute number of ESO in CRS % |
|---|---|---|---|---|
| **nasal symptoms** | | | | |
| Difficulty in nasal breathing | 54 | 98,1 | 46 | 95,8 |
| Sensation of a foreign body | 51 | 92,7 | 7 | 14,6 |
| Closed nasal voice (nasal speech) | 33 | 60,0 | 28 | 58,3 |
| Nasal discharge | 31 | 56,4 | 45 | 93,7 |
| Nosebleeds | 21 | 38,1 | 2 | 4,2 |
| Reduced sense of smell | 19 | 34,5 | 12 | 25,0 |
| **otological symptoms** | | | | |
| Ear congestion | 28 | 50,9 | 23 | 47,9 |
| Hearing impairment | 25 | 45,4 | 18 | 37,5 |
| Tinnitus (ringing in the ears) | 23 | 41,8 | 15 | 31,2 |
| Sensation of fluid in the ear | 11 | 20,0 | 16 | 33,3 |
| Autophony (hearing one's own voice loudly) | 10 | 18,1 | 12 | 25,0 |

Otological symptoms were more frequently identified in the main group: ear fullness was observed in 50.9% of patients compared to 47.9% in the comparison group; hearing impairment was present in 45.4% and 37.5%, respectively; and tinnitus occurred in 41.8% and 31.2%. However, the sensation of fluid movement in the ear was reported more often in the comparison group at 33.3% compared to 20.0% in the main group, while autophony was 18.1% in the main group and 25% in the comparison group.

Analysis of the medical history revealed that 41 patients (74.5%) in the main group reported unilateral processes, whereas in the comparison group, unilateral (26 patients, 54.2%) and bilateral (22 patients, 45.8%) processes were noted equally. The study identified the following clinical symptoms (Table 2):

The otomicroscopic picture of exudative otitis media associated with benign tumors of the nose, paranasal sinuses, and nasopharynx showed a classical presentation during otoscopy in both the main and comparison groups, including dull-gray and bluish coloration, congestive hyperemia, and reduced mobility of the tympanic membrane, along with the flattening of recognizable points and the presence of fluid levels and air bubbles in the tympanic cavity. Our study focused on the otomicroscopic picture of patients with exudative otitis media in DNN, ONP, and NG: against a backdrop of a cloudy, altered tympanic membrane, an engorged vascular network resembling bicycle spokes was noted, covering 50% or more of the lower part of the membrane—a sign of the "spoke wheel" (Figure 8).

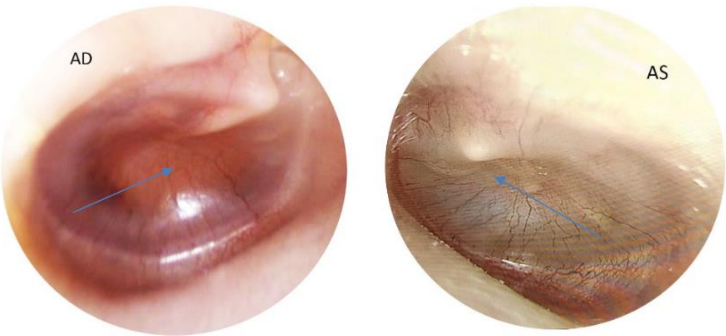



**Figure 8. "Spoke Wheel" Sign - Otomicroscopic Picture of Exudative Otitis Media Associated with Benign Tumors of the Nose, Paranasal Sinuses, and Nasopharynx.**

A series of photographs were obtained to show the appearance of the tympanic membrane, which were subsequently used to analyze the correlation of the diagnostic sign with the disease. A group of otolaryngologists was asked to review the photographs and indicate the presence or absence of the "spoke wheel" sign. These experts also evaluated the quality of each image, and data from 16 images (8 with the presence and 8 with the absence of the "spoke wheel" sign) were used to analyze the correlation of the diagnostic sign with the disease among the experts, calculated using the Fleiss Kappa coefficient. Statistical analysis was performed using computer software (R-studio, version 3.6.2; utilizing statistical packages “qwraps2,” “tidyverse,” “rstatix,” “ggpubr,” “epiDisplay”). The null hypothesis was rejected at $P < 0.05$.

To study the diagnostic potential of the "spoke wheel" sign in diagnosing exudative otitis media associated with benign tumors of the nose, paranasal sinuses, and nasopharynx, the values of diagnostic effectiveness indicators were calculated. The concepts of sensitivity, specificity, and diagnostic value are particularly relevant to these tasks.

Several outcomes are possible for a diagnostic test, including "positive," "negative," "false positive," and "false negative" results. A positive or true positive result refers to a finding in patients where the sign is present and the diagnosis is correct. A true negative result refers to a finding in patients without the sign, confirmed by the diagnostic test. A false positive result occurs when a patient is diagnosed with the presence of a sign that is not actually present. Similarly, a false negative result refers to a case where a patient with the sign is incorrectly diagnosed as lacking it.

Both false positive and false negative results undermine the diagnostic process by reducing the accuracy of test results and wasting resources.

The probability that a person with the disease will have a positive test result is called the test's sensitivity. Generally, the effectiveness of the method increases in direct proportion to its sensitivity and the frequency with which it can detect pathological changes. The following equation is used for this purpose:

$$Sensitivity = \frac{TP}{TP + FN} \cdot 100\%$$

The results of the assessment are compared with the results of another instrumental (laboratory) method recognized as the "gold standard," in this case, instrumental-pathological tympanography and the detection of exudate during tympanotomy. The gold standard method serves as the criterion for determining the presence or absence of the disease.

The percentage of patients for whom the test yields a positive result can be considered the a priori sensitivity of the test. The higher the sensitivity of the test, the greater the likelihood that it will detect signs of the disease, and consequently, the higher its overall effectiveness.

On the other hand, if a highly sensitive test yields a negative result, the risk of developing the disease is significantly reduced. As a result, such tests should be used to rule out the possibility of disease. In this regard, highly sensitive technologies are sometimes referred to as identifiers, and they are recommended for use in the early stages of the diagnostic process, when it is crucial to minimize the number of diseases that may potentially be present. However, highly sensitive tests can lead to a high number of "false alarms," which increases costs for further examination. This fact should also be taken into account.

Specificity refers to the ability to obtain a negative result among individuals who do not have the disease. Thus, the higher the specificity, the more reliably the method confirms the absence of the disease, making it more effective.

$$Specificity = \frac{TN}{TN + FP} \cdot 100\%$$

Diagnostic value refers to the proportion of correct results (both positive and negative) out of the total number of tests conducted.

$$Value = \frac{TP + TN}{TP + TN + FP + FN} \cdot 100\%$$

In the analysis of the otomicroscopic picture, each ear was evaluated separately: in the main group of 69 ears, the "spoke wheel" sign was found in 64 cases, resulting in a sensitivity of 92.7% (64/69). In the control group without disease, consisting of 40 ears, the sign was not detected in 38 cases, giving a specificity of 95% (38/40). The diagnostic value was determined to be 93.6% (102/109). In the comparison group of 70 ears, the "spoke wheel" sign was noted in only 16 cases, resulting in a sensitivity of 22.8% (16/70) and a diagnostic value of 49% (54/110). Thus, in the main group, the sensitivity of the method was 92.7% and the diagnostic value was 93.6%, while in the comparison group, sensitivity was 22.8% and the diagnostic value was 49%. In both the main and comparison groups, the specificity of the method was 95%.

From personal observations, we provide an example of exudative otitis media in a juvenile nasopharyngeal angiofibroma. Patient F.A., 16 years old, complained of hearing loss in both ears, predominantly on the left side, nasal congestion, tinnitus, autophony, and a sensation of fluid in the ear. He sought help from the ENT department of the First Clinic of Samarkand State Medical University. Upon thorough questioning, the patient also reported difficulty breathing through the nose and periodic nasal bleeding.

According to the medical history, the patient had been ill for 3 years and did not associate the disease with any specific cause. The first symptoms included periodic ear congestion and hearing loss in the left ear. He visited the local doctor, who diagnosed acute otitis and prescribed appropriate treatment. There was a temporary improvement, but after two weeks, the symptoms returned and hearing worsened. The doctor referred him to an ENT specialist for further examination, and based on the findings, an audiological study was recommended. The results led to a diagnosis of exudative otitis media. Appropriate treatment and monitoring were prescribed. After two months of treatment, the patient noticed hearing loss in the right ear as well, along with difficulty breathing through the nose. After eight months, he experienced nasal bleeding, prompting a consultation at the First Clinic of Samarkand State Medical University.

From his medical history, the patient is prone to colds and has not been hospitalized. He denies any allergies to food or medications. Upon examination, the external auditory canals were clear. In the right ear (AD), the eardrum was sharply retracted, with the handle of the malleus protruding and the light reflex absent. In the left ear (AS), the eardrum was bluish and dull gray, with reduced mobility of the eardrum noted. Identifying landmarks were flattened, and there was bulging of the eardrum.

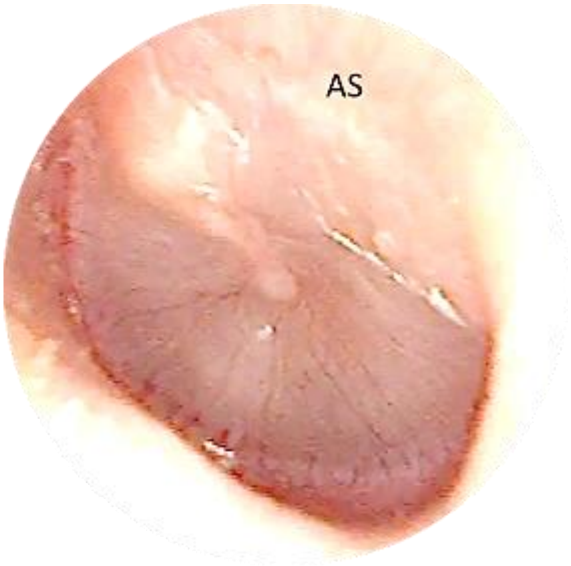



**Figure 9. Otomicroscopic picture of exudative otitis media in juvenile nasopharyngeal angiofibroma**

The patient exhibited the specific otoscopic sign known as the "spoke wheel" (Figure 9), which is characteristic of the presence of fluid in the middle ear. The "spoke wheel" sign was defined as a dull gray appearance of the eardrum with a swollen vascular network arranged in a pattern resembling the spokes of a bicycle wheel, covering 50% or more of the lower eardrum.

The nasal passages were filled with mucus; after cleaning, the posterior parts of the left nasal cavity were obstructed by a bluish-colored formation with a smooth surface. Fibroendoscopy revealed an asymmetrical, red-blue formation in the nasopharynx on the left side with a finely lobulated surface, completely occluding the left choana and partially obstructing the right. Upon digital examination of the nasopharynx, a dense, immobile, nodular formation was palpated. Nasal breathing was obstructed, with complete blockage on the left side.

Audiological testing indicated reduced hearing in both ears (AS: conductive hearing loss of grade II, with a speech frequency loss of 52 dB; AD: conductive hearing loss of grade I, with a loss of 32 dB). Tympanometry results showed type "B" on the left and type "C" on the right.

Based on the findings in the nasopharynx, the patient was referred for CT scanning. A series of computed tomography images revealed a nasopharyngeal tumor with infiltration into the nasal cavity (Figure 10).

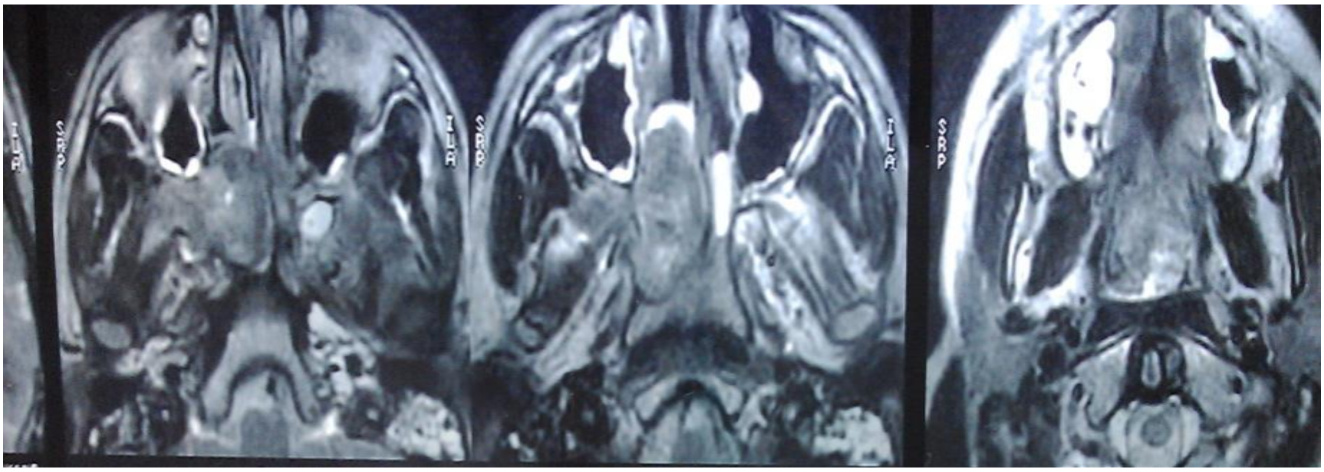


**Figure 10. CT scan of patient F.A., nasopharyngeal tumor**

The patient was scheduled for surgical treatment and was successfully operated on. The results of the histological examination confirmed the diagnosis of nasopharyngeal angiofibroma (Figure 11).

In patients diagnosed with chronic otitis media (COM), otitis media with effusion (OME), and nasopharyngeal conditions, Eustachian tube patency was assessed as follows: II degree in 15.9% of cases, III degree in 18.8%, IV degree in 49.3%, and V degree in 15.9%. In patients with chronic rhinosinusitis (CRS), Eustachian tube patency was found to be II degree in 15.7%, III degree in 18.6%, IV degree in 51.4%, and V degree in 14.3%. Prior to the initiation of therapy, no significant differences were observed in the frequency of various degrees of Eustachian tube patency among patients with benign tumors and chronic rhinosinusitis.

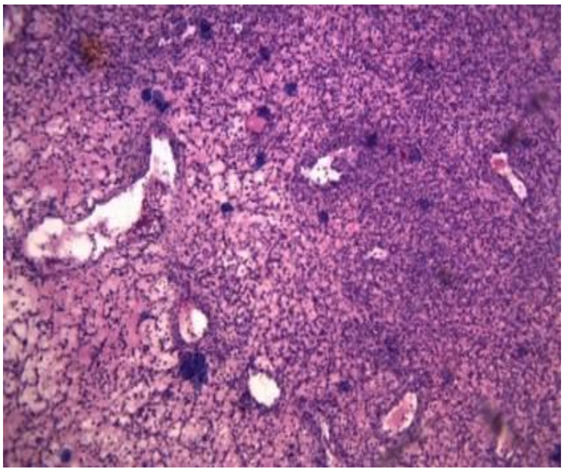


**Figure 11. Microscopic preparation of juvenile angiofibroma (stained with hematoxylin-eosin, magnification ×100)**

### *Comparative Functional Assessment of the Eustachian Tubes*

All patients underwent a comprehensive clinical examination prior to the initiation of therapy. The results of the assessment of Eustachian tube patency in patients with benign tumors of the nose, paranasal sinuses, and nasopharynx, as well as those with chronic rhinosinusitis, are presented in Figure 12.

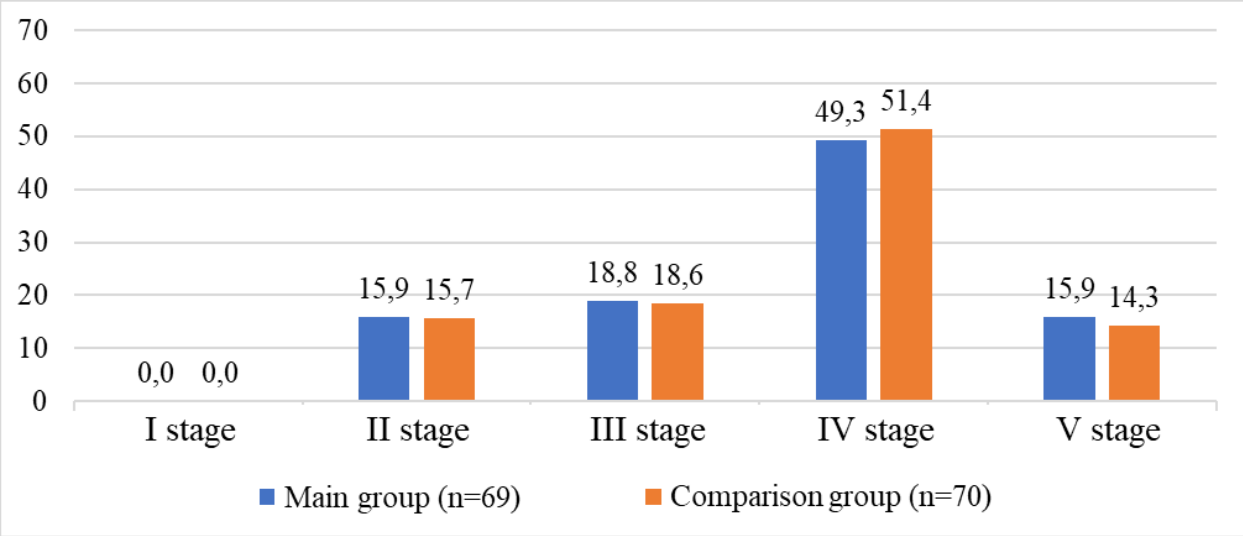



***Figure 12. Distribution of patients with Eustachian tube dysfunction by degree of patency before treatment***

## *Comparative Assessment of Pure-Tone Audiometry*

According to the generally accepted classification of hearing loss, patients in the initial examination exhibited conductive and mixed forms of hearing loss (Figures 13 and 14).

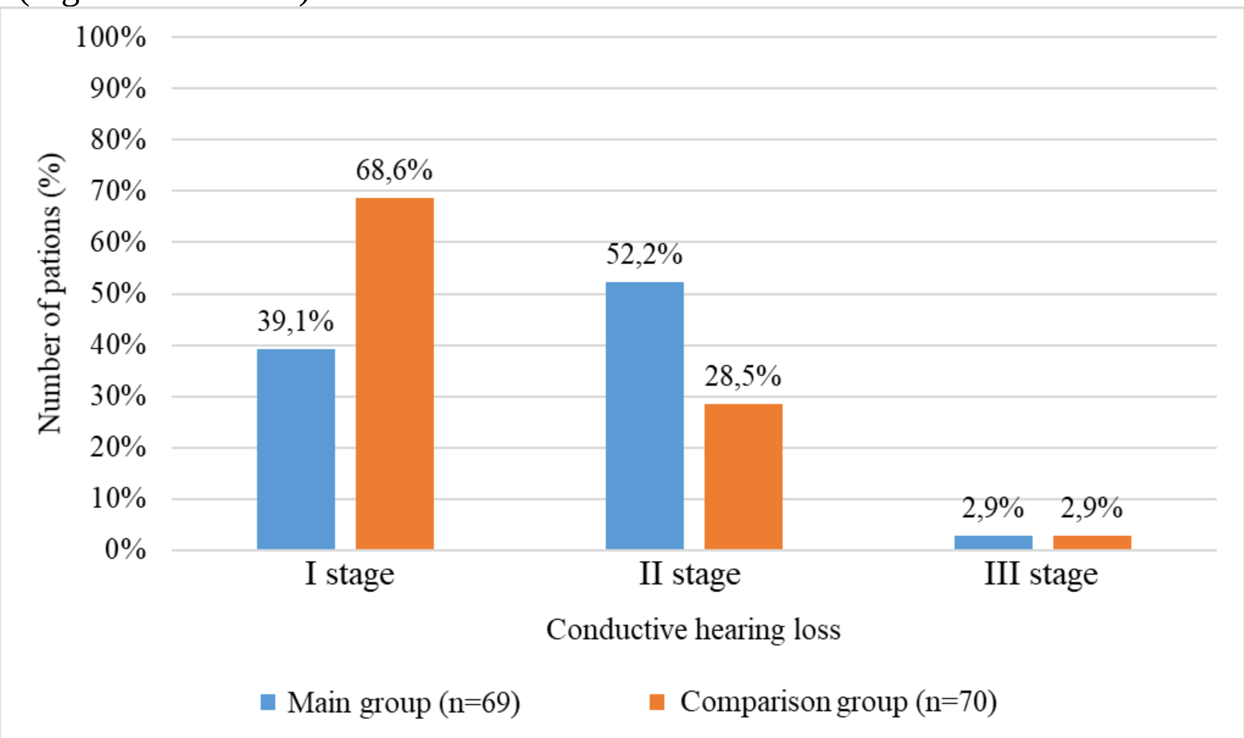



**Figure 13. Audiological indicators before treatment (conductive hearing loss)**

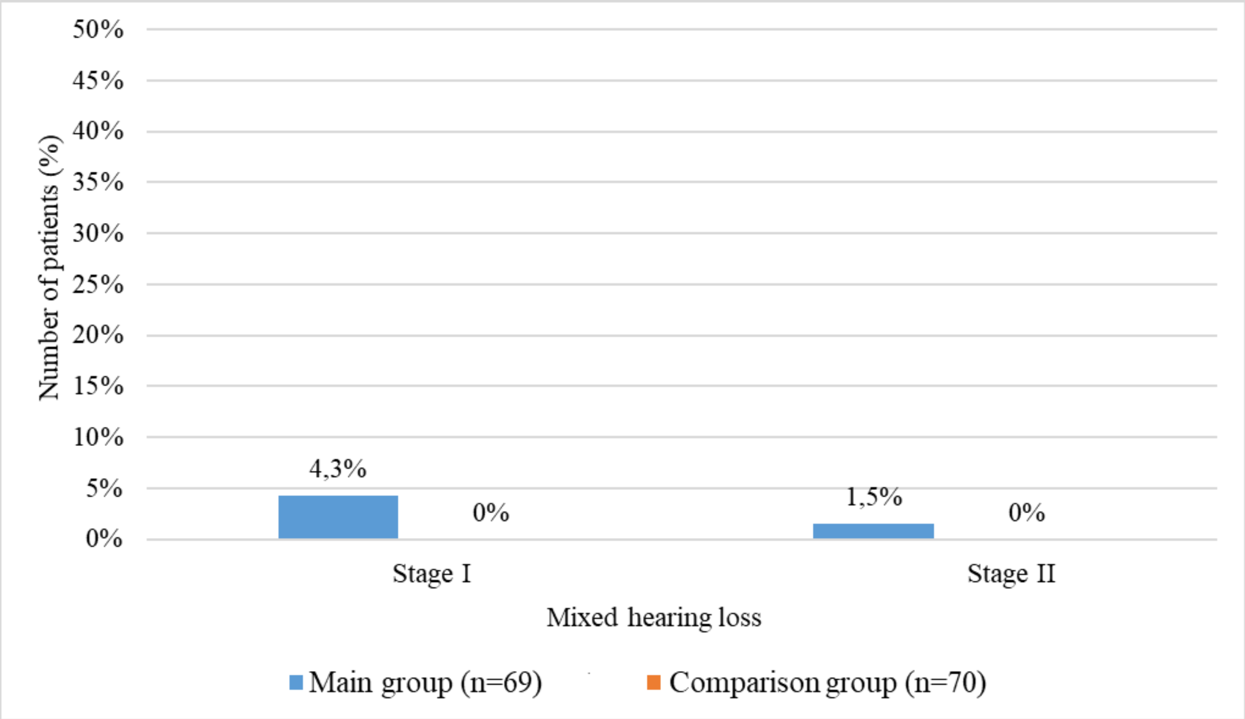



**Figure 14. Audiological indicators before treatment (mixed hearing loss)**

In patients with Eustachian tube dysfunction (ETD) associated with chronic otitis media (COM), otitis media with effusion (OME), and nasopharyngeal conditions, hearing impairment was observed as conductive in 94.2% of cases and mixed in 5.8%. In contrast, in the group with ETD associated with chronic rhinosinusitis (CRS), only conductive hearing loss (100%) was present. Patients with ETD related to COM, OME, and nasopharyngeal conditions had a significantly higher prevalence of grade II hearing loss (52.2%), whereas patients with ETD related to CRS predominantly had grade I hearing loss (68.6%).

It is important to note the differences in air conduction that were found between the two groups at each frequency examined. The thresholds for perceiving airborne sound were, on average, 1.4 times higher in patients with ETD related to benign tumors, which can be attributed to more pronounced pathological changes (Table 3).

**Table 3.**

**Average pure-tone audiometry thresholds in the studied groups before treatment (dB, Mean ± m) (each ear was assessed separately)**

| Frequency (Hz) | ETD in COM, OME, and NP (n=69), dB (Mean ± m) | ETD in CRS (n=70), dB (Mean ± m) | Mann-Whitney Criterion | P-value |
|---|---|---|---|---|
| Air Conduction | | | | |
| 500 Hz | 43.59 ± 4.83 | 35.26 ± 5.21 | <0.001 | |
| 1000 Hz | 45.81 ± 3.72 | 32.43 ± 3.76 | <0.001 | |
| 2000 Hz | 45.11 ± 4.98 | 31.19 ± 4.21 | <0.001 | |
| 4000 Hz | 43.79 ± 3.94 | 31.48 ± 3.83 | <0.001 | |
| Bone Conduction | | | | |
| 500 Hz | 10.83 ± 1.11 | 8.28 ± 0.81 | 0.03 | |
| 1000 Hz | 11.79 ± 0.84 | 10.94 ± 1.33 | 0.44 | |
| 2000 Hz | 13.59 ± 0.76 | 12.29 ± 0.73 | 0.19 | |
| 4000 Hz | 12.49 ± 0.71 | 11.69 ± 0.93 | 0.05 | |

**Note: p = significance level of differences between groups.**

In the assessment of bone conduction, a statistically significant difference was found at the frequency of 500 Hz. This phenomenon may be attributed to the obstruction of the labyrinth windows, involvement of the cochlear nerve, and potential intoxication [39; 96-98; 44; 68-72]. According to the literature, the mass of the vibrating elements in the middle ear increases acoustic impedance, thereby enhancing bone conduction [108, 109].

Among the studied patients, there was a significant variation in the values of the air-bone gap before treatment. Compared to patients with ETD related to rhinosinusitis, the average values of the air-bone gap in patients with benign tumors were approximately 1.5 times higher. This was associated with a more prolonged and severe course of the disease.

To accurately diagnose conductive hearing loss, one of the indicators that must be analyzed is the air-bone gap (Table 4).

Table 4.

**Average measurements of the air-bone gap before treatment (dB, Mean ± m) (each ear was assessed separately)**

| Frequency (Hz) | ETD in COM, OME, and NP (n=69), dB (Mean ± m) | ETD in CRS (n=70), dB (Mean ± m) | Mann-Whitney Criterion |
|---|---|---|---|
| 500 Hz | 32.76 ± 3.81 | 26.98 ± 3.89 | <0.001 |
| 1000 Hz | 34.02 ± 3.44 | 21.49 ± 3.71 | <0.001 |
| 2000 Hz | 31.52 ± 3.74 | 18.90 ± 4.01 | <0.001 |
| 4000 Hz | 31.30 ± 3.59 | 19.79 ± 3.72 | <0.001 |

**Note: p = significance level of differences.**

## Results of Microbiological Investigation

Bacterial cultures of nasal swab samples were conducted in each of the study groups. Figures 15 and 16 illustrate the qualitative composition of the microbial landscape, respectively.

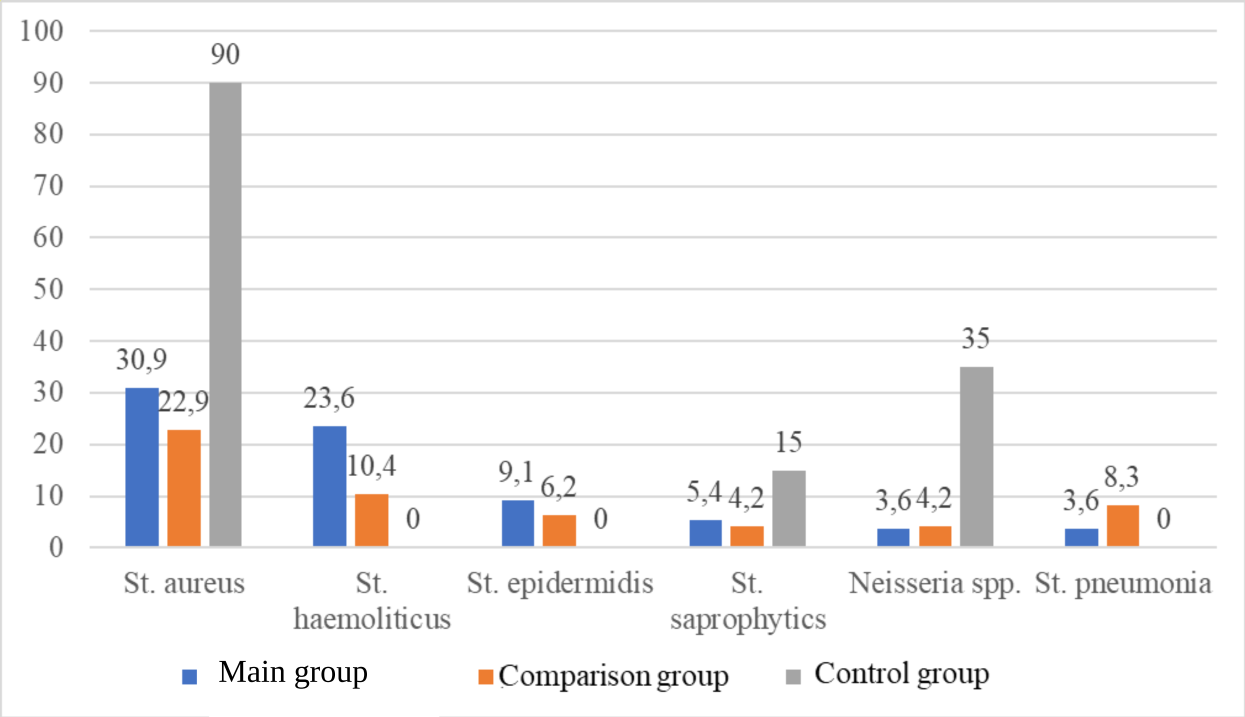



**Figure 15. Qualitative composition of the microbial landscape of the nasal mucosa**

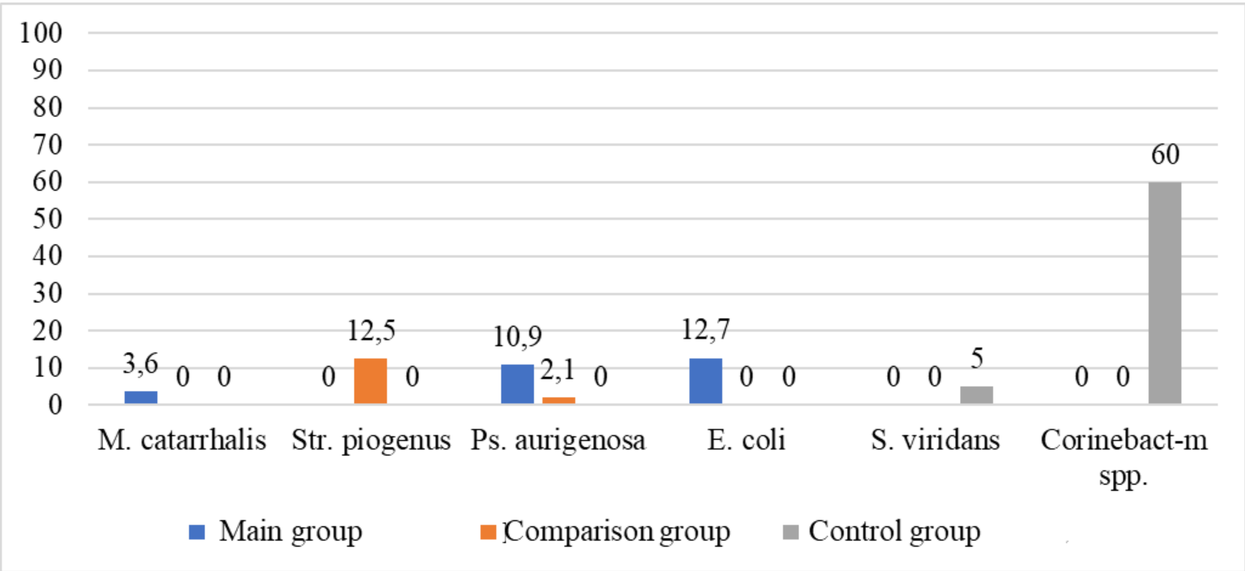



**Figure 16. Qualitative Composition of the Microbial Landscape of the Nasal Mucosa**

As seen in the figures, significant differences in the types of microbial agents on the nasal mucosa were found among patients in all three groups. In terms of frequency, patients with eosinophilic sinusitis with nasal polyps (ESO with NNP), chronic rhinosinusitis (CRS), and non-allergic rhinitis (NAR) predominantly harbored gram-positive anaerobic flora, with Staphylococcus aureus (30.9%), Staphylococcus haemolyticus (23.6%), and from gram-negative flora, Escherichia coli (12.7%) and Pseudomonas aeruginosa (10.9%). In contrast, patients with eosinophilic sinusitis with chronic rhinosinusitis predominantly exhibited Streptococcus pyogenes (12.5%). The predominance of anaerobic flora is associated with impaired nasal passage and natural ostia patency, creating favorable conditions for the survival of these types of microorganisms.

In the control group, 18 patients were carriers of Staphylococcus aureus (90.0%), as well as conditionally pathogenic microorganisms such as Corynebacterium spp. (60.0%) and Neisseria spp. (35.0%). In isolated cases, Staphylococcus saprophyticus (15%) and Streptococcus viridans (5%) were also detected.

Thus, the microbial landscape of the nasal mucosa in patients from the main and comparison groups does not significantly differ, but the degree of microbial growth activity varies. The predominance of anaerobic flora is associated with impaired nasal passage and natural ostia patency, which creates favorable conditions for the survival of these types of microorganisms.

We conducted a microbiological study of middle ear effusion in 62 samples. No microbial growth was detected in any of the examined effusion cultures.

## *Comparative Characteristics of Immunological Indicators*

During the study, immunological indicators in the compared groups were analyzed. The analysis of immune status indicators demonstrates that the relative content of various subpopulations in the blood was characterized by a decrease of 1.2-2.1 times in the average values of lymphocytes in patients with exudative otitis media in the main group compared to patients in the comparison group (Table 5).

In the comparison group, a large number of CD3+, CD8+, and T-helper cells - CD4+ were detected. As is known, chronic inflammation is associated with the activation of immune competent cells, which may explain the obtained results.

**Table 5.**

**Immune Status Indicators in Patients with ESO in Compared Groups**

| **Показатели** | **ЭСО with NNP, NAR and CRS (n=48) (M±m)** | **ЭСО with CRS (n=21) (M±m)** |
|---|---|---|
| CD3+ | 46,87±**7,57** | 61,77±**6,21*** |
| CD4+ | 26,39±**7,39** | 40,72±**6,43*** |
| CD8+ | 16,06±**2,45** | 33,50±**2,21*** |
| CD19+ | 20,21±**2,53** | 19,82±**2,51** |

| | | |
|---|---|---|
| IgA | 1,06±**0,21** | 1,32±**0,08*** |
| IgM | 2,81±**0,24** | 1,57±**0,25*** |
| IgG | 6,32±**0,79** | 10,46±**0,86*** |
| IgE | 96,2±**7,59** | 77,78±**6,26*** |

Thus, it can be stated that patients with eosinophilic sinusitis (ESO) against the background of non-allergic rhinitis (NAR), allergic rhinitis (AR), and nasal polyps (NP) showed a significant decrease (on average 1.5 times) in the relative quantity of CD3+ cells and their major subpopulations, CD8+ and CD4+, compared to patients with ESO associated with chronic rhinosinusitis (CRS).

The indicators of humoral immunity, specifically the concentration of serum immunoglobulins in the studied groups, also differed. In the main group, a significant reduction in IgA levels was found at 1.06 ± 0.21 g/L ($p < 0.01$), along with a decrease in IgG at 6.32 ± 0.79 g/L ($p < 0.05$). However, the level of IgM was significantly elevated at 2.81 ± 0.24 g/L ($p < 0.01$). The increase in the average level of serum immunoglobulins in the comparison group is associated with a decrease in the barrier function of the mucosal lining and the entry of bacterial products into the bloodstream.

Therefore, patients with ESO against the background of NAR, AR, and NP demonstrate suppression of both cellular and humoral components of systemic immunity.

## *Characteristics of the Cellular Composition of Middle Ear Effusion*

During the analysis of the results, it was found that the middle ear effusion in both studied groups contained the following elements: neutrophilic leukocytes, lymphocytes, monocytes, and eosinophils. The presence of a significant number of phagocytic cells in the effusion indicates their active participation in the inflammatory process.

**Table 6.**

**Average Indicators of the Cellular Composition of Middle Ear Effusion in the Studied Groups**

| **Indicators** | **ЭСО with NAR, AR and NP (n=69) (M±m)** | **ЭСО with CRS (n=70) (M±m)** | **Mann-Whitney criterion P-value** |
|---|---|---|---|
| Neutrophils (%) | 45,6±11,9 | 44,78±7,9 | 0.79 |
| Lymphocytes % | 15,6±7,9 | 33,2±8,7 | <0.001 |

| | | | |
|---|---|---|---|
| Eosinophils % | 2,92±1,3 | 1,92±0,8 | 0.43 |
| Monocytes % | 19,6±4,8 | 19,8±4,9 | 0.83 |
| % of Activated Cells (NST Test) | 37,8±7,5 | 44,7±7,2 | 0.06 |

The results of the study showed that in exudative otitis media, there is activation of monocytes and neutrophils in the bloodstream [94; 83-95]. A significant difference was found in the concentrations of lymphocytes ($p < 0.001$) between the compared groups. Many researchers believe that the increased production of lymphocytes observed in otitis media is due to immediate-type hypersensitivity [86; 495-500]. It is recognized that immediate-type hypersensitivity plays a certain role in the etiology of inflammation. In the middle ear effusion of patients in the comparison group, lymphocytes predominated. This can be explained by the fact that immediate-type hypersensitivity is characterized by increased vascular permeability for cellular components.

We also observed that there were no significant differences in the functional activity of neutrophils between the groups ($p = 0.79$). A decrease in the functional activity of neutrophils was noted in patients from the main group during the NST test. This result can be explained by a reduction in the reserve potential of the phagocytic component against the background of antigenic stimulation, which is consistent with the findings of several researchers [95; 97; 98].

### *Assessment of Local Humoral Immunity Indicators*

During the study of the effusion, three classes of immunoglobulins were detected: IgA, IgM, and IgG. According to the table, there were no statistically significant differences in the indicators between the patient groups, but it is important to note the low values in the main group.

**Table 7.**

**Results of the Study of Immunoglobulins in Middle Ear Effusion**

| **Pation groups** | **IgA, г/л** | **IgM, г/л** | **IgG, г/л** | **Protein levels, г/л** |
|---|---|---|---|---|
| **ЭСО with NAR, AR, AND NP(п=69)** | 0,26±0,09 | 0,14±0,02 | 3.93±1,12 | 1,02±0,23 |
| **ЭСО with CRS(п=70)** | 0,51±0,18 | 0,09±0,04 | 5,76±1,36 | 1,36±0,56 |
| **Mann-** | 0.06 | 0.57 | 0.28 | 0.43 |

| Whitney criterion p-value | | | | |
|---|---|---|---|---|

In the case of chronic inflammatory diseases, infectious pathogens persist in the middle ear for an extended period. This leads to a weakening of T- and B-cell responses, as well as functional exhaustion of the immune system [1; 4; 26]. This explains the lower levels of antibodies in the effusion of patients in the main group compared to those in the control group.

Extracellular infections activate the B-branch and mechanisms of nonspecific resistance. It is well-known that activated B-lymphocytes begin to produce antibodies intensively; however, due to the functional incapacity of these lymphocytes, activated B-lymphocytes undergo apoptosis, resulting in a weak or absent immune response [86; 495-500].

In this study, no significant difference was found in the level of total protein in the middle ear effusion between the patient groups. Nevertheless, as shown in Table 3.7, the protein concentration in the comparison group was 1.33 times higher (p = 0.43) than in the main group.

### *Assessment of Clinical Indicators in the Postoperative Period*

Pain was the most characteristic subjective symptom in the postoperative period. A Visual Analog Scale (VAS) was used to assess pain. The results of the pain syndrome indicators are presented in Table 8. On the first day after the operation, patients in both therapeutic groups experienced a relatively similar pain syndrome, predominantly of severe (48.1% and 42.9%) or moderate (40.7% and 42.9%) intensity.

**Table 8.**

**Results of Pain Syndrome Assessment Over Time**

| Degree of pain syndrome | Days after surgery | Traditional therapy (n=28) | | Complex therapy (n=28) | | X2/Fisher criterion |
|---|---|---|---|---|---|---|
| | | Абs. number | % | Абs. number | % | p- value |
| Severe pain syndrome | 1 days | 13 | 48,1 | 12 | 42,9 | >0,05 |
| | 5 days | 2 | 7,4 | 0 | 0 | NA |
| | 10 days | 0 | 0 | 0 | 0 | NA |
| Moderate pain | 1 days | 11 | 40,7 | 12 | 42,9 | >0,05 |

| | | | | | | |
|---|---|---|---|---|---|---|
| syndrome | 5 days | 9 | 33,3 | 3 | 10,7 | <0,05 |
| | 10 days | 2 | 7,4 | 0 | 0 | NA |
| Mild pain syndrome | 1 days | 3 | 11,1 | 4 | 14,3 | >0,05 |
| | 5 days | 13 | 48,1 | 11 | 39,3 | >0,05 |
| | 10 days | 11 | 40,7 | 4 | 14,3 | <0,01 |
| No pain | 1 days | 0 | 0 | 0 | 0 | NA |
| | 5 days | 3 | 11,1 | 14 | 50 | <0,01 |
| | 10 days | 14 | 51,9 | 24 | 85,7 | <0,01 |

On the 5th day of treatment, as seen in the table, pain syndrome was absent in the majority of patients receiving complex therapy (50%), or they experienced mild pain (39.3%). By the 10th day after the operation, moderate pain was noted in 40.7% of patients in the traditional treatment group, while 85.7% of patients in the complex therapy group reported no pain.

In terms of objective clinical signs, such as swelling and hyperemia post-operation and wound healing, statistically significant differences were also observed in favor of complex therapy (Figure 17).

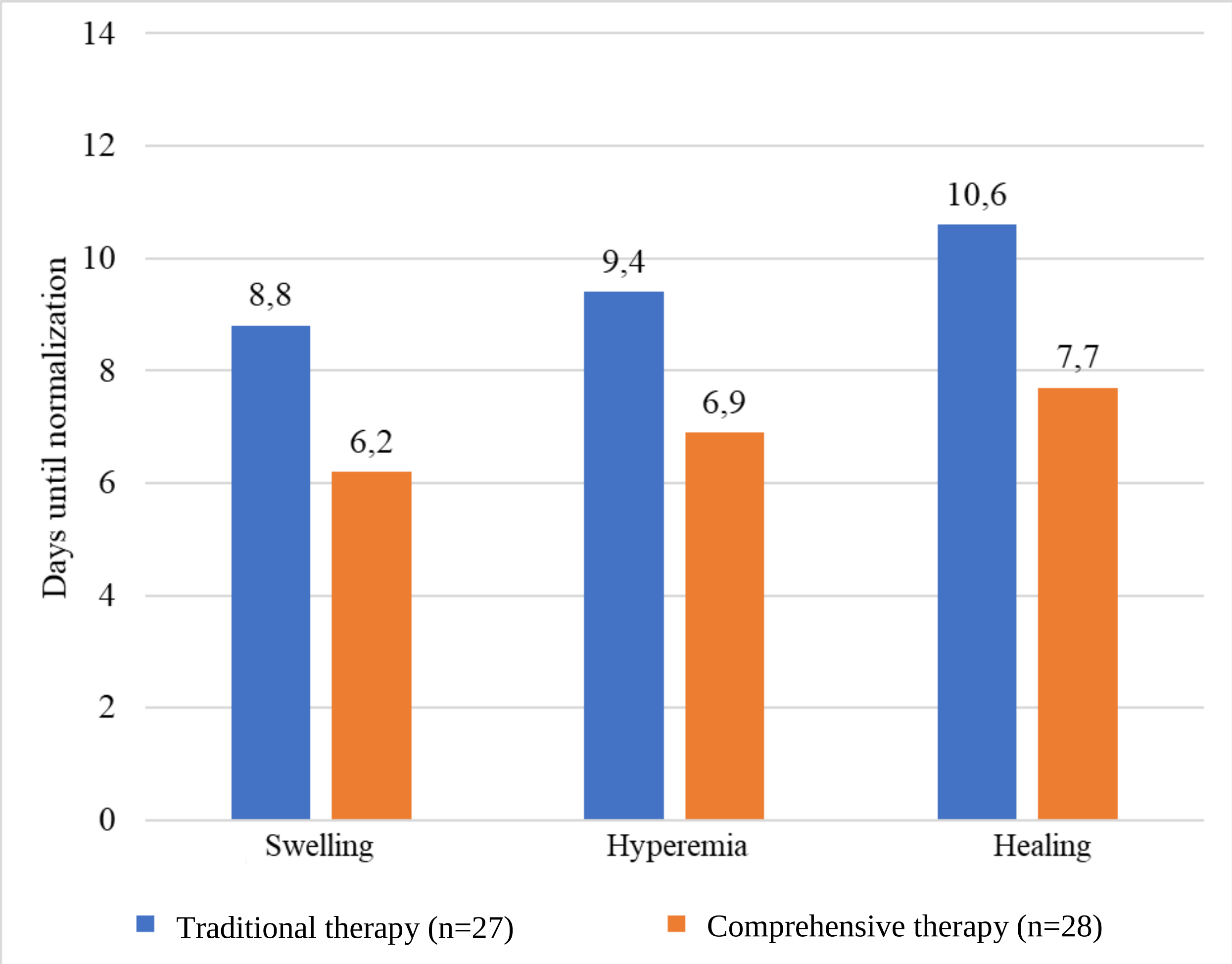



**Figure 17. Objective Clinical Indicators After Treatment**

In particular, patients receiving complex therapy experienced a reduction in swelling and hyperemia that took an average of 2.6 days less compared to those undergoing traditional therapy. Additionally, postoperative wound healing occurred an average of 2.9 days earlier in patients receiving complex treatment.

Thus, the complex treatment involving the use of the drug "Gepone" and the spray "Sinulor" in the postoperative period contributed to the early alleviation of pain syndrome, reduction of swelling and hyperemia, and acceleration of wound healing.

## Characteristics of Key Clinical Indicators of Exudative Otitis Media Over Time

All patients were surveyed regarding subjective signs of the disease. Figure 18 illustrates the changes occurring in the main clinical indicators characteristic of exudative otitis media following therapy.

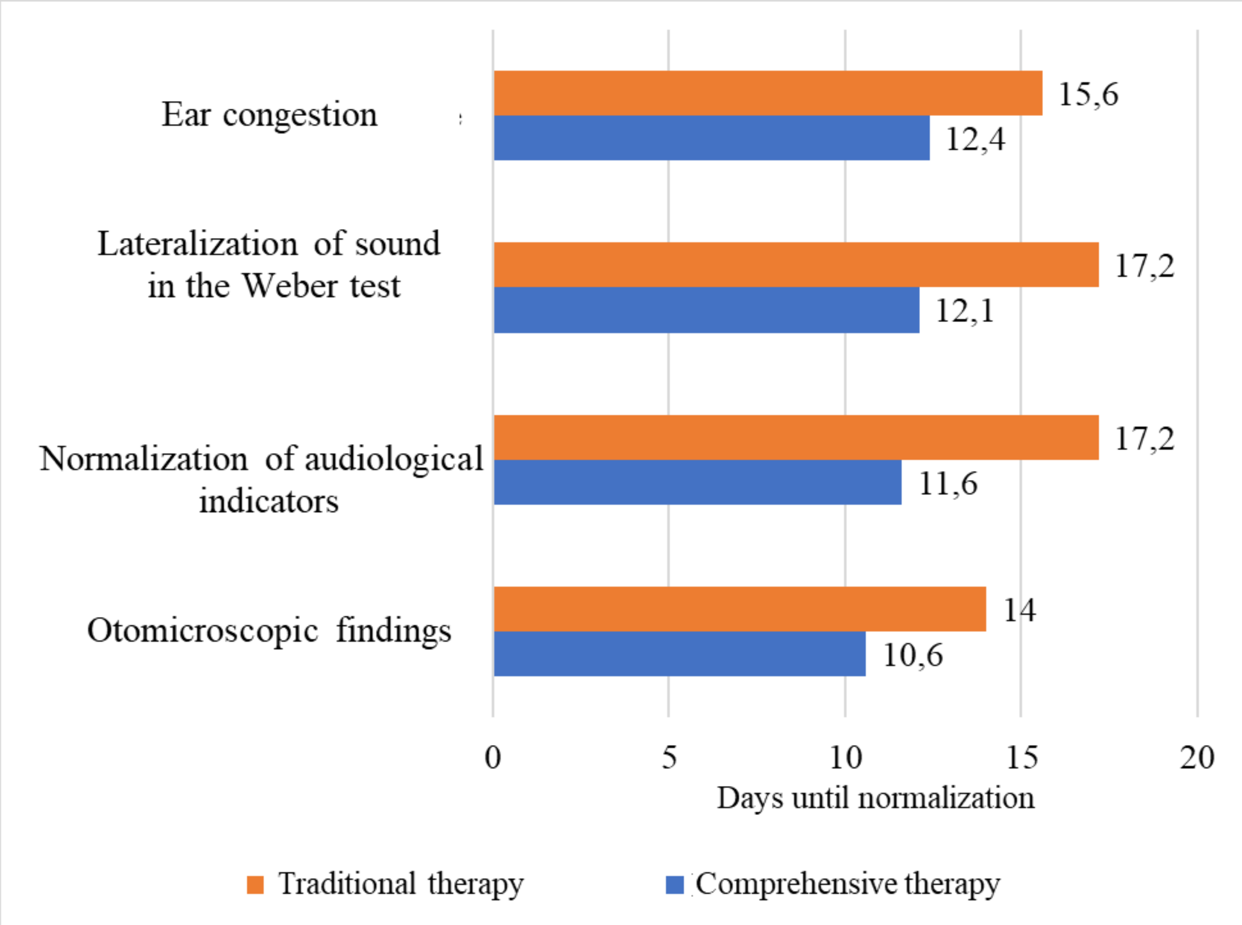



**Figure 18. Dynamics of Clinical Indicators in Patients with Exudative Otitis Media (EOM) During Treatment (Differences in All Parameters are Statistically Significant at $p < 0.05$)**

All patients in both groups experienced a positive effect during treatment, with differences observed in the duration of recovery based on the aforementioned indicators. Patients with EOM related to NAR, AR, and NP in the combined treatment group reported that ear congestion resolved an average of 3.2 days earlier than in patients receiving traditional therapy. Compared to the Weber experiment, daily acoustic assessments revealed a significantly faster reduction in sound lateralization. In the group of patients with EOM receiving combined treatment, the absence of sound lateralization was noted 5.1 days earlier than in the traditional therapy group. Objective examinations showed that otomicroscopic findings normalized, and the membrane returned to its normal curvature 3.4 days sooner. Normalization of audiological indicators in patients receiving complex treatment occurred 5.6 days earlier.

At the time of discharge (day 14), four patients (14.2%) still experienced ear congestion, and sound in the Weber test localized to the affected ear in the combined therapy group (28 patients). The efficacy of combined therapy during the inpatient course reached 24 patients (85.7%). At discharge (day 14), 14 patients (51.8%) receiving traditional therapy reported ongoing ear congestion. Moreover, these patients localized sound in the Weber test to the affected ear.

Thus, a more rapid regression of disease symptoms was observed in the group receiving combined treatment alongside traditional therapy, which included immunomodulatory therapy with "Gepone" and nasal spray "Sinulor."

**Restoration of Eustachian Tube Ventilation Function During Treatment**

Before treatment, Eustachian tube patency was graded as follows: Grade II in 15.9% of patients, Grade III in 18.8%, Grade IV in 49.3%, and Grade V in 15.9% of cases (Figure 19).

In the traditional therapy group, 15.6% of patients achieved Grade I patency of the Eustachian tube, while 40.6% demonstrated Grade II patency. In the combined therapy group, Eustachian tube patency was fully restored in 62.2% of patients, and Grade II patency was observed in only 21.6% of cases after treatment.

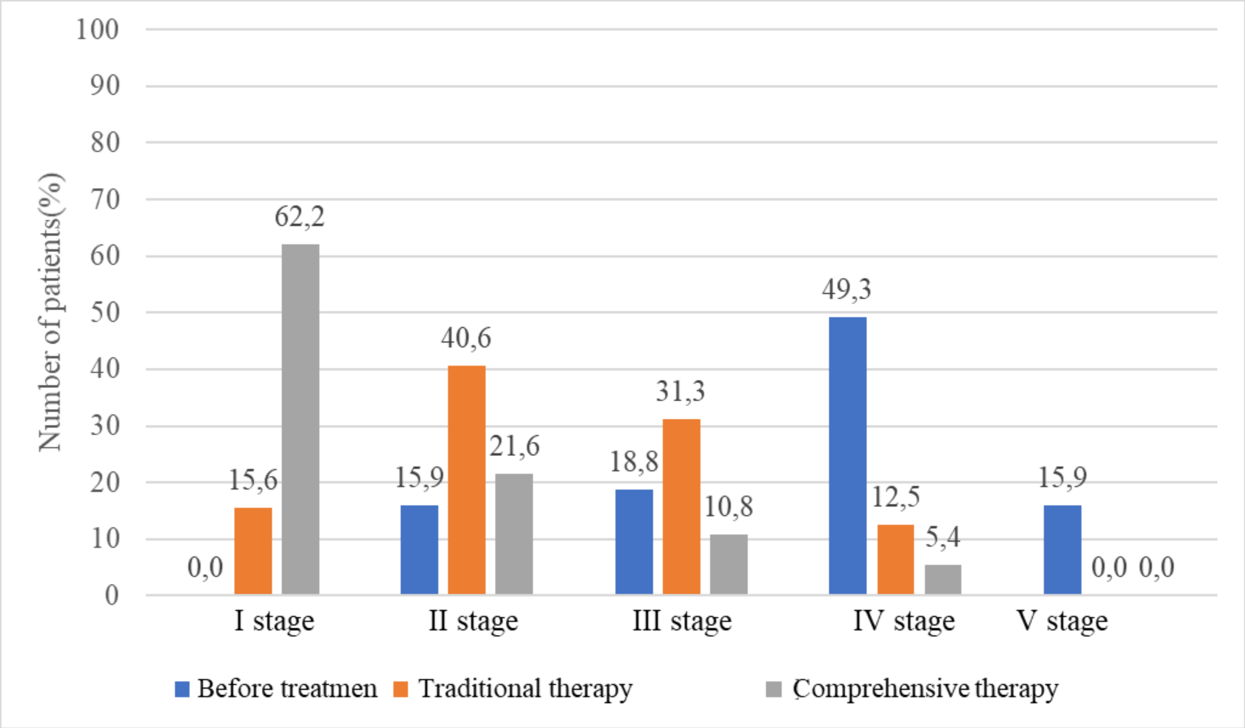



**Figure 19. Assessment of Eustachian Tube Ventilation Function During Treatment in Patients with Exudative Otitis Media (EOM) Related to NAR, AR, and NP**

After treatment, Grade III patency was observed in 31.3% of patients in the traditional therapy group, while only 10.8% of patients in the combined therapy group exhibited this level. Among the remaining patients, Grade IV patency was found in 12.5% of cases in the traditional therapy group and in 5.4% in the combined therapy group.

Thus, the additional introduction of the immunomodulator "Gepone" and the nasal spray "Sinulor" into the traditional therapy for patients with EOM related to NAR, AR, and NP led to a significant improvement in Eustachian tube patency (to Grade I-II) in 83.8% of patients in the combined therapy group. In contrast, this figure reached only 56.2% in the traditional therapy group.

## Tone Threshold Audiometry Results in Patient Groups After Treatment

The results of threshold audiometry are presented in Tables 9 and 10 for the patient groups assessed both before the start of therapy and at the end of the observation period, which lasted 21 days.

**Table 9.**

**Average Air Conduction Thresholds in Patient Groups Before and After the Observation Period, dB (M ± m) (Each ear was evaluated separately)**

| Frequency (Hz) | | Before treatment | Traditional Therapy (n = 32) | Comprehensive Therapy (n = 37) |
|---|---|---|---|---|
| **Bone conduction** | 500 | 43,59±4,83 | 9,42±2,79* | 8,67±1,84* |
| | 1000 | 45,81±3,72 | 11,43±2,57* | 10,11±1,98* |
| | 2000 | 45,11±4,98 | 11,56±2,41* | 9,48±1,76* |
| | 4000 | 43,79±3,94 | 10,18±2,18* | 10,17±1,93* |

**Note: - Statistically Significant Difference Before and After Treatment**

At the end of treatment, there was a decrease in auditory perception thresholds at all tested frequencies of air conduction. On average, in the traditional therapy group, this reduction was 4.4 times, while in the combined therapy group, it was 5 times.

Regarding bone conduction, significant differences were registered in the traditional therapy group at frequencies of 2000 and 4000 Hz, while in the combined therapy group, significant changes were observed at frequencies of 1000 and 2000 Hz. Bone conduction thresholds, which were reduced before treatment, increased by 4-5 dB by the end of the observation period. It is worth noting that the dynamics of bone conduction indicators in our study were minimal, which can be explained by the initially low perception thresholds (Table 10).

**Table 10.**

**Average Bone Conduction Thresholds in Patient Groups Before and After the Observation Period, dB (M ± m)**
**(Each ear was evaluated separately)**

| Frequency (Hz) | | Before treatment | Traditional Therapy (n = 32) | Comprehensive Therapy (n = 37) |
|---|---|---|---|---|
| **Bone conduction** | 500 | 10,83±1,11 | 9,69±1,56 | 8,75±1,82 |
| | 1000 | 11,79±0,84 | 9,81±1,73 | 9,38±1,53* |
| | 2000 | 13,59±0,76 | 10,16±1,94* | 8,13±1,72* |
| | 4000 | 12,49±0,71 | 8,71±1,98* | 9,47±1,33 |

**Note: - Statistically Significant Difference Before and After Treatment**

The air-bone gap is one of the key indicators that must be investigated for diagnosing conductive hearing loss (Table 11).

During treatment, there was a reduction in air-bone gap measurements in both the traditional and combined therapy groups, with a minimum decrease of 30 dB and statistically significant changes at all frequencies before and after treatment.

These data indicate recovery in both the traditional and combined therapy groups; however, the combined therapy group exhibited significantly lower air-bone gap values, and at frequencies of 500 and 4000 Hz, there was no air-bone gap observed.

**Table 11.**

**Average Indicators of Bone-Air Gap Before Treatment and at the End of Follow-Up, dB (M ± m) (Each Ear Assessed Separately)**

| Frequency (Hz) | Before treatment | Traditional Therapy (n = 32) | Comprehensive Therapy (n = 37) |
|---|---|---|---|
| | | 21 days | 21 days |
| **500** | 32,76±3,81 | 0,69±0,42* | 0 |
| **1000** | 34,02±3,44 | 1,86±0,72* | 0,89±0,68* |
| **2000** | 31,52±3,74 | 1,36±0,69* | 1,47±0,82* |
| **4000** | 31,3±3,59 | 1,89±0,81* | 0 |

## *Results of Tympanometry After Treatment*

An important diagnostic procedure for exudative otitis media is tympanometry [108,109]. According to the inclusion criteria for the study, all patients were diagnosed with a pathological type B tympanogram. Tympanometry showed significant improvements in the functional indicators of the middle ear condition in individuals diagnosed with exudative otitis media due to DN, ONP, and NG in both research groups (Figure 20). Only 18.7% of patients in the traditional treatment group had an A-type tympanogram recorded on day 14, while 81.3% of the tympanometric curves were categorized as B and C types. Positive dynamics were higher in the comprehensive therapy group: by day 14, the tympanogram normalized in 64.9% of patients, with B and C type tympanograms registered in only 35.1% of patients. According to the tympanometry results conducted at the end of the observation period, 53.1% of patients in the traditional treatment group showed signs of recovery, but 46.9% still had a B or C type tympanogram. In contrast, in the comprehensive therapy group, 81.1% of patients had normalized tympanograms (A type) by the end of the observation period. Thus, the use of comprehensive therapy, including a local immunomodulator and nasal spray, was more successful for patients with exudative otitis media compared to traditional therapy.

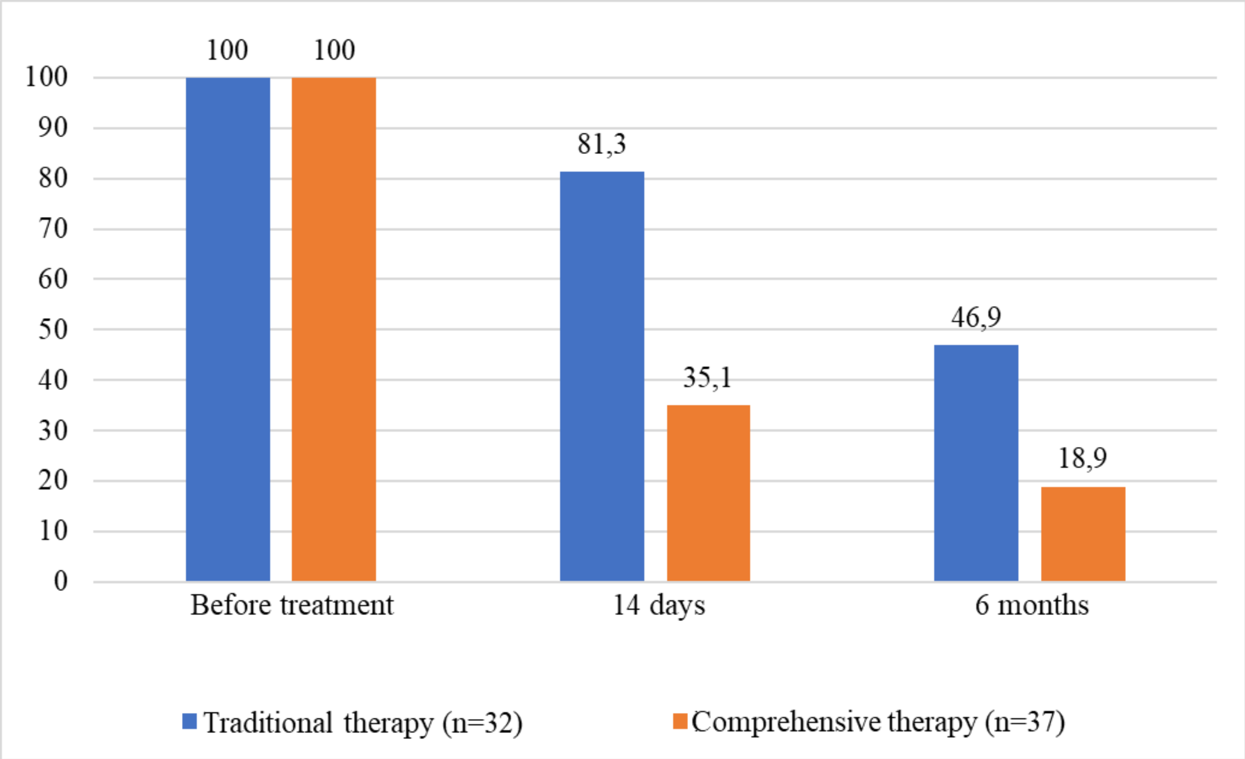



**Figure 20. Number of Patients with Pathological Tympanograms in Patient Groups Over Time.**

### *Results of the Microbiological Landscape of the Nasal Mucosa After Treatment*

As shown in the figure, the pathogenic microbial flora significantly decreased in both therapeutic groups after treatment. Specifically, in 8 patients (29.6%) receiving traditional treatment, five different pathogenic microorganisms were isolated 21 days post-treatment: St. haemolyticus in 3 patients (11%), St. epidermidis in 1 (3.7%), Str. pyogenes in 1 (3.7%), Ps. aeruginosa in 1 (3.7%), and E. coli in 2 patients (7.4%). In contrast, no pathogenic microbes were detected in patients after comprehensive treatment, who instead exhibited isolates consistent with the normal flora of the nasal mucosa. Thus, the inclusion of the nasal spray "Sinulor" and the immunomodulator "Gepone" in the comprehensive treatment led to the normalization of the microbial landscape of the nasal mucosa. Bacteriological analysis of the nasal mucosa flora was repeated 21 days after therapy (Figure 21).

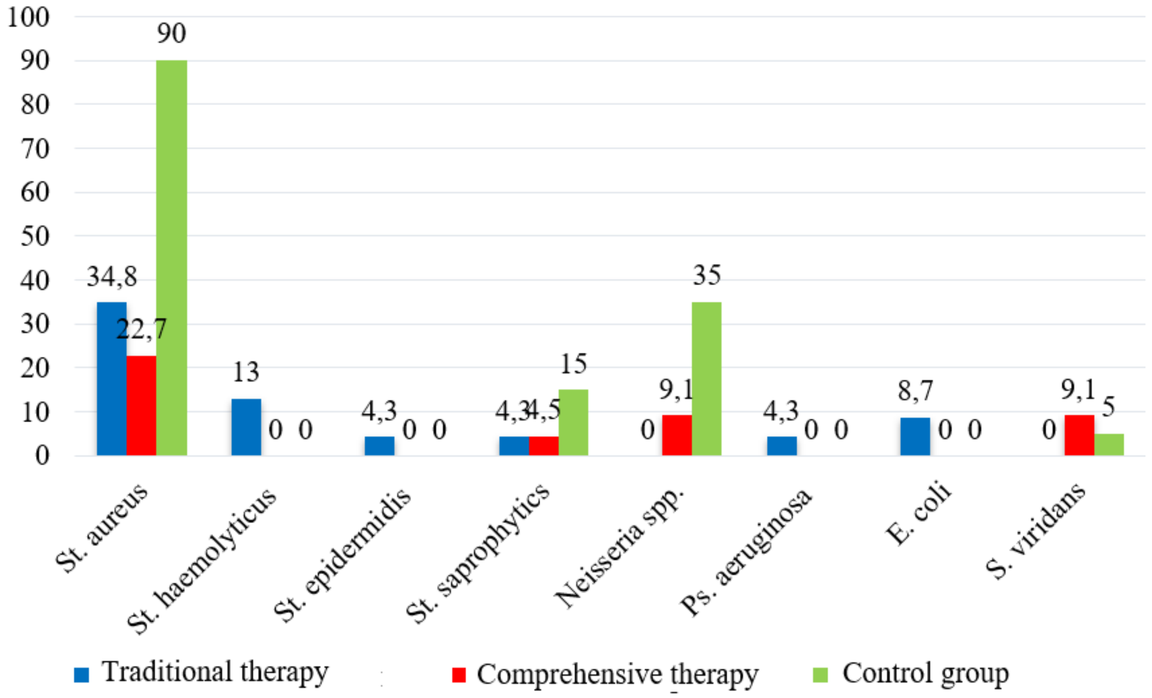



**Figure 21. Qualitative Composition of the Microbial Landscape of the Nasal Mucosa in Patients with Exudative Otitis Media Due to DN, ONP, and NG After Treatment.**

### *Evaluation of Immune Status Indicators After Treatment*

Table 12 summarizes the results of systemic immunity indicators. Before therapy, there were no statistically significant differences between the groups, indicating that all samples based on immune status indicators were comparable. Comparing the average immune status parameters of patients with exudative otitis media before and after comprehensive therapy, we found a significant increase in the number of mature T-lymphocytes (CD3+), which was 1.3 times higher than before treatment; T-helper cells (CD4+) were 1.8 times higher; CD8+ cells were 1.6 times higher; and B-lymphocytes (CD19+) were 1.3 times higher compared to pre-treatment levels. In contrast, the traditional treatment group showed positive dynamics, though less pronounced: a 1.2-fold increase in mature T-lymphocytes (CD3+), a 1.6-fold increase in T-helper cells (CD4+), a 1.5-fold increase in CD8+, and a 1.1-fold increase in B-lymphocytes (CD19+). Regarding humoral immunity indicators, significant results were observed: in the comprehensive therapy group, there was a 2.6-fold increase in IgA, a 2.1-fold increase in IgG, a 2.4-fold decrease in IgM, and a 1.3-fold decrease in IgE compared to baseline levels. Meanwhile, in the traditional treatment group, IgA increased by 2.1 times, IgG by 1.8 times, IgM decreased by 2.0 times, and IgE by 1.2 times. The results presented above indicate a successful restoration of the functional integrity of mucosal barriers after the addition of the immunomodulator to the comprehensive treatment plan.

**Table 12.**

**Average Immunological Indicators in Patient Groups Before and After Treatment (M ± m)**

| Indicators | Before Treatment | Traditional therapy (n = 23) | Comprehensive therapy (n = 25) |
|---|---|---|---|
| | | 21 days | 21 days |
| CD3+ | 46,87±7,57 | 58.01±11,41 | 64,58±12,01* |
| CD4+ | 26,39±7,39 | 41,43±8,41* | 48,89±8,14* |
| CD8+ | 16,06±2,45 | 23,72±4,43 | 25,22±4,82* |
| CD19+ | 20,21±2,53 | 23,12±4,4 | 25,73±5.69* |
| IgA | 1,06±0,21 | 2,23±0,49 | 2,77±0,387 |
| IgM | 2,81±0,24 | 1,38±0,29* | 1,18±0,22 |
| IgG | 6,32±0,79 | 11,58±1,71* | 13,78±2,41 |
| IgE | 96,2±7,59 | 78,72±17,48* | 72,65±18,82* |

Note: - statistically significant difference before and after treatment.

Comparison of the indicators between the two groups showed that the comprehensive treatment, which included Gepone, had an activating effect on T-helper cells. This effect was manifested in an increase in the number of CD3+, CD4+, CD8+, and CD19+ lymphocytes. Furthermore, the treatment exhibited a selective immunomodulatory effect, evident in the increase of immunoglobulins A and G, and a decrease in the levels of immunoglobulins M and E. In the group with immunocorrection, the increase reached statistically significant differences compared to the indicators in the traditional therapy group.

## *Results of Recurrence Study*

An important criterion for the effectiveness of treatment is the number of recurrences over a specified period. After the completion of treatment, the recurrence rates were studied in the following six months among the research groups. The results were as follows: one or two recurrences occurred in 33.3% of patients in the traditional therapy group, compared to 10.7% in the comprehensive therapy group. Three or more recurrences within six months occurred in 7.4% of the traditional therapy group and 3.5% in the comprehensive therapy group (Figure 22).

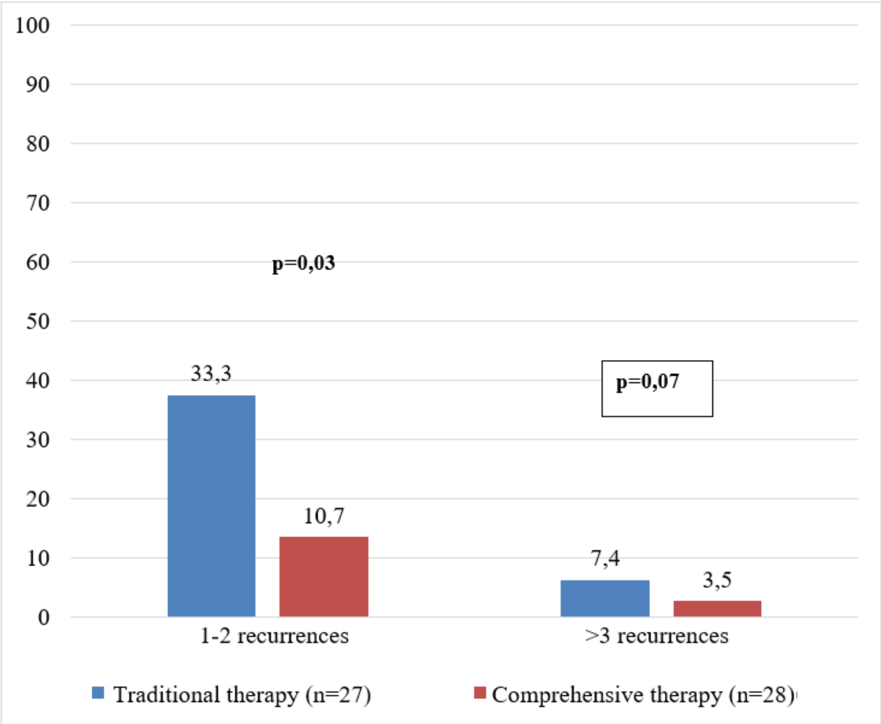



**Figure 22. Number of Recurrences Within 6 Months After Treatment**

The number of recurrences of exudative otitis media decreased by 2.7 times in patients treated with the comprehensive method. The difference between the groups was significant after treatment, as determined by Fisher's exact test. The results of the analysis of recurrence rates within 6 months after treatment confirm that the use of the immunomodulator "Gepone" in combination with "Sinulor" as part of the comprehensive therapy for exudative otitis media in patients with DN, ONP, and NG during the postoperative period demonstrated comparative effectiveness in preventing recurrences of exudative otitis media.

# CONCLUSION

Based on the results obtained during the study, the following conclusions can be made:

1. In cases of exudative otitis media against the background of benign tumors of the nose, paranasal sinuses, and nasopharynx, alongside gradually worsening otological symptoms characterized by unilateral functional impairment of the ear (74.5% prevalence of impaired ventilation function of the Eustachian tube grade III-IV, conductive and mixed hearing loss of grades I-II, and the presence of pathological tympanograms of type B), nasal symptoms are also observed (impaired nasal breathing, sensation of a foreign body, nasal bleeding). The combination of these symptoms may serve as a criterion for oncological vigilance.

2. Exudative otitis media in the context of benign tumors of the nose, paranasal sinuses, and nasopharynx is characterized by a prolonged presence of exudate in the tympanic cavity, indicated by the characteristic endoscopic sign of a "spoke-wheel." The sensitivity of this method was found to be 92.7%, specificity 95%, and diagnostic value 93.6%.

3. The immune status of patients with exudative otitis media due to benign tumors of the nose, paranasal sinuses, and nasopharynx is characterized by a 1.5-fold reduction in the average levels of T-lymphocytes. Specifically, a significant decrease in the relative count of CD3+ cells and their main subpopulations (CD8+, CD4+) was observed. Additionally, a significant deficiency of IgA and IgG was noted, alongside significantly elevated levels of IgM.

4. The use of the drug "Gepone" in combination with the nasal spray "Sinulor" in the comprehensive treatment of exudative otitis media associated with benign tumors of the nose, paranasal sinuses, and nasopharynx is justified. Positive effects on both cellular and humoral immunity were observed, manifested in an increase in the total number of T-helper subpopulations and T-cells, an increase in IgA and IgG levels, and a significant decrease in IgM levels. Comprehensive treatment of exudative otitis media resulted in a reduction of patient treatment duration by 2-4 days, which was statistically confirmed ($p<0.05$).

# PRACTICAL RECOMMENDATION

1. The identification of the "spoke-wheel" sign during otomicroscopy will allow for the diagnosis of exudative otitis media in patients with benign tumors of the nose, paranasal sinuses, and nasopharynx, thereby enhancing oncological vigilance among physicians (see appendix).

2. For patients with exudative otitis media associated with benign tumors of the nose, paranasal sinuses, and nasopharynx, it is recommended to include nasal irrigation in the treatment regimen post-surgery. This should involve irrigating the mucosa of the nasopharynx and the openings of the Eustachian tubes with 9.0 ml of a 0.02% solution of the immunomodulator "Gepone," followed by transtympanic administration of 0.5 ml and the use of the nasal spray "Sinulor" at a dose of one spray in each nasal passage four times daily.

3. Patients with exudative otitis media due to benign tumors of the nose, paranasal sinuses, and nasopharynx should be monitored by an otorhinolaryngologist for six months post-treatment for preventive examinations and to determine the necessity of surgical intervention for exudative otitis media.

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