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FUNCTION OF THE MUCOCILIARY EPITHELIUM IN
PATIENTS WITH FUNGUS BALL OF THE MAXILLARY SINUS

321.16 - Otorhinolaryngology

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The thesis was elaborated at the Otorhinolaryngology Department of the Public Institution of the State University of Medicine and Pharmacy “Nicolae Testemitanu” and in the Otorhinolaryngology department of IMSP the Republican Clinical Hospital “Timofei Moşneaga”.

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INTRODUCTION

The actuality and importance of the approached problem: Fungal rhinosinusitis (FRS) is an important pathological entity, an extremely controversial topic in today's medical world for the various directions of research it offers [1, 2, 3]. In recent years, the incidence of FRS has increased significantly, possibly due to air pollution, increased allergies, climate change and contemporary diagnostic methods [2, 4, 5]. Currently, the RSF classification includes: invasive forms with three subtypes (acute RSFI, chronic RSFI and granulomatous RSFI) and non-invasive forms with two forms (fungus ball and allergic RSF) [6, 7, 8, 9].

Fungus ball (FB) of the paranasal sinuses is the most common subtype of RSF, defined as chronic non-invasive RSF, without allergic mucin, which usually develops in immunocompetent individuals [4, 6]. Complete removal of the lesion and adequate drainage of the sinus by endoscopic surgery is the preferred therapeutic approach for the treatment of this condition with a low recurrence rate after surgery [10].

Despite the recognition of FRS as a serious entity for over two centuries and all the studies that have taken place in recent years, the disease remains a controversial disease, with evasive pathophysiology, incomplete knowledge of epidemiology and medical mycology. Further research is needed to elucidate the exact etiological and pathogenetic role of fungal species in chronic rhinosinusitis (CRS), perfecting the diagnosis and treatment of FRS for a better prognosis [3, 6, 11].

Based on the above, we set the next **purpose of research** – a prospective comparative study of microbiological, histopathological features and functionality of nasal pseudostratified ciliated epithelium *in vitro* in patients with FB of the maxillary sinus to optimize the diagnosis and treatment.

In order to achieve this purpose, the following **research objectives** were stipulated:

1. The study of the morbidity rate of fungus ball of the maxillary sinus in the variety of rhinosinusal diseases.
2. Determination of the functionality of the mucociliary epithelium *in vitro* (optical microscopy) and histopathological particularities in patients with fungus ball of the maxillary sinus.
3. Establishing the diversity of microbiological agents involved in fungus ball of the maxillary sinus.
4. Development of a standardized diagnostic and treatment algorithm for patients with fungus ball of the maxillary sinus.

The **general methodology of the research** was developed based on the publications of local authors [12, 13] and abroad [6, 14, 15, 16]. For the research and solution of the problems approached in the thesis we used the methods: analytical, historical, clinical, anamnestic, paraclinical, statistical, mathematical, monitoring and evaluation.

To achieve the purpose and objectives of the research we proposed to perform two studies: 1) a retrospective study which evaluated the epidemiological aspects of fungus ball in the spectrum of rhinosinusal diseases and 2) a prospective comparative study which analyzed the microbiological, histopathological features and functionality of the pseudostratified ciliated epithelium *in vitro* in patients with fungus ball of the maxillary sinus for the correct adjustment of the diagnostic and treatment protocol.

Scientific novelty of the obtained results:

1. We analyzed the characteristic of clinical forms and the diversity of microbiological agents involved in fungus ball of the maxillary sinus.
2. We estimated the importance and efficiency of optical microscopy and histopathological examinations in the clinical approach of patients with fungus ball of the maxillary sinus.
3. We studied the dynamic evolution of the nasal functional state and the nasal pseudostratified ciliated epithelium in vitro in patients with fungus ball of the maxillary sinus for the correct adjustment of the diagnosis and treatment protocol.
4. We proposed criteria for conservative treatment of the fungus ball of the maxillary sinus, complementary to surgical treatment, depending on the functionality of the mucociliary epithelium.
5. We performed a demanding monitoring on the evolution and prognosis of patients with fungus ball of the maxillary sinus, depending on the methods of conservative treatment associated with surgical treatment.

The **applicative value** of the paper consists in the elaboration of a standardized diagnosis and treatment algorithm for patients with fungus ball of the maxillary sinus and its implementation in the national clinical protocol.

Approval of the thesis results. The results of the study were presented and discussed in the following national and international scientific forums:

- XXX Marius S. Plouzhnikov International Conference of Young Otorhinolaryngologists. May 23, 2018, St. Petersburg, Russian Federation. Awarded with first place in the Rhinology category.
- National ENT Conference with international participation "Updates in the diagnosis and treatment of ENT diseases, May 17, 2019, Chisinau, Moldova.
- 5th Congress of the Romanian Rhinology Society, September 4-7, Eforie Nord, Romania, 2019.
- Conference of the Days of the State University of Medicine and Pharmacy "Nicolae Testemitanu", October 17, 2019, Chisinau, Moldova.

The thesis was discussed and approved at the Meeting of the Department of Otorhinolaryngology of IP USMF "Nicolae Testemitanu" (verbal process no. 7 from 24.06.2020) and at the Meeting of the Scientific Seminar of Otorhinolaryngology-Ophtalmology (verbal process no. 12 from 03.07.2020).

The opinion of the Research Ethics Committee for the research study (verbal process no. 65 of June 17, 2016) was positive.

Keywords: fungal rhinosinusitis, FB, mycological examination, microbiological examination, histopathological examination, allergy, invasive, nasal mucociliary epithelium, optical microscopy.

FUNGAL RHINOSINUSITIS

1.1. General criteria for etiology, pathophysiology, diagnosis and treatment of fungal rhinosinusitis

FRS is a clinical condition with various manifestations, ranging from simple colonization to acute invasion, a disease with confusion and controversy over its exact pathogenesis and effective treatment, which should be considered in all immunocompromised patients and all patients with CRS [1, 9, 18]. Fungal infections of the paranasal sinuses can manifest as two distinct

entities. Invasive forms include 3 subtypes: acute invasive fungal rhinosinusitis (IFRS), chronic RSFI and granulomatous IFRS. Non-invasive forms include 2 subtypes: FB and allergic FRS (AFRS). The most severe (invasive) infections occur in patients with compromised immunity and are relatively easily recognized by the extent of symptoms and sudden evolution. The mortality rate is quite high in the case of IFRS, and early diagnosis and appropriate treatment are vital [19]. Non-invasive infections are chronic and, unfortunately, are often confused and treated for long periods of time as bacterial CRS, until the exact recognition of the etiology of the disease [1, 6, 7, 20]. However, each form of FRS has a characteristic clinical presentation and evolution, and the immune status of the host plays a critical pathophysiological role. The correct diagnosis and early initiation of treatment allow to obtain optimal results, avoiding the development of complications or a fatal result [9, 18, 21].

The diagnosis of FRS is primarily histological. The distinction between IFRS and non-invasive FRS is based on histopathological evidence of fungal invasion of the sinus mucosa and bone, and possibly spread to adjacent structures and tissues (orbit, anterior skull base and pterygopalatine fossa). In non-invasive FRS the fungal infection is limited to the sinus cavity, without fungal invasion of the mucous membrane and bones. However, a clinical-radiological correlation is required in the exact diagnosis of FRS, a condition that frequently misleads [10, 19].

FRS treatment is divided into two main directions: 1) surgical treatment, which aims to eliminate the fungal antigen, and is, most commonly, the main treatment and 2) conservative treatment, which tries to prevent recurrences, but is not standardized so far and there is no clear evidence of the efficacy of any of the therapeutic agents used. Sinus endoscopic surgery is used in conjunction with long-term conservative treatment, oral and intranasal glucocorticosteroids, immunotherapy, antifungal medication, and antimicrobial agents [22].

An increasing amount of scientific evidence suggests that herbal medicines may be helpful as an adjunctive and auxiliary treatment in rhinosinusitis. Sinupret® (Bionorica, Neumarkt, Germany) was developed by phytoneering processes, which allows a higher concentration and purification of active ingredients in plants, used to maintain the normal function of sinus cavity membranes. The preparation contains active ingredients in the form of powder from 5 plants, is available in the form of pills or solution, has a complex action (mucolytic, bronchodilator, anti-inflammatory, antiviral, antibacterial, secretolytic and immunostimulant), a low level of side effects and is effective for the treatment of rhinosinusitis [23, 24].

Sinupret has been widely used in Europe for over 70 years in the treatment of respiratory diseases, associated with inadequate mucociliary clearance (CMC) - as a mucoactive agent for acute rhinosinusitis or CRS - and has an excellent safety and efficacy profile. Sinupret is an important adjuvant that provides a faster and clinically relevant remission of symptoms, imaging and ultrasonographic findings and improves quality of life, thus improving the results of pharmaceutical treatment in ARS, CRS, respiratory viral infections in children and adults [23, 24].

1.2. Diagnosis and contemporary management of non-invasive fungal rhinosinusitis

Fungus ball of the paranasal sinuses is a distinct clinical entity, a discrete non-invasive form, localized, not at all or slightly aggressive, extramucosal, occurring especially in immunocompetent patients and defined as an accumulation of dense fungal elements in the cavity of a single sinus. The condition occurs more frequently in elderly patients, with a mean age of 64 years, and is predominantly female. Classically, the disease involves a single paranasal sinus in

over 90% of cases, most commonly the maxillary sinus [6, 20, 25, 26]. The condition has been identified in 4-26%, and according to recent studies data about 0.29-5.4% of all cases of inflammatory CRS undergoing surgery [4, 28]. However, the incidence of FB in recent years has shown a marked increase, and an occasional decrease in immunity may be the cause of the transformation of this condition into an invasive form [6, 20, 25, 26].

The most commonly involved pathogen is *Aspergillus* (in 90-96% of cases), mainly *Aspergillus fumigatus* (in 93% of cases), less frequently *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus nidulans*. In second place are the species *Mucorales* and much less often other species of fungi are detected [6, 25, 29]. The pathophysiology of FB remains largely unknown and more research on this issue is indispensable. For the development of the disease, 2 conditions are necessary: the penetration of the hyphae and fungal spores into a paranasal sinus and the creation of the environment that contributes to the growth of fungi. These conditions occur when some pathologies disrupt normal CMC and/or obstruct the sinus ostium. 3 possible theories of FB development have been suggested: aerogenic, odontogenic and mixed [26, 28].

The clinical picture in patients with FB is nonspecific, often identical to the symptoms in paucisymptomatic, recurrent bacterial CRS, resistant to antibiotic treatment (observed in 58.5% of patients). Characteristic imaging findings and histopathological examination confirm the diagnosis. Calcifications and/or erosion of the inner wall of the sinus on computed tomography (CT) scanning are considered the most specific signs and have a strong suggestive role for a correct diagnosis. The histopathological image is characteristic - luminal aggregation of fungal hyphae [6, 20, 25, 26].

FB is usually diagnosed occasionally during bacterial CRS treatment. Positive diagnosis of FB of the paranasal sinuses is established based on clinical-pathological criteria, suggested by deShazo:

1. Imaging evidence of sinus opacification with or without the association of flocculating calcifications.
2. Mucopurulent material such as syrup or clay in a sinus.
3. A dull and dense conglomeration of hyphae (fungal ball), separated from the respiratory mucosa of the sinus.
4. Chronic non-specific inflammatory response of varying intensity in the mucosa adjacent to the fungal elements (the response may include lymphocytes, plasma cells, mast cells and eosinophils, but allergic mucin, granulomas and predominance of eosinophils are absent).
5. Absence of histological evidence of fungal invasion of the mucosa, blood vessels or bone, visualized microscopically in staining for fungi [21, 27, 28].

The purpose of treating patients with FB is surgical ablation of the mass of the fungal hyphae with restoration of drainage and ventilation of the affected sinus. In most cases, the condition is managed by endoscopic techniques [9, 18, 22]. Both intraoperatively and postoperatively, it is essential to irrigate the sinuses with saline solutions, which increase CMC, facilitate the elimination of mucous secretions and the removal of any fungal residues [26, 27, 28, 29]. Also, intraoperative cortisone instillations can be used intraoperatively (due to the anti-inflammatory effect) [26, 28, 29]. Because FB is a non-invasive form of FRS and the outcome of surgical treatment is usually excellent, systemic or topical antifungal treatment is rarely required [22, 26, 28, 29].

Therefore, the diagnosis of FB is often delayed, because the symptoms are generally similar to those of bacterial CRS, the evolution of the disease is slow, oligosymptomatic and non-

invasive [29]. FB should be suspected in immunocompetent and non-atopic patients with recurrent or resistant unilateral sinusitis. CT scan is the imaging examination of choice with typical, non-pathognomonic, signs that include heterogeneous opacification of the affected sinus, usually the maxillary sinus, associated with hyperdense foci, and uncommon sinus bone wall sclerosis [18, 27, 28]. Medical history, clinical examination, endoscopic examination and imaging examination present valuable information only for the suspicion of FB, the definitive diagnosis is based on macroscopic evaluation, biopsy and histopathological examination of surgical pieces [6]. Endoscopic sinus surgery is the basic treatment with excellent results and limited morbidity that does not require local or systemic antifungal treatment [18, 27, 28].

Allergic fungal rhinosinusitis is a clinically distinct and common form of RSF with the formation of nasal polyps, an immunologically mediated non-invasive fungal inflammation, a chronic, hypertrophic and stubborn (refractory) sinus disease, with a marked propensity for recurrence. The disease is characterized by the accumulation of allergic fungal mucin in the nasal sinuses, hypersensitivity type I (allergic reaction to extramucosal fungi in the sinus cavity), characteristic histological image and a predilection for mucus formation and bone erosion [6, 18, 30].

The major diagnostic criteria for AFRS are: a) eosinophilic/allergic mucin, often with Charcot-Leyden crystals, no evidence of tissue fungal invasion, b) the presence of fungi under direct microscopy, no fungal invasion in sinus tissue, or sinus content culture, c) PN with an incidence ranging from 75% to 100% of cases, d) characteristic imaging signs that reflect the structure of the growths developed in the sinuses and e) type I hypersensitivity to fungi (history, skin or serological tests). However, not all 5 criteria are necessary for the diagnosis of AFRS. In some cases, the macroscopic appearance of eosinophilic mucus is sufficient for diagnosis, in other cases it is considered positive fungal cultures of nasal or sinus mucus in the absence of appropriate fungal elements. Some authors dispute the need to demonstrate a fungal allergy. Recently, a group of international experts redefined RSFA as “histological confirmation of eosinophilic mucus and the presence of type I fungal hypersensitivity in patients with CRS” [20, 30].

The other 6 criteria are minor: 1) history of asthma, 2) unilateral predominance, 3) imaging evidence of bone erosion, 4) positive rhinosinusal fungal culture, 5) presence of Charcot-Leyden crystals in samples taken during surgery and 6) eosinophilia serum [2, 6].

Therefore, RSFA is a unique entity with controversies in classification, pathogenesis, diagnostic criteria and management protocols. The condition usually occurs in young, immunocompetent patients who often have a history of atopy, including allergic rhinitis and/or asthma, or a long-term clinical picture of CRS, refractory to antibiotic treatment. Nasal polyps are present in almost all patients, and extra-sinus complications - in a proportion of patients. The composition of inflammatory cells in the mucous membranes is mainly characterized by eosinophils and lymphocytes [18, 30]. The disease is a complex interaction of IgE-mediated systemic / local hypersensitivity to fungal antigens, host defense mechanisms (innate and adaptive) and possibly superantigens. There is usually involvement of several sinuses, including pansinusitis and rhinitis. The condition tends to be bilateral and there is a common nasal component. The diagnosis of RSFA combines clinical, radiological, microbiological and pathological examination, but the definitive diagnosis can be made only by examining surgical specimens - the characteristic appearance of eosinophilic mucin is the safest indicator of RSFA [6, 7, 18, 30]. RSFA management is largely surgical along with an important role for oral corticosteroids and a developing role for immunotherapy and antifungal remedies [2].

1.3. Clinical features of diagnosis and treatment of invasive fungal rhinosinusitis

RSFI is a condition that requires emergency diagnosis and early treatment due to the vital and functional prognosis reserved for initiating aggressive surgical and systemic antifungal treatment. Essentially, this condition occurs in immunocompromised patients - with neutropenia, who administer immunosuppressive therapy, with malignant hematological diseases, with organ and bone marrow transplantation, infected with advanced human immunodeficiency virus, corticosteroids, with diabetes and malnutrition. Much less frequently (but cases are reported), RSFI can occur in immunocompetent individuals. Thus, most patients with RSFI already have poor physical development, due to previous diseases or associated with treatment, and the prognosis is reserved and high mortality. In addition, these factors contribute to difficulties in the diagnosis and treatment of RSFI, which can progress rapidly with significant disorders [6, 25].

The following diagnostic criteria are proposed for the diagnosis of RSFI: 1) rhinosinusitis confirmed on imaging examination, 2) histopathological evidence of fungal invasion of the mucosa, submucosa, blood vessels or bones of the paranasal sinuses and 3) necrotic tissue with minimal infiltration of inflammatory cells [6, 8, 25].

Acute invasive fungal rhinosinusitis is generally a rare condition, but the most dangerous form of FRS and the most common form of IFRS, with an evolution of up to 4 weeks, which occurs in patients with immunocompromised status, progresses rapidly, puts in life-threatening and requires immediate medical attention. Patients with this disease previously had survival rates of 20-75%, which correlates with the control of the underlying condition. Recent studies have shown, along with improved diagnosis, treatment and prophylaxis (active surveillance of the high-risk population, reversal of neutropenia and other causes of immunosuppression, reversal of diabetic ketoacidosis, prompt aggressive surgical debridement and systemic antifungal chemotherapy), amelioration of relief mortality from 50-80% to about 18% [9, 18, 20].

Chronic invasive fungal rhinosinusitis, unlike acute IFRS, is much rarer, progresses over a longer period (4 to 12 weeks or more) and has a much slower destructive process. Insidious progression takes place over several months to years, in which fungal organisms invade the mucosa, submucosa, blood vessels and bone walls of the paranasal sinuses. Extension to the vascular network or adjacent structures and inflammatory reactions are very rare. The most affected are the ethmoid bone or sphenoid sinuses, but can involve any paranasal sinuses [9, 18, 20].

Granulomatous invasive fungal rhinosinusitis, also known as primary paranasal granuloma and indolent FRS, is found in patients with an easily identifiable immune deficiency. The evolution is slowly progressive, longer than 12 weeks and can last from a few months to several years, and symptoms include chronic migraines and gradual edema of the face, until vision can be affected [7, 20].

In conclusion, FRS is a common condition, the main clinical manifestations include nasal congestion, purulent or bloody rhinorrhea, headache and/or a feeling of impaired sense of smell. In recent years, the incidence of FRS has increased considerably, due to increasing numbers and diversity of pathogenic fungi involved in the disease, increasing life expectancy of the population, contemporary diagnostic equipment and increasing the frequency of conditions that favor fungal infections. Currently, 5 types of FRS are recognized: non-invasive (FB, AFRS) and invasive (acute IFRS, chronic IFRS, granulomatous IFRS). Each of the FRS subtypes has a different clinical

presentation, distinct from other forms and partially overlapping, is associated with unique imaging features and specific treatment. The diagnosis of RSF is primarily histological. The distinction between RSFI and non-invasive RSF is based on histopathological evidence of fungal invasion of the sinus mucosa, bone, blood vessels, and possibly spread to adjacent structures and tissues (orbit, anterior skull base, and pterygopalatine fossa). In non-invasive FRS the fungal infection is limited to the sinus cavity. Effective management of FRS requires correct diagnosis and histological classification, because the evolution, treatment and prognosis of FRS caused by different species, especially *Aspergillus* and *Mucorales*, are radically different. Treatment includes complete removal of the lesion and proper drainage of the sinus by surgery, combined with antifungal and immunomodulatory treatment.

STUDY MATERIAL AND METHODS

The work was performed within the Department of Otorhinolaryngology of the State University of Medicine and Pharmacy "Nicolae Testemitanu". The research was carried out in the Department of Functional Surgery, Speech Therapy and Otorhinolaryngological Recovery of the Public Medical-Sanitary Institution Republican Clinical Hospital "Timofei Moşneaga", the laboratory of the Department of Histology, Cytology and Embryology of the Public Institution State University of Medicine and Pharmacy "Nicolae Testemitanu" and laboratory Synevo in accordance with the methods applied or developed [17].

In order to achieve the research purpose and objectives, we set out to conduct two studies: a prospective study and a retrospective study. The retrospective study evaluated the epidemiological aspects of FB in the spectrum of rhinosinusal disorders. In order to determine the incidence of FB among hospital rhinosinusal diseases, we selected all patients with rhinosinusal diseases, treated during 2011-2015 in the Department of Functional Surgery, Speech Therapy and Otorhinolaryngological Recovery of the Public Medical-Sanitary Institution of the Republican Clinical Hospital "Timofei Mosneaga". The prospective study was conducted at the Department of Otorhinolaryngology of the Public Institution State University of Medicine and Pharmacy "Nicolae Testemitanu" and in the Department of Functional Surgery, Speech Therapy and ENT Recovery of the Public Medical-Sanitary Institution Republican Clinical Hospital "Timofei Moşneaga" during 2016- 2019.

The prospective comparative study of the microbiological, histopathological features and functionality of the nasal pseudostratified ciliated epithelium in vitro in patients with FB of the maxillary sinus to optimize the diagnosis and treatment protocol was performed on a group of 60 adult patients aged 18-68 years with FB of the maxillary sinus. We divided the general study group into 2 sublots: 1) study group 1 (30 patients) treated by functional endoscopic sinus surgery (FESS) and conservative (washing with saline and topical vasoconstrictor solutions); 2) study group 2 (30 patients) treated with FESS and conservative (lavage with saline solutions, topical vasoconstrictors and Sinupret oral extract until and after FESS).

The study protocol was approved by the Ethics Committee of IP USMF "Nicolae Testemitanu". Informed consent was obtained from each patient prior to inclusion in the study. All patients were informed about the benefits and risks of surgery and conservative treatment for FB of the maxillary sinus.

We used the following methods of investigation: clinical, laboratory, special laboratory (microbiological examination, histopathological examination, cytological examination, optical

microscopy examination), instrumental (nasal endoscopy), imaging (radiological examination, computed tomography of the paranasal sinuses with score estimation Lund-Mackay, magnetic resonance imaging), evaluation of quality of life using the SNOT-22 questionnaire, evaluation of olfactory function through questionnaires.

Primary data processing was performed using the functions and modules of the "Statistical Package for the Social Science" (SPSS) version 16.0 for Windows (SPSS Inc., Belmont, CA, USA, 2008) and Microsoft Office Excel on the personal computer through statistical procedures. descriptive (frequency tables, graphs, numerical indicators - lowest and highest values, average, average error, etc.) and inferential (assessing the characteristics of a population and testing statistical hypotheses). The 't' test for independent samples was used to estimate the significant differences between the means of two groups. The dynamics of the group mean values was evaluated by the "t" test for pair-samples. Contingency table data were analyzed by the method of variational statistics (χ^2). Differences with bilateral value $p < 0.05$ were considered statistically significant.

3. DIAGNOSIS AND TREATMENT OF PATIENTS WITH FUNGUS BALL OF THE MAXILLARY SINUS

3.1. The morbidity rate of fungus ball of the maxillary sinus in the variety of rhinosinusal diseases

During 2011-2015 in the Department of Functional Surgery, Speech Therapy and Otorhinolaryngological Recovery of the Public Medical-Sanitary Institution Republican Clinical Hospital "Timofei Moşneaga" were admitted, diagnosed and treated 7696 patients with rhinosinusal disorders, including 51 patients with FB, cumulative prevalence of 0.66%. Against the background of a relatively stable annual number of patients with rhinosinusal diseases, the number of patients with FB of the maxillary sinus increases (from 0.07% in 2011 to 0.13% in 2012, 0.32% in 2013, 1.11% in 2014 to 1.67% in 2015), a fact probably explained by alerting clinicians to the presence of fungi, improving diagnostic methods, correct guidance of clinicians in making the diagnosis and differential diagnosis of RSF.

3.2. Patients with maxillary sinus fungus ball treated with FESS and conservative (washing with saline solutions, topical vasoconstrictors)

The mean age of the patients in study group 1 was 42 ± 2 years. In this group predominated women (70.0%) and people working in the field of work (90.0%). Harmful factors at work found 25.9% and a history of rhinosinusal pathology - all 100.0% patients.

The onset of the disease was slow in all patients with FB of the maxillary sinus. Most commonly, patients reported nasal discharge or rhinorrhea (100.0%), headache (100.0%), difficult nasal breathing (96.7%), pain in the maxillary sinus region with irradiation in the teeth of the maxillary arch (93.3 %), pain in the projection of the affected maxillary sinus (86.7%), permanent nasal obstruction (70.0%) and foreign body sensation in the nasal cavity (66.7%). Objective examination noted nasal secretions (100.0%), olfactory disorders (100.0%), difficult nasal breathing (93.3%), sensitivity to palpation (93.3%), closed rhinolalia (63.3%) and soft tissue edema in the cheek region (70.0%). Nasal endoscopy found nasal mucosa and affected middle

nasal horns (100.0%), nasal secretions (100.0%) and hypertrophy of the unciform apophysis (63.3%).

In patients in study group 1, the laboratory examination revealed altered hemoleukogram (60.0%), bacterial flora (80.0%) and fungal agents (63.3%) in nasal secretion. The nasal mucus content included fungal conglomerates (56.7%), neutrophils (60.1%) and eosinophils (10.0%). The most common changes on CT examination were opacification of the maxillary sinuses (100.0%), blockage of the ostiomeatal complex (63.3%) and opacification of ethmoidal cells (26.7%).

Conservative treatment until hospitalization was administered in 100.0% and topical glucocorticosteroids - 70.0% patients in study group 1. All patients in this study group underwent treatment by antrostomy with FB ablation, combined with other surgical methods (anterior ethmoidotomy, submucosal resection of nasal cornets, septoplasty). The vast majority of patients (90.0%) were satisfied with the outcome of treatment and showed a favorable postoperative evolution (improvement of nasal respiration, restoration of smell, absence of pre-hospitalization complaints, increased ciliary beats frequency (CBF), reduced severity of symptoms).

Histopathological examination found disorders of the integrity of the mucociliary epithelium in 60.0% of cases, infiltration with inflammatory cells (polymorphonuclear and mononuclear) of the mucociliary epithelium, lamina propria, submucosa and periglandular space (100.0%), disorders of the alveolar glands 90.0 % and blood vessel disorders 90.0%. Histopathological examination in FB was positive in 66.7% of cases.

3.3. Patients with maxillary sinus fungus ball treated with FESS and conservative (washing with saline solutions, topical vasoconstrictors, Sinupret oral extract until and after FESS)

The mean age of the patients in study group 2 was 40 ± 2 years. In this group predominated women (76.7%) and people working in the field of work (76.7%). Harmful factors at work were found by 43.5% of patients and a history of rhinosinusal pathology - all 100.0% of patients.

The onset of the disease was slow in all patients with FB of the maxillary sinus. The most common charges were difficult nasal breathing (100.0%), nasal discharge or rhinorrhea (96.7%), pain in the affected maxillary sinus region (96.7%), headache (93.3%), pain in the region maxillary sinus with irradiation in the teeth of the maxillary arch (86.7%), permanent nasal obstruction (66.7%) and foreign body sensation (66.7%). Objective examination noted nasal secretions of various types (100.0%), olfactory disorders (100.0%), difficult nasal breathing (96.7%), sensitivity to palpation (93.3%), closed rhinolalia (60, 0%) and soft tissue edema in the cheek region (56.7%). Nasal endoscopy found damage to the nasal mucosa and middle nasal turbinates (100.0%), nasal secretions (100.0%) and hypertrophy of the unciform apophysis (36.7%).

In the patients from group 2 of the study, the laboratory examination found modified hemoleukogram (43.3%), bacterial flora (60.0%) and fungal agents (60.0%) in the nasal secretion. The nasal mucus content included fungal (60.0%) and neutrophil (40.0%) conglomerates. On CT examination, opacification of the maxillary sinuses (100.0%), blocked ostiomeatal complex (73.3%) and opacification of ethmoidal cells (40.0%) were detected.

Conservative treatment until hospitalization was administered by all 100.0% of patients and topical glucocorticosteroids - 70.0% of patients. All patients in this study group underwent antrostomy treatment with FB extraction, combined with other surgical methods (anterior ethmoidotomy, posterior ethmoidotomy, total ethmoidotomy, left unilateral submucosal resection of the left nasal turbinate, submucosal resection of the nasal turbinate) and septum. All patients

(100.0%) were satisfied with the outcome of treatment, showed a favorable postoperative evolution (improvement of nasal respiration, restoration of smell, absence of pre-hospitalization complaints, increased CBF, reduced severity of symptoms and lack of postoperative complications). Histopathological examination found disorders of the integrity of the mucociliary epithelium (73.3%), infiltration with inflammatory cells (polymorphonuclear and mononuclear) of the mucociliary epithelium, lamina propria, submucosa and periglandular space (100.0%), disorders of the alveolar glands (86, 7%) and disorders of blood vessels (93.3%). Histopathological examination of FB was positive in 63.3% of cases.

3.4. Efficacy of treatment in patients with maxillary sinus fungus ball treated with FESS and conservative (lavage with saline solutions, topical vasoconstrictors or lavage with saline solutions, topical vasoconstrictors, Sinupret oral extract before and after FESS)

The study groups were similar depending on the socio-demographic characteristics (sex, education, living environment, work activity, workplace), risk factors of FB (hereditary rhinosinusal history, pathological history, occupational noxious factors), history medical (systemic conservative treatment, local conservative treatment, frequency of rhinosinusogenic complications), clinical picture (onset of the disease, frequency of accusations, prevalence of concomitant diseases), results of otorhinolaryngological examination (objective, laboratory and instrumental), current surgical treatment, histopathological examination and postoperative evolution (figure 1, 2, 3).

Patients in study group 1, compared to patients in study group 2, had statistically significantly more frequent uncinata process hypertrophy (63.3% and 36.7%, respectively; $p < 0.05$), (63.3% and 36.7%, respectively; $p < 0.05$), although the analysis according to location did not find statistically significant differences. Caseous nasal secretions (16.7% and 0%, respectively; $p < 0.05$), determined on inspection, and the mean value of the Lund-Mackay score (2.8 ± 0.5 and 1.5 ± 0.4 ; $p < 0.05$), determined imagistically, were found to be statistically significantly more frequent in patients in study group 2 (Figure 4).

Although palpation sensitivity was generally similar in both study groups, sensitivity in the right canine fossa (66.7% and 36.7%, respectively; $p < 0.05$) was statistically significantly higher in patients in the study group 1, and sensitivity in the canine fossa left (66.7% and 36.7%, respectively; $p < 0.05$) - statistically significantly more frequent in patients of study group 2.

This fact can be explained by the higher frequency of damage to the maxillary sinus in each study group.

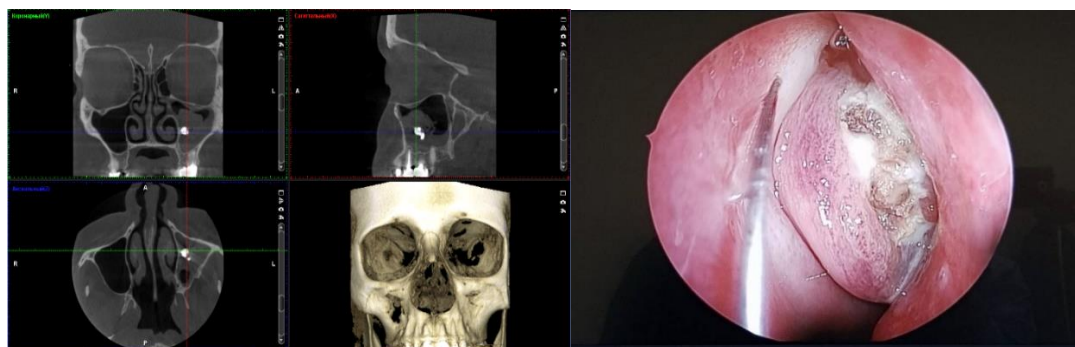


Figure 1. Diagnostic and treatment protocol. A - patient, 48 years old. Fungus ball of the left maxillary sinus with specific metallic calcifications. B - surgical method: left maxillary

antroostomy with maxillary fungus ball ablation, migration of the fungal body in the region of the left ostiomeatal complex.

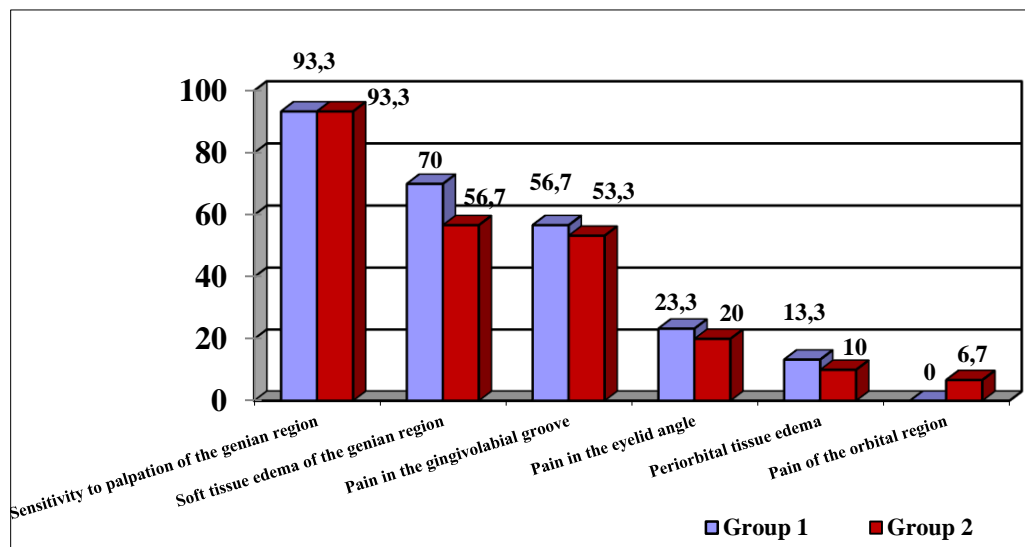


Figure 2. Frequency of complaints (%) in patients of the study groups

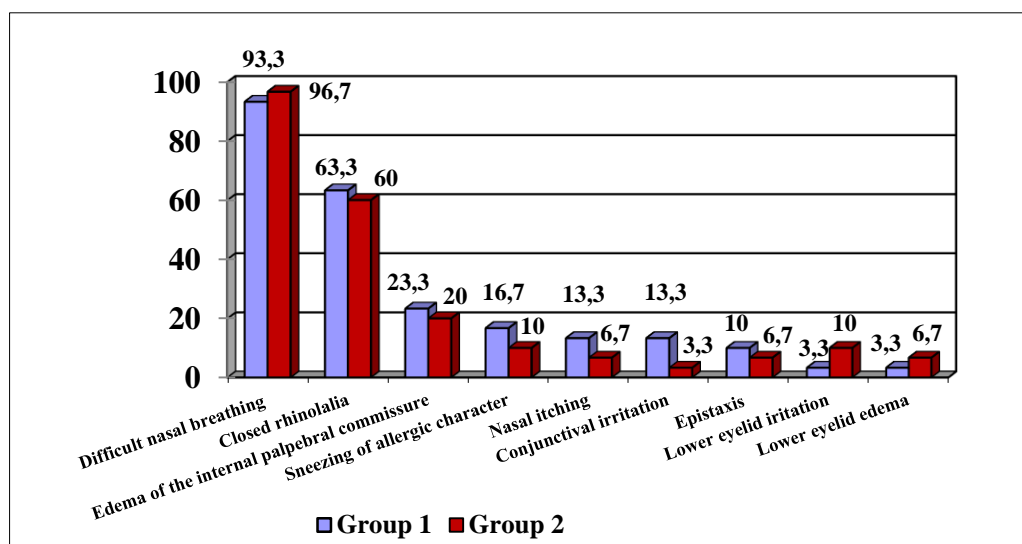


Figure 3. Frequency of clinical manifestations (%) at the objective otorhinolaryngological examination in patients of the study groups.

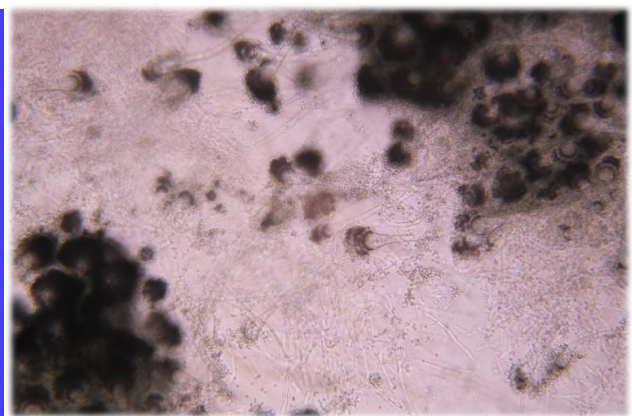
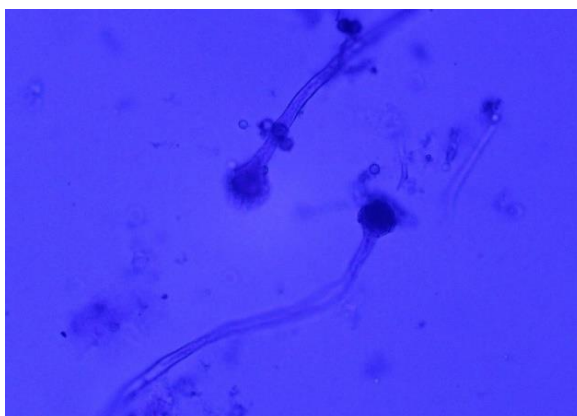


Figura 4. **Fungal hyphae: A – *Aspergillus fumigatus*, B – *Aspergillus niger*.**

Frequency of culture determination of the mycotic agent in nasal secretion, determination of mycotic agent by direct mycological examination and histopathological examination, content pathological content of the nasal secretions, the CT scanograms modifications were similar in both study groups.

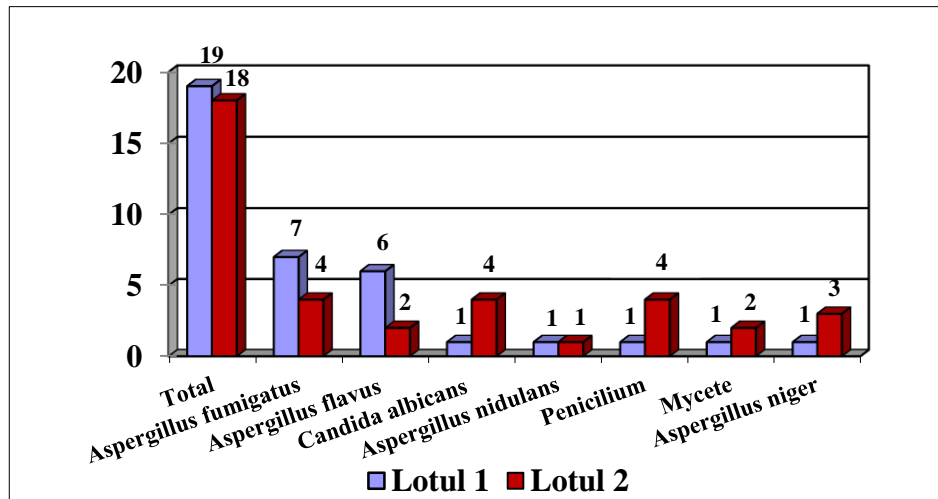


Figura 5. **Mycotic agents (absolute numbers) detected on culture media in patients of the study groups.**

Despite similar parameters, from a statistical point of view of the favorable postoperative evolution and satisfaction with the treatment result in patients in both study groups, in patients of study group 2 there was a tendency to increase of these parameters, but did not reach statistical certainty.

Histopathological examination showed no statistically significant differences in both groups, except for mucociliary epithelial hyperplasia (60.0% and 26.7%, respectively; $p < 0.05$) and mucoid degeneration in large areas (40.0% and 13, 3%, respectively; $p < 0.05$), which were found statistically significantly more frequently in patients in study group 1, and mucoid degeneration in small areas - in patients in study group 2 (23.3% and 3, 3%, respectively; $p < 0.05$).

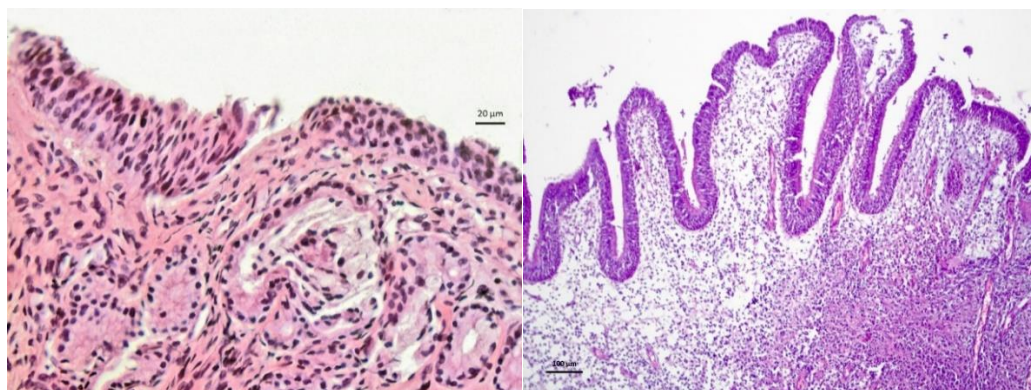


Figure 6. **Tissue fragments of the maxillary sinus mucosa taken intraoperatively. Hematoxylin-eosin staining. A - microphotogram x20; B –microphotogram x10**

Statistically significant differences were revealed in the evaluation of FBC, determined in vitro, after one month post-treatment: FBC of 1-5 Hz was statistically significantly higher in patients in study group 1 (26.7% and 3.3%, respectively, $p < 0.01$), and the mean value of FBC (12.07 ± 0.3 Hz and 6.87 ± 0.3 Hz; $p < 0.001$) and FBC > 5 Hz (96.7% and 73.3%, respectively; $p < 0.01$) were statistically significantly higher in patients in study group 2 (figure 7).

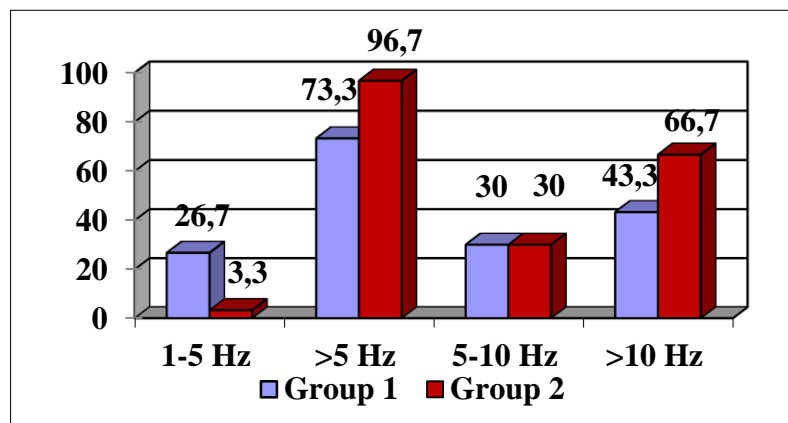


Figura 7. Frequency of ciliary beats 1 month after treatment in patients of the study groups

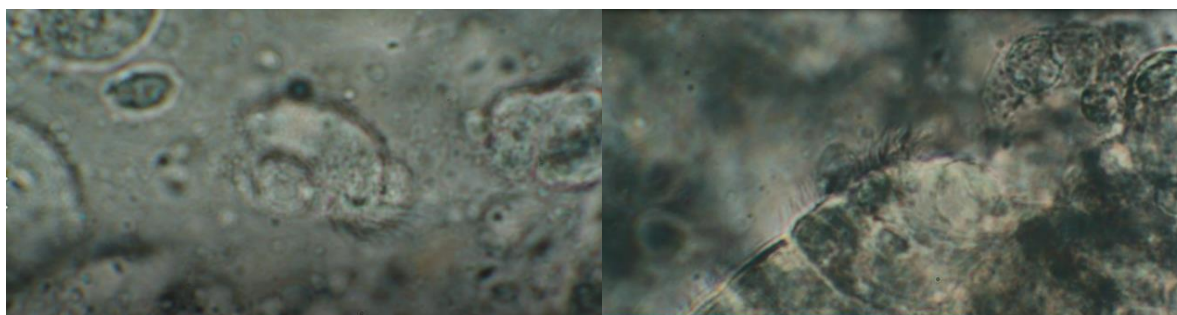


Figure 8. A - phase contrast optical microscopy of the cells of the nasal mucociliary epithelium, in active phase of movement (x40); B - phase contrast optical microscopy of the nasal mucociliary epithelium, in the active phase of movement (x40).

The evaluation of the quality of life according to the SNOT-22 questionnaire revealed higher scores in both study groups (mainly > 60 points), and the average value of the SNOT-22 score (92.33 ± 1.1 points and 70.0 ± 2.8 points; $p < 0.001$) and the score 81-100 points (83.3% and 56.7%, respectively; $p < 0.05$) were statistically significantly more common in patients in study group 1 (figure 22). Surgical treatment of patients with FB contributed to a statistically significant reduction in the severity of symptoms in both study groups: 1 month after treatment, scores > 60 points disappeared and lower scores were found, mostly 0-20 points.

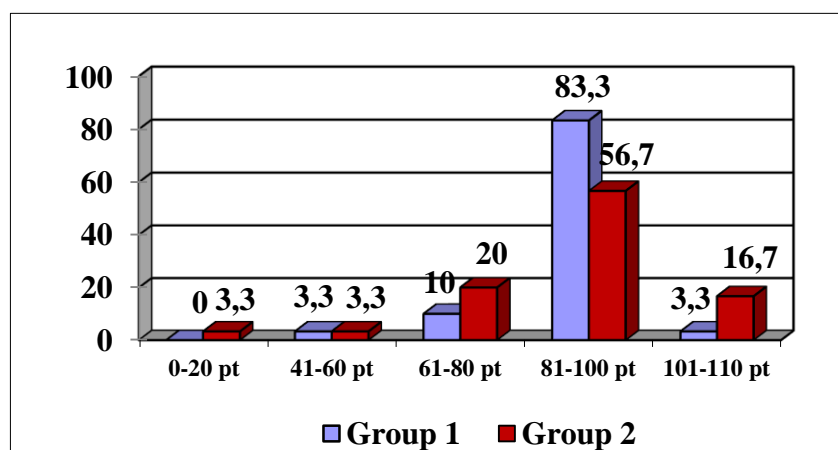


Fig 9. Quality of life at hospitalization, assessed according to the questionnaire SNOT, in patients of the study groups

However, the mean value of the SNOT-22 score (3.0 ± 0.5 points and 17.4 ± 2.7 points; $p < 0.001$) was statistically significantly lower and the score 0-20 points (96.7% and 76.7%, respectively; $p < 0.05$) was statistically significantly more frequent in patients of study group 2, and the score was 21-60 points - statistically significantly more common in patients of study group 1 (23, 3% and 3.3%, respectively; $p < 0.05$) (figure 9).

SUMMARY OF THE RESEARCH RESULTS

FB of the maxillary sinus is the most common form of chronic RSF in adults, usually with unilateral involvement, with a predominance of females and among immunocompetent people. Although the etiology, pathogenesis and natural history of RSF have been extensively studied, especially in relation to the cytokine profile, inflammatory and remodeling processes, they are far from being fully understood. For this purpose, additional molecular, macroscopic, experimental and epidemiological studies are needed [11, 28].

Clinical presentation and endoscopic findings are nonspecific, and cultures are often negative. CT imaging suggests, by characteristic signs, a correct diagnosis, which is based on histological identification of fungal hyphae. FB treatment of the maxillary sinus is surgical with conservative postoperative treatment. Our experience confirms the concept that a purely endoscopic approach (FESS), including antrostomy with complete ablation of FB is an extremely effective treatment in patients with FB of the maxillary sinus. Sinupret brings its clinical benefits, at least in part, by stimulating the secretion of Cl- transepithelial, FBC and CMC. Increasing fluid and electrolyte secretion is a means of improving CMC in people with FB of the maxillary sinus. Because FB is a non-invasive form of FRS and has a very low rate of postoperative complications, systemic and/or topical antifungal treatment is not indicated [28]. The SNOT-22 questionnaire is a useful tool for quantifying the change in symptoms and can be used to predict the extent of postoperative improvement [42, 58, 60, 119]. Based on data from the literature and the results of our study, we developed the following algorithm for standardized diagnosis and treatment of patients with fungal ball of the maxillary sinus (Figure 10).

Level of primary health care and specialized outpatient health care

Addressing symptoms:

1. Repeated rhinosinusal disorders, refractory to drug treatment, predominantly unilateral.
2. Periodic, persistent headache.
3. Facial pain located unilateral in the projection of the maxillary sinus and upper teeth.
4. Difficult nasal breathing, predominantly unilateral.
5. Mucopurulent or purulent rhinorrhea, predominantly posterior, unilateral.
6. Odor disorders.



Level of specialized outpatient care (ENT)

1. Objective ENT examination (nasal endoscopy): hyperemia and edema of the nasal mucosa unilaterally, reactive hypertrophy of CNI, CNM; nasal polyps in MNM with uncinate process hypertrophy; partial migration of the fungus ball in the region of the OM complex.
2. Complementary dental examination.



Computed tomography of the paranasal sinuses

1. In 90% of cases partial or total heterogeneous opacification of the involved sinus.
2. Microcalcifiers or "spots" with dense metallic characteristics.



Level of specialized outpatient (ENT) and primary care

1. Dynamic monitoring with the administration of the phytoproduct Sinupret extract until complete rhinosinusal functional restoration (SNOT-22: 0-20 points).
2. Immunological consultation.
3. Repeated ENT control over 3,6,12 months in patients with histomorphologically confirmed squamous cell metaplasia



Level of specialized hospital care

1. Surgical treatment by FESS.
2. Histopathological examination of FB material and maxillary sinus mucosa.
3. Microbiological examination of sinus contents.
4. Administration of the phytoproduct Sinupret extract pre- and postoperatively.
5. If necessary, complementary dental treatment.

GENERAL CONCLUSIONS

1. Impairment of the integrity of the mucociliary epithelium leads in evolution to characteristic chronic histopathological changes, with disruption of the function of mucociliary clearance and alteration of the inflammatory phases necessary for the functionality of the nasal mucosa.
2. The morbidity rate of patients with fungus ball of the maxillary sinus among patients with rhinosinusal disorders was 0.66%. Against the background of a relatively stable annual number of patients with rhinosinusal diseases, the number of patients with fungus ball of the maxillary sinus increases: from 0.07% in 2011 to 1.67% in 2015, which can probably be explained by alerting otorhinolaryngologists to the presence of fungi, improving diagnostic methods, correct guidance of clinicians in concretizing the diagnosis and differential diagnosis of fungal rhinosinusitis.
3. Statistically significant differences were found in the evaluation of the dynamic activity of the mucociliary epithelium determined in vitro, after one month post-treatment: the frequency of ciliary movements was statistically significantly higher in patients in study group 2 (12.07 ± 0.29 ; $p < 0.01$), compared to group 1 (6.87 ± 0.33). Videomicroscopic examination of the mucociliary epithelium revealed the complete restoration of the integrity of the epithelium and its dynamic activity, according to its physiological pattern. In the case of study group 1, the dynamic pattern showed altered ciliary movements and alternating mobile phases of cell cilia compared to group 2. Histopathological examination did not show statistically significant differences in both groups of our study, except mucociliary epithelial hyperplasia and degeneration mucoids in large areas. The presence of squamous cell metaplasia epithelial changes attests the need to use histopathological examination to establish the evolution and prognosis of this clinical entity.
4. In the general group of patients with fungus ball of the maxillary sinus of our study, the fungal flora detected included: *Aspergillus fumigatus*, *Aspergillus flavus*, *Candida albicans*, *Penicilium*, *Aspergillus niger* and *Aspergillus nidulans*. The most common bacterial agents were: *Staphylococcus aureus*, *Citrobacter Koseri*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Klebsiella oxytoca*, *Proteus vulgaris*, *Escherichia coli*, etc.
5. Medication with Sinupret improves the clinical picture of patients and restores the functional activity of the postoperative mucociliary epithelium, determining a prevalence of increased ciliary movement in patients in study group 2, but does not substantially change the histopathological pattern of maxillary sinus mucosa affected by chronic inflammation. Restoring the function of the mucociliary epithelium is the basic condition in improving the quality of life of our patients.

PRACTICAL RECOMMENDATIONS

1. It is recommended for general physicians and otolaryngologists to use the phytoproduct Sinupret extract in the pre- and postoperative protocol in order to restore the pattern of the condition and functional activity of the nasal mucociliary epithelium in patients with fungal rhinosinusitis.
2. CT examination of the nasal and nasal sinuses is recommended in patients treated with chronic rhinosinusitis, resistant to antibacterial treatment, in order to early diagnosis of fungal rhinosinusitis and conduct effective treatment.
3. It is recommended to otolaryngologists in university clinics, the use of pre- and postoperative optical videomicroscopy, in patients diagnosed with fungus ball in order to monitor the functionality of the nasal mucociliary epithelium, minimizing the risks of relapses with a promising postoperative clinical evolution.

4. It is recommended to otolaryngologists in hospital care to introduce histopathological examinations in patients with fungus ball of the maxillary sinus to assess the risks of squamous cell metaplasia and appropriate postoperative clinical monitoring.
5. It is recommended to otolaryngologists in hospital care to use the histopathological method as a true and reliable diagnostic method in patients with fungus ball of the maxillary sinus to establish the causal etiological agents and assess the degree of tissue invasion, for a correct clinical classification of fungal rhinosinusitis.
6. It is recommended to otolaryngologists to use the SNOT-22 questionnaire to quantify the change in clinical symptoms and monitor the postoperative condition, establishing correct treatment criteria for patients with fungus ball of the maxillary sinus.

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