REVIEW ARTICLE

INDEX COPERNICUS INTERNATIONAL

Inflammation of the nasal mucosa and paranasal sinuses

Zapalenie błony śluzowej nosa i zatok przynosowych

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Article history: Received: 04.03.2019 Accepted: 10.03.2019 Published: 16.03.2019

STRESZCZENIE: Zapalenie zatok przynosowych jest powszechnym schorzeniem obejmującym górne drogi oddechowe. Patomechanizm i przebieg zapalenia zatok jest złożony, zależny od czynników etiologicznych, długości trwania procesu chorobowego, anomalii anatomicznych i dodatkowych schorzeń nasilających stan zapalny błony śluzowej nosa i zatok przynosowych. Złotym standardem diagnostyki obrazowej jest tomografia komputerowa zatok (TK), wykonywana w szczególnych przypadkach. Pomocniczym badaniem jest rezonans magnetyczny służący do obrazowania tkanek miękkich przy podejrzeniu procesu nowotworowego, czy zewnątrz- i wewnątrzczaszkowych powikłań zapalenia zatok. Leczenie pacjentów z zapaleniem zatok jest często złożone i długotrwałe, związane między innymi ze stosowaniem kortykosteroidów donosowych lub ogólnoustrojowych, antybiotyków, lekami antyhistaminowymi, suplementami ziołowymi czy irygacją solą fizjologiczną. Leczenie dobierane jest indywidualnie do stanu pacjenta i fenotypu zapalenia zatok, a w szczególnych przypadkach podejmowana jest interwencja chirurgiczna. Obecnie trwają prace genetyczne, molekularne oraz immunologiczne, szukające nowych i bardziej skutecznych metod leczenia zapalenia zatok przynosowych.

SŁOWA KLUCZOWE: nieżyt nosa, makrolidy, astma oskrzelowa, cyklooksygenaza, tomografia komputerowa, błona śluzowa, klarytromycyna, dwoinka zapalenia płuc

ABSTRACT: Inflammation of the paranasal sinuses is a common condition that affects the upper respiratory tract. The pathomechanism and course of sinusitis are multifaceted, depending on etiological factors, duration of the disease, anatomical abnormalities, and additional conditions exacerbating the inflammation of the nasal mucosa and paranasal sinuses. The gold standard of diagnostic imaging is computed tomography (CT), performed in particular cases. An auxiliary examination method is magnetic resonance imaging (MRI) for soft tissue imaging when there is a suspicion of a neoplastic process, external or intracranial complications of rhinosinusitis. The treatment of patients with rhinosinusitis is very complex and long-lasting, associated with the use of nasal or systemic corticosteroids, antibiotics, antihistamines, herbal supplements, as well as irrigation with physiological saline. Treatment is selected individually in regards to the patient's condition or sinus inflammation phenotype, and in exceptional cases, surgical intervention is undertaken. Nowadays, genetic, molecular and immunological researches are underway to find new and effective methods for rhinosinusitis treatment

KEYWORDS: rhinitis, macrolides, bronchial asthma, cyclooxygenase, computed tomography, mucosa, clarithromycin, colon pneumoni?

INTRODUCTION

Inflammation of the sinus and nasal mucosa

Inflammation of the sinus and nasal mucosa (rhinosinusitis) is one of the most common diseases which affects 16% of the population, nearly 31 million people in the United States [1] and approx. 4-6 million people in Poland [2]. The name rhinosinusitis is more precise than sinusitis, because the nasal mucous membrane passes into the sinus lumen in a continuous manner without a distinctive border, together forming a morphological and functional whole. Sinusisits rarely occurs without simultaneous rhinitis and is usually preceded by it [3]. The term rhinosinusitis was introduced in 1999 in the United States by the Agency for Health Care Policy and Research in a document concerning the diagnosis and treatment of bacterial rhinosinusitis [4]. The Polish practice has accepted the term "sinusitis", which can be considered as equivalent to the American equivalent rhinosinusitis.

Document: "The European Position Paper on Rhinosinustits and Nasal Polyps 2012; EPOS 2012", sets the current guidelines on epidemiology, diagnosis and treatment of sinusitis and nasal polyps [5,6]. According to the latest findings of EPOS 2012, acute rhinosinusitis (ARS) is defined as a sudden occurrence of 2 or more symptoms, one of which should include nasal congestion or nasal discharge (anterior or posterior rhinitis) and pain/a sensation of distension of the face or a sense of smell, with a duration of

less than 12 weeks. ARS may be recurrent if there are asymptomatic periods within 3 months. Acute rhinosinusitis usually develops suddenly and subside to 4 weeks. After proper treatment, the symptoms and symptoms disappear completely. The division along with the characteristics of acute rhinosinusitis according to EPOS 2012 is shown in Table 1.

Chronic sinusitis (CS) is defined in the case of occurrence of symptoms presented in Tab.2. It has been assumed that CS is a heterogeneous disorder with two basic phenotypes: CS with polyps, the diagnosis of which requires to visualise the presence of polyps bilaterally in the central nasal cavities in endoscopic examination. In a situation where endoscopic examination does not reveal polyps in the nasal cavities (also after nasal contraction, e.g., Xylometha-zoline), we refer to CS without nasal polyps.

Pathogenesis of rhinosinusitis

Inflammation of the nasal cavities and paranasal sinuses is a disease of complex pathophysiology, in which the main symptoms are inflammatory edema of the nasal mucosa and sinuses, constriction of the natural sinus outlets and a decrease in the activity of the mucociliary system. Obstruction of the ostiomeatal complex, impaired mucociliary clearance, biofilm formation and disturbed immunological barrier leading to local congenital or acquired immunodeficiency constitute a supplement to the proposed theories explaining the basis of inflammation in CS [7].

The ostiomeatal complex plays a key role in the pathomechanism of sinusitis, which constitutes the basic functional unit of the nose and central regions of the nasal cavity with the outlets of the forehead and maxillary sinuses as well as ethmoidal sinuses, and the mucous membrane which lines it. Good construction and functioning of the ostiomeatal complex enables drainage and ventilation of these sinuses. Patency disorders occurring in this area (nasal edema, proliferative lesions, anatomical abnormalities, foreign bodies) and disorders of mucociliary transport may lead to the blockage of natural sinus outlets and thus initiate a cycle of processes leading to the development of chronic rhinosinusitis. Fig. 2. shows the CT of a patient's sinus with bilaterally obstructed ostiomeatal complexes.

Inflammation that develops in the nasal mucosa and paranasal sinuses may result from infection or the action of toxic, allergic, immunological or irritant factors. The most common factors affecting drainage and sinus ventilation include nasal congestion associated with viral, bacterial or allergic rhinitis. A significant role is also played by congenital disorders of mucociliary transport in the course of cystic fibrosis, primary ciliary dyskinesia , as well as Cartagener and Young syndrome. Anatomical defects of the septum and lateral wall of the nose (nasal septum deviation visible in the CT scan of paranasal sinuses in Fig. 3, deformated hamulus or ethmoidal bulla, presence of Haller cells, swollen nasal turbinates, the so-called 'concha bullosa' shown in Fig. 4), as well as adenoid hypertrophy, polyps, tumors, Wegener granulomatosis may reduce nasal cavity and sinus patency, also contributing to the development of inflammation. Congenital immunodeficiency disorders and acquired immune disorders (e.g., AIDS, CVID) favor frequent relapses and chronic inflammation of the nasal mucous membrane and paranasal sinuses. In women, hormonal abnormalities in the course of hypothyroidism, pregnancy or postmenopausal are also conducive to impaired sinus drainage. The course of tooth infection or the period after tooth extraction usually involves an inflammatory process which typically includes the maxillary sinus. What is more, iatrogenic factors (gastric tube, artificial ventilation, nasal tamponade) contribute to local damage to the nasal mucosa, sometimes pressure ulcers at the pressure site, constituting an outbreak of infection. In recent years, special attention has been paid to the role of gastroesophageal reflux disease , or GERD and laryngophageal reflux, or LPR in the pathogenesis of rhinosinusitis [2,4].

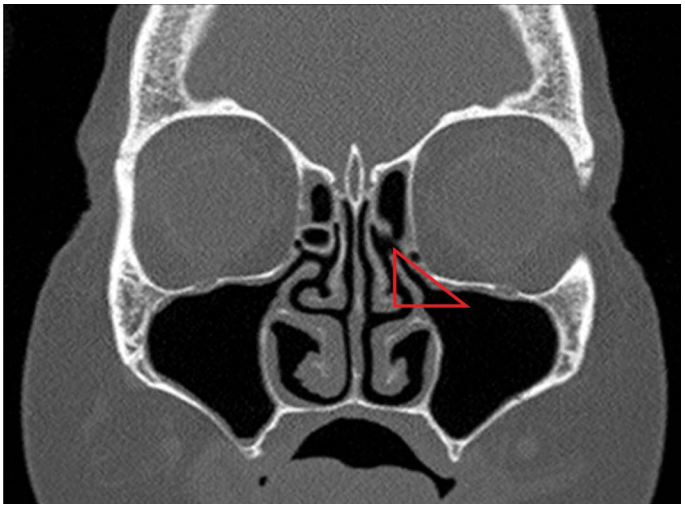

Fig. 1. CT scan of paranasal sinuses in frontal projection of patient with normal nasal sinuses and maxillary sinus. The field marked with a triangle corresponds to the unobstructed ostiomeatal complex.

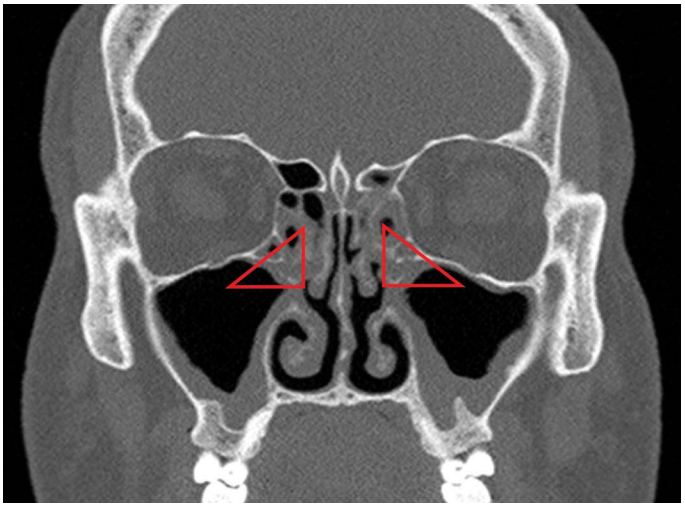

Fig. 2. CT scan of paranasal sinuses in frontal projection of patient with bilaterally obstructed ostiomeatal complex (marked with a red triangle). Mucosal thickening in the maxillary and ethmoid sinuses.

CLINICAL EVALUATION

Acute sinusitis

The most frequent origin of acute rhinosinusitis is viral. It is believed that only about 1.5% of infections of the paranasal sinuses are

Tab. I. Characteristics of acute rhinitis of the nose and paranasal sinuses according to EPOS 2012.

ACUTE VIRAL SINUSITIS	ACUTE VIRAL RHINOSINUSITIS	ACUTE BACTERIAL SINUSITIS IN ADULTS	ACUTE BACTERIAL SINUSITIS IN CHILDREN
Symptoms <10 days	Increase of symptoms > 5 dni	Increase of symptoms > 5 dni	Increase of symptoms > 5 dni
Sudden occurrence of 2 or more symptoms	Persistence of symptoms >10 days (up to 12 weeks)	Persistence of symptoms > 10 days (up to 12 weeks)	Persistence of symptoms > 10 days (up to 12 weeks)
The most common symptoms: nasal discharge or nasal obstruction: +/- pain/a sensation of distension of the face; +/- dysosmia (in adults); +/- cough (during the day or at night) (in children).	Symptoms from the respiratory system	Occurrence of at least 3 symptoms: - discoloured runny nasal discharge (with one-sided predominance) and purulent discharge in the nasal cavities; - severe local pain (with one-sided predominance); - fever (> 38oC); - increased OB/CRP; - "relapse of condition" (i.e., deterioration after initial, mild phase of the disease).	Occurrence of at least 3 symptoms: - discoloured runny nasal discharge (with one-sided predominance) and purulent discharge in the nasal cavities; - severe local pain (with one-sided predominance); - fever (> 38oC); - increased OB/CRP; - "relapse of condition" (i.e., deterioration after initial, mild phase of the disease).
Rarely fever, usually subsides with general symptoms within 24-48h			Additional symptoms: - cough; - nasal voice; - snoring; - bad breath.
General symptoms: headache and muscle pain			
Peak of respiratory symptoms in the 3rd-5th day			

of bacterial etiology, among which the most frequent pathogens cultured from sinus lavage fluid include Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis [8]. Diagnosis of AS can be made on the basis of thorough interview and physical examination. Most cases of AS are caused by a viral infection and are diagnosed when the symptoms of upper respiratory tract infection last less than 10 days. In the case of bacterial AS, symptoms usually intensify within 5 days and persist over 10 days [9]. During physical examination, patients may experience tenderness of the sinuses during palpation, redness and swelling of the nasal mucosa, as well as colored nasal and mouth secretion. On the basis of clinical symptoms and performed anterior rhinoscopy or nasal endoscopy, diagnosis of AS or CS may be made, and CT or MRI measurements should be considered upon suspicion of anatomical anomalies or presence of alarming symptoms shown in Fig. 1 [9].

Chronic sinusitis and acute recurrent sinusitis

CS is characterized by symptoms similar to those of recurrent acute rhinosinusitis, however, fever and pain during sinus palpation are rather uncommon. A weakened sense of smell is particularly characteristic of CS with nasal polyps. In some patients with a history of long-term CS or recurrent AS, a detailed endoscopic sinus and nasal exam should be considered and imaging should be performed, especially in cases of nasal haemorrhage, liquorrhoea, nasal obstruction, unilateral headache, orbital soft tissue swelling [9,10]. Computed tomography is considered the golden standard for imaging of the paranasal sinuses. It is performed to assess the scope of disease and location of obstacle in the acute or chronic phase of disease [11]. Sinus CT should be performed 4 to 6 weeks after the beginning of pharmacological treatment and is required before surgical intervention or suspected complications of rhinosinusitis [9]. Fig. 4. Shows an exemplary CT scan of the paranasal sinuses of a patient with symptoms of pressure and spreading around the nasal bridge and the right frontal region. If the patient has unilateral symptoms of CS syndrome, imaging should be performed to exclude tumor, anatomical defect or foreign body. In turn, MRI (magnetic resonance imaging) is the preferred method of imaging if soft tissue assessment is required, most often with a suspicion of neoplastic proliferation.

Treatment of acute sinisutis

Initial conduct with uncomplicated AS is based on symptomatic treatment including the use of analgesics, nasal corticosteroids, nasal irrigation with nasal saline. Although the evidence is limited, additional nasal irrigation can provide relief of symptoms. Antibiotic treatment is recommended for uncomplicated acute bacterial sinusitis only if the symptoms persist longer than 10 days or the symptoms worsen after the initial period of short-term improvement [9]. Antibiotics currently approved by the FDA for bacterial AS are azithromycin, clarithromycin, amoxicillin with clavulanic acid, cefprozil, cefuroxime, loracarbef, levofloxacin, trimethoprim--sulfamethoxazole and moxifloxacin. Due to increasing resistance, the Infectious Diseases Society of America recommends amoxicillin with clavulanic acid as the first line treatment, while doxycycline, levofloxacin and moxifloxacin in patients allergic to penicillin [12].

Due to the common occurrence of hypersensitivity or allergy to beta-lactam antibiotics, it is recommended to perform a skin test and/or an oral test to assess the tolerance of beta-lactam antibiotics, if the antibiotic is the most suitable for treatment [9]. In turn, nasal corticosteroids may be used as monotherapy or adjuvant therapy with antibiotic therapy in patients with bacterial AS [9]. Many studies have shown improvement in symptoms' relief when using nasal corticosteroids alone compared to placebo or antibiotic therapy [13,14]. A review of the literature of the Cochrane base indicated a small beneficial effect of the use of nasal steroids in terms of symptoms' regression or improvement when used as an additive to antibiotics in patients with bacterial AS [15]. In contrast to nasal steroids, systemic corticosteroids have not been subject to such numerous studies and the data is limited. Venekamp et al. [16] published a randomised, double-blind, placebo-controlled trial comparing patients who received 30 mg of monotherapy

with prednisolone daily for placebo for 7 days, without finding a beneficial effect on alleviating symptoms in patients receiving systemic corticosteroids.

The latest review of the Cochrane database found that systemic corticosteroids are effective as an additive to oral antibiotics, although the data was limited and there was a significant risk of error [17]. There is currently insufficient evidence that supplements such as zinc and vitamin C, antihistamines and decongestants are beneficial in bacterial AS [17,18]. Evidence is also limited when nasal cavities are rinsed with physiological saline, although irrigation may help reduce the severity of complaints and facilitate the removal of mucopurulent secretions from the nasal cavities and paranasal sinuses [19].

Local medications that reduce nasal congestion may temporarily relieve the feeling of nasal congestion. Phenylephrine, oxymetazoline and xylometazoline are commonly available topical decongestants. In the form of a spray or a drop, they act by narrowing the small blood vessels in the nasal mucosa. These vessels are controlled by α1 and α2 adrenoceptors [20]. A1-receptor agonists that include phenylephrine are preferred because they do not lead to disturbances of blood flow through the mucosa compared to selective α 2 -receptor agonists (oxymetazoline), which predisposes to impaired or abnormal healing of the nasal mucosa by reducing the blood flow rate [21]. After nasal administration of α-mimetics, local vasoconstriction occurs within 10 minutes regardless of the drug used. This effect lasts longer with oxymetazoline (8-12 h) and xylometazoline. This can be explained by slower mucociliary clearance due to reduced blood flow in the mucous membrane. Side effects of topical nasal decongestants include stinging sensation, dryness or ulceration of the nasal mucosa. Long-term use (> 10 days) of nasal vasoconstrictors may lead to tachyphylaxis and recurrence of nasal edema (drug-induced rhinitis). The use of topical decongestants should therefore be limited to <10 days. Both in AS and CS , α-mimetics do not affect the shortening of the disease process.

Oral mucosal congestion agents (pseudoephedrine, ephedrine, phenylephrine) are commonly used. They are usually prescribed for a short period to provide quick relief. Oral decongestants have a weaker effect in relieving nasal obstruction compared to local nasal decongestants. However, they do not cause rebound phenomenon, so they can be transcribed for a longer period. After oral administration, nasal shrinkage occurs within 30 minutes and persists up to 6 hours. Phenylephrine demonstrates a high first-pass metabolism and is therefore the least effective. Oral decongestants have some side effects, including agitation and nervousness, drowsiness and arrhythmias. They should be avoided in combination with alcohol, monoamine oxidase inhibitors or sedatives. There is usually no significant increase in blood pressure in patients with stable hypertension. However, caution is recommended in patients with ischemic heart disease, glaucoma or prostatic hyperplasia [22].

The treatment of AS also includes anticholinergic drugs that block the muscarinic receptors of the blood vessels and the nasal glands. Parasitic stimulation causes watery discharge via acetylcholine and dilation of blood vessels. Topical anticholinergics such as ipratropium bromide in the form of nasal spray are mainly used to control the symptoms of rhinorrhea [23]. This has no significant effect on

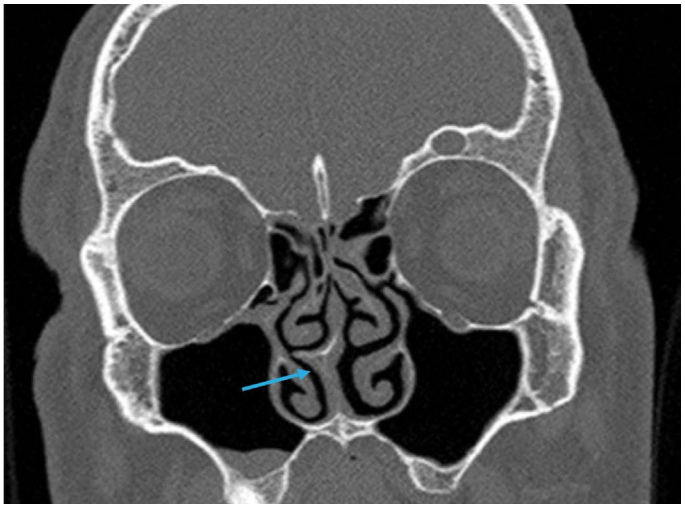

Fig. 3. CT scan of sinuses in frontal projection. Visible right-sided curvature of nasal septum in the form of protruding nasal spine (blue arrow).

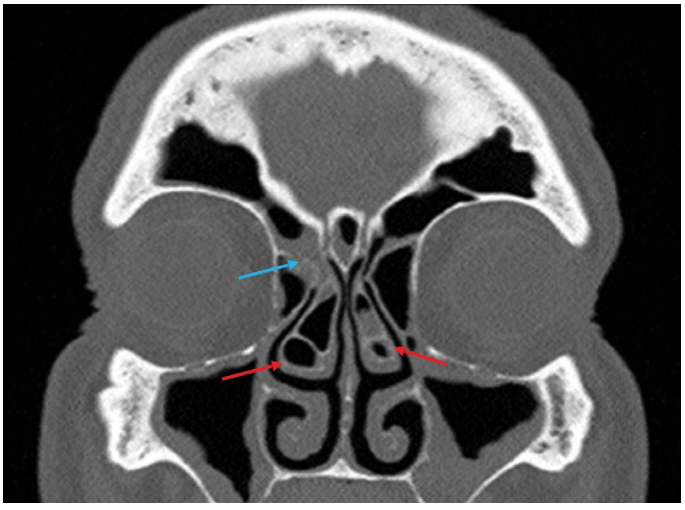

Fig. 4. CT scan of sinuses in frontal projection. Visible swollen middle nasal concha, so-called 'concha bullosa' (red arrows), obstructed right-sided frontonasal duct (blue arrow) and maxillary sinus mucosal hypertrophy.

nasal congestion, pruritus and sneezing. Long-term use of these drugs has no effect on smell and ciliary movement. The clinical appearance of the nasal mucosa remains unchanged. However, these drugs demonstrate a positive effect on reducing the severity of watery rhinorrhea in patients with symptomatic GERD or LPR. Anticholinergics are often combined with mucolytic drugs that reduce the density of secretions, but their effect on the shortening of symptoms' duration has not been demonstrated [23].

No clinical trials support the use of antihistamines in the treatment of acute rhinosinusitis. They can probably be beneficial due to their anti-inflammatory effect [23]. On the other hand, the anticholinergic effect of first-generation antihistamines may weaken clearance by thickening mucus [24]. The use of second-generation antihistamines in acute inflammation of the paranasal sinuses is not recommended.

Treatment of chronic sinusitis

Pharmacotherapy in CS involves nasal or oral corticosteroids, nasal irrigation and, in justified cases, antibiotic therapy. Nasal cor-

Tab. II. Characteristics of chronic rhinosinusitis according to EPOS 2012.

CHRONIC SINUSITIS	ADDITIONAL SYMPTOMS
2 or more symptoms, one of which should be: - runny nose (front/rear) or - pain/a sensation of distension of the face or - impaired/loss of smell with duration of ≥ 12 weeks	- headache; - fever; - bad breath; - chronic fatigue; - upper teeth pain; - cough; - earache and/or a feeling of fullness in the ear.

ticosteroids in the form of a spray or aerosol are recommended for the treatment of both CS with nasal polyps as well as without nasal polyps. Published studies have consistently shown that nasal corticosteroids are superior to placebo in improving nasal patency, reducing mucosal edema, polyp size, and improving quality of life [9,12]. As part of adjunctive therapy in patients with CS, it is also recommended to irrigate nasal cavities and paranasal sinuses, which improves the quality of life, reduces inflammatory indexes, as well as the incidence of infection [25,26]. Distilled or boiled water should be used to rinse the sinuses, and the patient should be advised to clean the device to prevent bacterial contamination [27].

Antibiotic therapy in patients with CS is controversial due to limited evidence, although current recommendations suggest the supply of systemic antibiotics in acute exacerbations of CS [9]. The most common example of clinicians' use of antibiotics is persistent purulent discharge from the paranasal sinuses [28]. If the discharge of pus persists despite the use of antibiotics, it is strongly recommended to perform a culture of rinsings from the sinus cavities [28]. Clinical trials showing a beneficial effect of long-term use of macrolide antibiotics are limited and there are no clear differences in their use in the case of CS with nasal polyps or CS without polyps [9]. Observational studies of 3-6 weeks courses of antibiotic therapy provided by nasal irrigation or nebulization showed an improvement in symptoms [29], improvement in endoscopic examination [30] and an increase in the incidence of mucous membrane inflammation without infection [31]. Examples of the antibiotics investigated included mupirocin [31] and topical aminoglycosides [32] for therapy-resistant CS with a positive culture of Staphylococcus aureus. It is worth pointing to the fact that topical aminoglycosides should be used with caution and only for a limited period of time, because there is measurable but poor systemic absorption through the nasal blood vessels [9,33]. In one of the studies conducted on the group of patients with cystic fibrosis and CS, it was observed that 23% of people developed sensorineural hearing loss after frequent irrigations with physiological saline and aminoglycoside [34].

There are limited data on prolonged antibiotic treatment in cases refractory to standard therapy, although historically it has been recommended for patients with CS without nasal polyps [9]. One of the studies on the use of roxithromycin in adult patients with CS without polyps demonstrated beneficial effects from systemic antibiotic therapy, consisting of reducing the symptoms' severity, although this study was carried out on a small population [35]. Based on research published by Dubin et al. [36], adult patients with CS without nasal polyps, resistant to prior antibiotic therapy were administered 150 ml of clindamycin three times a day (13 patients), amoxicillin/clavulanic acid (2 patients) or doxycycline (1 patient) for 6 weeks. Computed tomography (CT) of the paranasal sinuses was performed at the beginning of the study, at week 3 and then at week 6 of treatment. Lund-MacKay scores were improved in 6 patients between weeks 3 and 6, and only one of these 6 patients was recommended for endoscopic surgery of the paranasal sinuses after 6 weeks of treatment. Therefore, some patients with CS without nasal polyps may benefit from prolonged antibiotic treatment. However, in a recent published study by Sreenath et al. [37] there was no difference in the clinical outcome between 3- and 6-week antibiotic therapy in patients with CS.

In patients with CS with polyps, it turned out that doxycycline causes statistically significant reduction in polyp size, and thus a significant reduction in the level of lipoprotein secretion [38]. It is worth noting that doxycycline did not cause statistically significant improvement in peak inspiratory flow rate [39]. In turn, the supply of oral corticosteroids demonstrated significant benefits in the treatment of CS. Another study compared the results obtained by patients using amoxicillin/clavulanic acid in patients receiving concomitant amoxicillin/clavulanic acid in combination with oral corticosteroids for the treatment of CS in a prospective randomized trial [40]. In a group of patients receiving simultaneous amoxicillin/clavulanic acid together with oral corticosteroids, better results were achieved in reducing the severity of symptoms and regression of inflammatory lesions in radiological examination. The study involved patients with both CS without nasal polyps and CS with nasal polyps. It has been shown that the short duration of oral corticosteroid therapy in patients with CS with polyps reduces polyp size and reduces the severity of symptoms, leading to transient improvement of smell [9].

Finally, it has been demonstrated that the use of topical antifungal drugs (aerosols or irrigations) [9,41], or systemic terbinafine [9,42] is not beneficial in the treatment of CS, because no beneficial effects have been reported in this type of treatment in published clinical trials. Patients with fungal infections of the paranasal sinuses usually require endoscopic paranasal sinus surgery (ESS). Fig. 5. Shows a CT scan of the paranasal sinuses in frontal projection of patient with extensive inflammatory lesions and mycelium in the right maxillary sinus. Pharmacological treatment was ineffective in the case of this patient.

Research is currently underway to create a new form of therapy in patients with CS, especially in CS with polyps, consisting in the use of anti-IgE monoclonal antibodies (omalizumab) or IL5 (mepolizumab and reslizumab). In a study carried out by Gevaert et al. [43], researchers noted a significant decrease in the total number of nasal polyps assessed by endoscopy after 16 weeks of treatment with omalizumab compared to the placebo control group. The authors also noted the resolution of symptoms of the lower respiratory tract, as well as improvement in the quality of life assessment. Patients enrolled in this study were diagnosed with allergic or non-allergic chronic rhinitis and paranasal sinuses with bronchial asthma.

Anti-IL-5 monoclonal antibody (mepolizumab) also showed a beneficial effect in treating CS with polyps. In a randomized double-blind placebo control duty published by Gevaert et al. [44], the effects of mepolizumab in patients with CS with polyps that did not improve after standard treatment were evaluated. Treatment with mepolizumab was associated with a significant reduction in nasal polyp size as early as 1 month after mepolizumab administration, with no correlation between the mepolizumab response and the level of IL-5 in the nose [43]. Recently, the FDA approved mepolizumab in severe eosinophilic asthma. In turn, reslizumab, another antagonist of the anti-IL-5 antibody, was also tested in patients with CS with polyps who also reported regression of symptoms and a reduction in the nasal polyps' weight [44].

The role of phytotherapy in the treatment of rhinosinusitis

Although less than 90% of upper respiratory tract infections are of viral origin with a tendency to self-limiting within 3-7 days, in practice the tendency to include antibiotic therapy is often observed already at the early stage of infection. The result is an increase in drug resistance or prolonged inflammation. According to the EPOS 2012 guidelines [6,7], routine treatment of acute uncomplicated rhinosinusitis should not be administered with antibiotics, but only nasal corticosteroids or decongestants. On the other hand, phytopharmaceuticals are also recommended as adjuvant and complementary treatment. Many studies have shown that phytopharmaceuticals have mucolytic, antiviral, antibacterial, anti-inflammatory and also secretolytic properties [45]. The use of phytopharmaceuticals also reduces the severity of symptoms in acute and chronic rhinosinusitis in the population of children and adults, and at the same time is characterized by a high level of tolerance and safety.

Plant immunomodulatory preparations have a stimulating effect on the immune system and act as inhibitants on the multiplication of pathogens. The antibacterial properties of herbal medicines have been evaluated in vitro, inter alia in relation to Staphylococcus aureus, methicillin-resistant S. aureus (MRSA), Streptococcus pyogenes, Escherichia coli and Haemophilus influenzae. In case of infection with Streptococcus pneumoniae, the use of herbal preparations reduces the layer of biofilm in the paranasal sinuses and improves nasal patency, or reduces inflammation of the nasal mucosa [46]. In turn, active substances contained in purple sea urchin (Echinacea purpurea) intensify the phagocytosis process, activate macrophages, neutrophils, granulocytes and NK cells, stimulating the secretion of interferon beta or interleukin 1. They also demonstrate the ability to inhibit inflammation by blocking cyclooxygenase enzymes (COX-1 and COX-2) or the production of PGE2 prostaglandins in inflammatory exudate [47]. Among phyto-therapeutics an important role is played by bromelain obtained from pineapple, a mixture of enzymes with anti-inflammatory properties (regulation of pro-inflammatory cytokines, including IL-5 and IL-10), antimicrobial as well as anti-cancer [48]. Bromelain has been used, inter alia, in the treatment of rhinosinusitis, bronchitis, veins and joints. Its properties are also used in the regulation of digestive processes and acceleration of healing after surgical procedures [49].

Herbal products also display antiviral properties by blocking the activity of reverse transcriptase or viral protease, which results in suppression of adenovirus C subtype 5 (Adeno 5) replication, rhinovirus B subtype 14 (HRV 14), HSV-1, HSV-2 and syncytial viruses (RSV) [50]. Plant preparations showing antiviral properties include eucalyptus oil and its main product, 1.8-cineol with antimicrobial activity, which limits the multiplication of Staphylococcus aureus, MRSA, Escherichia coli and Candida albicans as well as MRSA as Pseudomonas aeruginosa in the biofilm of the paranasal sinuses [51]. Flavonoids have a similar effect, and among them naringenin displays activity against RSV virus and routine against influenza and parainfluenza virus. Flavonoids are currently being tested for use in the control of HSV and HIV (Human immunodeficiency virus). Flavonoids are commonly found, among others, in citrus fruits, skullcap (Scutellaria baicalensis), hawthorn(Crataegus sp.), buckwheat (Fagopyrum sp.), sorrell (Rumex sp.) or elderberry (Sumbucus nigra) [52].

The phytolytic activity of phytopharmaceuticals was evaluated in in vivo studies in rabbits by analyzing mucus in the trachea. Supplementation with preparations from herbal products, in particular an extract from European verbena (Verbena officinalis) and gentian root (Radix Gentianae), statistically more frequently led to an increase in fluidity of the secretion compared to the baseline ($p < 0.05$ in all cases) [53]. Other plants with rich secretolytic properties include the root of cowslip primrose (Radix Primulae), liquorice root (Radix Glycyrrhizae), as well as soapwort root (Radix Saponariae), which are characterized by a high content of saponins. Oral use of saponins stimulates the ends of the parasympathetic fibers located in the mucous membrane of the nose and paranasal sinuses, leading to a reduction in the surface tension of the water and liquefaction of the secretion, thus facilitating its drainage [40]. In addition, some saponins have anti-inflammatory, fungistatic, hypocholesteric, antiviral, bactericidal and immunostimulating properties [54].

Although phytotherapy has so far been regarded as ancillary treatment in a population of people with symptoms of acute or repetitive AS, it has become useful in reducing the duration of symptoms and the length of standard therapy. It should be kept in mind that herbal preparations have been designated as commonly used in the treatment of AS, but only a few randomized, double-blind, placebo-controlled studies have demonstrated their effectiveness. Products available on the market subject to standard registration procedures are used to treat the first symptoms of colds, as well as provide support in chronic inflammation of the mucous membrane of the nose and paranasal sinuses.

Sinusitis and surgical treatment

In surgery of the paranasal sinuses, optimization of patient selection is necessary to achieve successful results. Surgical intervention may be required in bacterial AS to provide drainage when there is a significant risk of intra- or extracranial complications.

Many patients with chronic rhinosinusitis can be effectively treated conservatively. In the case of the use of all available drugs and therapeutic failure, surgical treatment of the sinuses should be considered. Patients with CS often manifest persistent swelling of the nasal mucous membrane, as well as the presence of

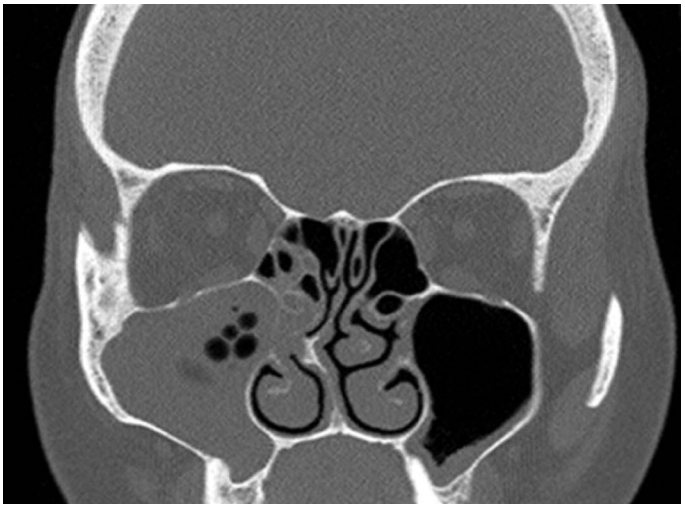

Fig. 5. CT scan of sinuses in frontal projection. Visible chronic inflammatory process covering the right maxillary sinus with centrally visible mycelium. Nasal septum deviated ipsilaterally.

thick secretion despite properly selected corticosteroid therapy or antibiotic therapy. Other patients are found with anatomic anomalies on the basis of laryngological, endoscopic or radiological examinations leading to impaired secretion drainage and limited access of nasal drugs. Surgical treatment is aimed at removing the diseased mucous membrane, unblocking the ostiomeatal complexes and the remaining outlets of the sinuses to restore proper ventilation and mucociliary clearance. Sinus surgery also allows to prepare the patient for further local treatment. SNOT-22 questionnaire (sinonasal outcome test) proves to be a helpful tool in assessing the quality of life in patients with CRF both before and after surgery, on the basis of which many clinical centers have demonstrated a significantly better improvement in the quality of life of patients with PED with polyps after endoscopic paranasal sinus surgery (ESS), detected (inter alia) in nasal endoscopy (Fig. 6A) and in CT scan of the paranasal sinuses (Fig. 6B), compared to patients treated conservatively [55]. The analysis of various subtypes of CS with polyps has demonstrated the influence of many factors on post-operative results. For example, patients with polyps with idiopathic etiology demonstrated a significantly better improvement after surgical intervention compared to polyps associated with a systemic process, such as aspirin intolerance or bronchial asthma [56]. In cases of eosinophilia, associated with CS with polyps, inferior surgical results were demonstrated - increased percentage of recurrent polyps [57]. It may be associated with a reduced number of cilia along the sinus mucosa in this subgroup of patients [58]. However, eosinophilia is not inherent in all cases of CS with polyps, an example of which is demonstrated by nearly 80% of patients with CS with polyps, with a predominance of neutrophils in inflammatory infiltrate [57,58]. There are many factors in the group of patients with CS with polyps that can affect the likelihood of relapse. Patients with cystic fibrosis, or CF form a unique group, in whom there is permanent ciliary dysfunction and impaired removal of thick, viscous secretion. These patients usually require frequent surgical revision, although after subsequent sinus surgery, their quality of life improves [59]. In addition, it is believed that ESS helps in reducing CF infiltrate by removing one of the bacterial reservoirs of Pseudomonas aeruginosa [60]. In addition, surgical revision improves the quality of life and reduces the severity of discomfort. On the other hand, the next surgical intervention carries a number of complications, including those associated with impaired anatomy, inflamed structures and a greater risk of bleeding.

It has been demonstrated that pre-operative supply of systemic steroids reduces inflammation, polyp size, length of surgery and bleeding during surgery, and also allows better visualization during endoscopy in patients with PED with polyps. Although intraoperative benefits were observed, there was no effect of corticosteroids on the reduction of recurrent polyps and improvement of quality of life in patients with CS with polyps after surgery [61-63]. Also, the inclusion of nasal corticosteroids prior to surgery has a significant impact on the shortening of the procedure performed, as well as a reduction in the severity of bleeding during surgery. Many researchers believe that systemic and intranasal corticosteroids have a significant impact on the quality and length of surgery, hence they should be included in the preparation of patients for ESS [62,63].

The scope of surgical intervention in the treatment of CS and recurrent AS is widely varied and is still under discussion. However, over the last decade, otolaryngologists have begun to seek a more personalized surgical approach for each patient, based more on the CS phenotype and co-morbidities. Therefore, the differentiation of both subtypes of CS with polyps and CS without polyps with recurrent AS often plays a role in determining the extent of surgical treatment.

In the case of CS with polyps, surgeons often prefer a more extensive surgery, including a wide opening of all sinuses. As a rule, this more aggressive approach is based on an extensive inflammatory process that occurs in the majority of patients with CS with polyps. Therefore, the goal of surgical treatment in CS with polyps is not only to remove the diseased tissue, but also to improve sinus drainage, expose more tissues to the local administration of drugs and reduce the burden of inflammation [64]. Such a radical approach is associated with a lower rate of relapses compared to minimally invasive techniques.

Balloon sinus dilation is another surgical technique that has gained popularity in the treatment of recurrent CS and AS without polyps in the last decade. This procedure involves the extension of the maxillary, forehead and/or sphenoid sinuses, which in turn allows better drainage and access of nasal drugs to these particular sinuses. Another advantage of this technique involves the ability to perform the procedure without the need for general anesthesia. So far, many studies have shown comparable efficacy with ESS in reducing symptoms, decreased the recurrence of sinus episodes and improving the quality of life for patients [65, 66]. However, many experts agree that this method should be used in a selected group of patients based on the CS phenotype, sinus anatomy and concomitant diseases.

CONCLUSIONS

The current guidelines based on EBM are consistent with the diagnosis and treatment of CS. The efficacy of nasal corticosteroids has been well established in many randomized clinical trials that recommend their use in CS [13-15]. This also applies to antibiotics

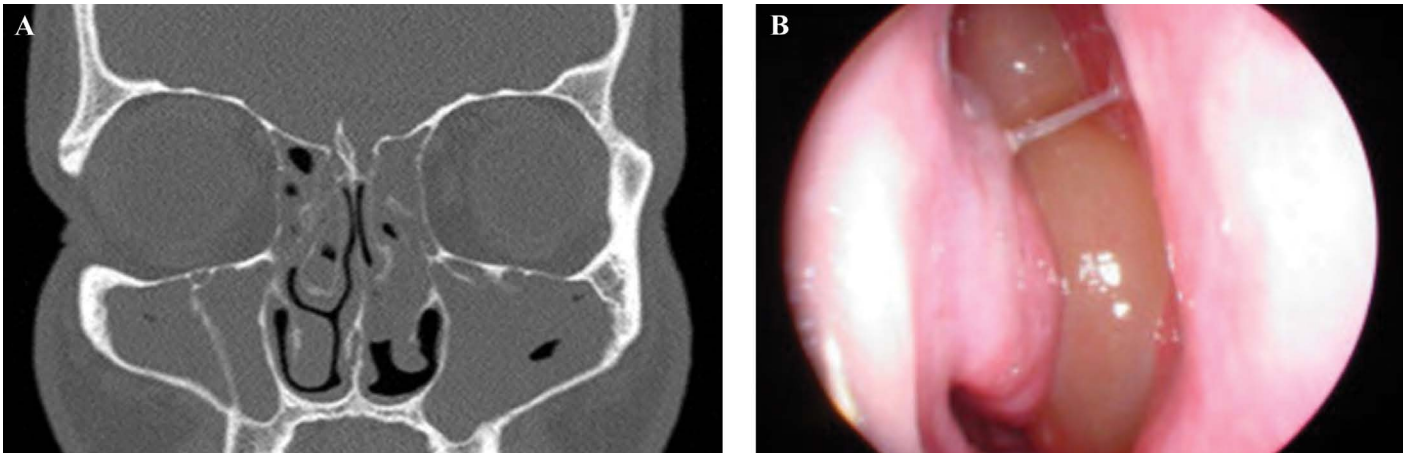

Fig. 6. CT scan of paranasal sinuses in frontal projection. Extensive polypoid lesions filling the maxillary and ethmoid sinuses as well as middle and superior nasal meatus. The patient was qualified for ESS surgery (A). Polypoid lesions filling the ethmoid cells and the superior and middle nasal meatus visible in nasal endoscopy (B).

in patients with severe symptoms of CS [13, 23, 37]. Despite clinicians' knowledge about the fact that CS is most often self-limiting, about viral etiology, the phenomenon of abuse of antibiotic therapy is still observed in the early and benign phases of CS. Although all guidelines recognize the severity of symptoms as a decisive factor for inclusion of antibiotics, the tools used to assess the severity of symptoms vary depending on the consensus, starting with the VAS scale (Visual-Analogue Scale) in EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps), or BSACI (British Society of Allergy and Clinical Immunology) through different scales used in CPG (Clinical Practice Guidelines) based on the presence of alarming symptoms in the form of fever, facial pain, purulent secretion in the nasal cavities or periorbital edema [6,8].

In contrast to CS, evidence-based studies on CS are much less consistent, probably due to the greater complexity and diversity of this condition and the scarcity of clinical trials in this area. No consistent consensus was reached on the treatment of CS. Recommendations formulated by the EPOS guidelines regarding pharmacological treatment of CS help fill the gap in the literature, however sometimes there is a lack of rigorous evidence (including in the case of long-term use of macrolides). There have been few clinical trials comparing the treatment of CS without polyps, CS with polyps or fungal SS as separate entities, despite the promotion of this type of research, the need to verify current knowledge and the need to harmonize guidelines for the diagnosis and treatment of these disease entities. There still remain numerous questions about optimal patient selection and surgical strategies. Nevertheless, the update of EPOS and other guidelines is a very good sign, as significant progress has been made in the area of diagnostic methods, basic research and classification of CS subgroups as well as the selection of appropriate treatment.

Future clinical trials should establish appropriate strategies for diagnostic tests to identify pathogens (e.g., allergic, infectious, fungal) and determine which drugs and treatments are most effective for patients with SS. From a practical point of view, allergy tests (as recommended by EPOS and BSACI) are valuable for patients with long-term or recurrent complaints, especially when these symptoms persist despite irrigation of the paranasal sinuses and the use of nasal corticosteroids. Such tests are likely to play a role in future

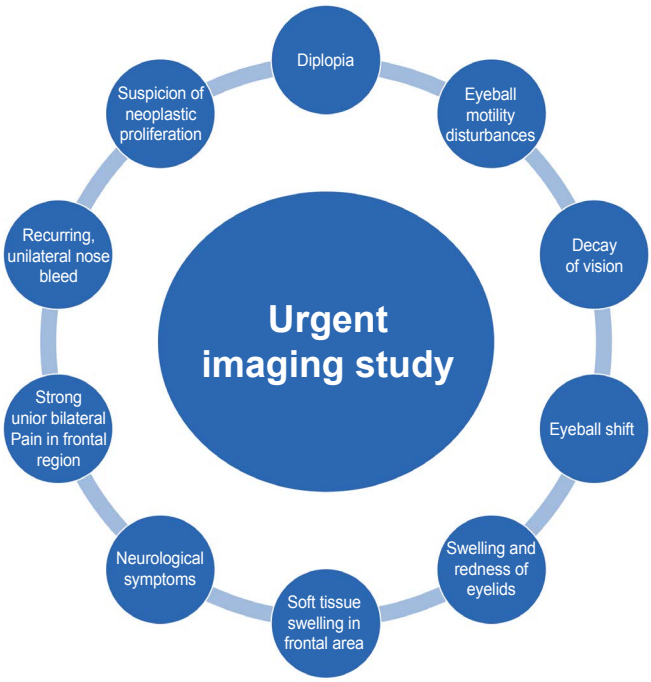

Fig. 7. Alarming symptoms of sinusitis requiring urgent imaging diagnostics.

treatment strategies, which should be more targeted at assessing the cause of CS. A big problem is also incorrect response of the patient with SS after proper qualification for pharmacological or surgical treatment. Therefore, more and more often attention is paid to the essence of unconventional treatment with the use of phytopharmaceuticals. It is worth paying attention to herbal medicines subject to registration procedures for efficacy, which has been confirmed in randomized clinical trials. These drugs have primarily anti-inflammatory, antimicrobial and immunomodulatory properties, and their use is safe in both children and adults.

Finally, it is worth mentioning the intensive research on biological medicines and the use of phagocytes in the therapy of rhinosinusitis. Their role can prove to be invaluable in cases of lack of a correct response to conventional treatment. Future clinical trials are expected to improve recommendations for practicing clinicians to improve the outcomes of treatment for patients with rhinosinusitis.

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Word count: 7110 Tables: 2 Figures: 7 References: 66

Access the article online: DOI: 10.5604/01.3001.0013.1412 Table of content: https://otorhinolaryngologypl.com/issue/11876

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Competing interests: The authors declare that they have no competing interests.

Cite this article as: Wos J., Remjasz A.: Inflammation of the nasal mucosa and paranasal sinuses; Pol Otorhino Rev 2019: 8(1): 16-26