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REVIEW ARTICLE

Position Paper on Rhinosinusitis and nasal Polyps (EPOS 2012) oraz American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS 2014)

Postępowanie w przewlekłym zapaleniu zatok przynosowych u dzieci wg zaleceń European

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ABSTRACT: Pediatric rhinosinusitis is defined as a presence of two or more symptoms and one of them should be either nasal blockage or nasal discharge and headache/facial pain or cough. Chronic rhinosinusitis - CRS is recognized when the four most common symptoms as cough, rhinorrhea, nasal congestion and post nasal drip with a slightly higher predominance of chronic cough are presented for more than 12 weeks and influence the quality of life. CRS should be considered in respect of unique conditions because of the differences in predisposing factors (immunological and others) and the anatomy of the sinuses between children and adults. The adenoids are a prominent contributor to CRS in young children, both from bacteriologic and immunologic status. The older children suffer from CRS in the same manner as adults. During evaluation a child with symptoms of CRS , one should always consider the possibility of underlying disease as a contributing factor. Diseases impacting sinuses and nasal function include CF, primary ciliary dyskinesia (PCD) and a variety of normal immune deficiencies, including the still-developing immature immunity of healthy young children. Surgical intervention for rhinosinusitis is usually considered for patients with CRS who have failed maximal pharmacological treatment. There are two important consensus statements for pediatric chronic sinusitis (CRS): European Position papers on Rhinosinusitis and Nasal Polyps – EPOS 2012 and Clinical Consensus Statement: Pediatric Chronic Sinusitis American Academy Otolaryngology – Head Neck Surgery 2014. Both of them contain necessary information and recommendation for diagnosis and treatment of CRS in children.

KEYWORDS: chronic rhinosinusitis, children, sinuses, adenoid, infection

STRESZCZENIE: Zapalenie zatok przynosowych u dzieci rozpoznawane jest na podstawie dolegliwości związanych z zaburzeniami drożności nosa lub/i nieżytem nosa, którym towarzyszą bóle głowy lub rozpieranie w obrębie twarzy oraz kaszel. Przewlekłe zapalenie zatok rozpoznajemy, gdy dolegliwości – z których najdokuczliwszy jest kaszel – utrzymują się, i wpływają na jakość życia przez ponad 12 tygodni. Zapalenie zatok przynosowych jest rezultatem miejscowej i ogólnoustrojowej odpowiedzi organizmu na czynniki środowiskowe, dlatego w populacji dziecięcej konieczne jest uwzględnienie dojrzałości układu immunologicznego oraz rozwoju (wykształcenia) narządów pod względem anatomicznym i funkcjonalnym. Powyższe uwarunkowania są podstawą do podziału przewlekłego zapalenia zatok przynosowych (PZZP) na chorobę występującą w populacji dzieci młodszych i starszych, podkreślając – u młodszych – rolę migdałka gardłowego oraz decyzje dotyczące leczenia zachowawczego i operacyjnego. W populacji dziecięcej trzeba uwzględnić choroby, takie jak: mukowiscydoza, pierwotna dyskineza rzęsek, a także różnego rodzaju zaburzenia odporności, które przebiegają z dużym nasileniem zmian w zatokach przynosowych. Wymaga to specjalnego postępowania w leczeniu oraz rozważenia działań chirurgicznych dostosowanych do przebiegu choroby. Zasady

postepowania, dotyczące zarówno diagnostyki, jak i postępowania leczniczego, zostały opracowane w postaci dokumentu European Position Papers on Rhinosinusitis and Nasal Polyps – EPOS, uaktualnionego w 2012 roku. W 2014 roku powstał dokument Clinical Consensus Statement: Pediatric Chronic Rhinosinusitis opracowany przez American Academy of Otolaryngology – Head and Neck Surgery. Oba konsensusy zawierają niezbędne informacje oraz wskazania dotyczące diagnostyki i leczenia PZZP u dzieci.

SŁOWA KLUCZOWE: przewlekłe zapalenie zatok przynosowych, dzieci, zatoki przynosowe, migdałek gardłowy, zakażenia

According to EPOS 2012, chronic rhinosinusitis (CRS) in children is described as a sickness that prevails for over 12 weeks with at least two symptoms, of which one is nasal obstruction or rhinitis (frontal or posterior), as well as pain/feeling of spreading on the face and/or cough [1]. Similarly as in the case of adults, two forms of this sickness are distinguished, namely CRS with nasal polyps and CRS without nasal polyps. Nasal polyps in CRS in children are most often diagnosed in sicknesses such as: cystic fibrosis and other genetically determined ciliary mechanism disorders or in immune disorders, or they are antrochoanal polyps. A significant supplement to this definition is significant deterioration of quality of life caused by the durability and burdensomeness of ailments in the course of the disease [2].

Chronic rhinosinusitis is a sickness diagnosed both in adults as well as in children; however, maturity of immunological mechanisms partaking in the inflammatory response influences the difference of pathophysiological mechanisms of this illness, in particular in younger children [3].

PATHOGENESIS OF CHRONIC RHINOSINUSITIS IN CHILDREN

Development of CRC in children is a result of disorders in functioning and influence of local and systemic mechanisms, as well as environmental factors. Nasal and paranasal sinuses play the role of a mechanism preparing inhaled air for introduction to the respiratory tracts, filtering, heating and hydrating it. In adults, cavities of the nose and paranasal sinuses are fully developed, whereas in children, they reach their final size above 10 years of age, while the frontal sinus even over the age of 18. Anterior and posterior ethmoidal cells develop in the 3rd-6th month of fetal life, during infancy they are already functioning air spaces, however they fully develop around the age of 10-12. In the first year of life, maxillary sinus is the size of ethmoid cells; it has two phases of growth, depending from the appearance of deciduous teeth, and permanent teeth after. It reaches its final size around the age of 15. The frontal sinus in an infant comprises a recess, and around the sixth year of age, it is a marked air space, with its final shape obtained around the age of 20. In an infant, sphenoidal sinus is a recess, and around the fourth year of age, it is a marked cavity, with its final shape obtained around the age of 15 [4]. The presented pattern of development may be altered by various disease processes, for example by cystic fibrosis [5]. Knowledge about the dynamics of paranasal sinuses' development in children is key in diagnostics of pathology, clinical evaluation and imaging.

Functioning of the sinuses is conditional on the nasal and paranasal sinus mucosa as well as patency of their natural ostium. Anatomical irregularities such as concha bullosa, distortions of the nasal septum, nasal polyps, as well as damage caused by mechanical trauma or foreign bodies put into the nose, disrupt the patency of nasal passages and natural ostiums of sinuses [6, 7]. Impairment of physiological mechanisms of purification causes retention, disruption of ventilation and impairment in the functioning of natural defense mechanisms that protect the respiratory tract from colonization of pathogens. The factor conducive to infections and development of bacterial biofilm in nasopharyngeal space is frequent antimicrobial therapy of airway inflammation in children, which destroys saprophytic bacteria colonizing the upper respiratory tract mucosa [8.9]. Among bacteria isolated in microbiological cultures, similarly to acute sinusitis, there are: Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, however the most significant role is given to Staphylococcus aureus, as well as anaeorobic Gram-negative bacilli [10]. On the other hand, the role of fungal infection in development of CRS is controversial [11]. There is currently research that confirms the significant role of Staphylococcus aureus endotoxins and maintenance of inflammation through formed bacterial biofilm [12]. In children with chronic diseases of the upper respiratory tract, there is biofilm in the nasopharynx [13].

Sicknesses and factors that influence functioning of the mucous membrane as well as possibility of CRS development are: allergic rhinitis, gastroesophageal reflux disease (GERD) as well as irritants found in air pollution and tobacco smoke [14].

A special group is comprised by patients who suffer from cystic fibrosis, primary ciliary dyskinesia (PCD) as well as patients suffering from various types of immune disorders, most often

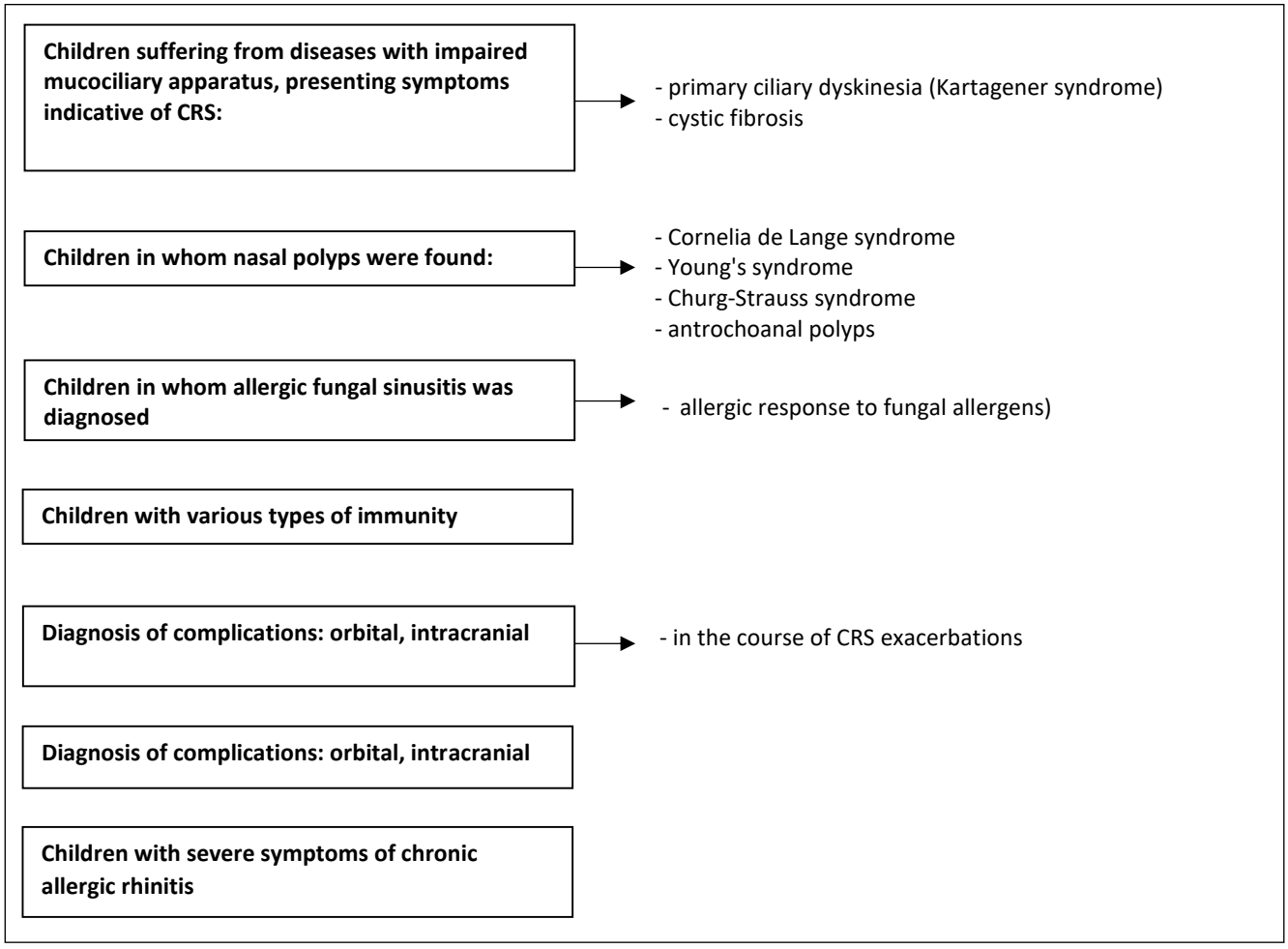

Fig. 1. Patients with CRS who require individual diagnosis and treatment.

IgA deficiency or common variable immunodeficiency [15]. Expanded diagnostics and most frequently, surgical treatment is required by children who suffer from: Cornelia de Lange, Young, Churg-Strauss syndromes, who have nasal polyps, as well as patients with antrochoanal polyps. A special group that requires individual medical decisions is comprised by children with diagnosed allergic fungal sinusitis (Fig. 1).

CLINICAL DEFINITION OF SINUSITIS IN CHILDREN AS PER EPOS 2012

The definition of rhinosinusitis in children concerns the presence of two or more symptoms, amongst which one is nasal obstruction or discharge in the nasal duct or discharge flowing down the posterior pharyngeal wall, or pain in the face and cough, with polyps coexisting in endoscopic examination, mucopurulent discharge in the middle nasal meatus and/or edema/obstruction of the middle nasal meatus. CT imaging showed obstruction of the ostiomeatal complex and/or lesions in paranasal sinuses. Chronic sinusitis in children can be diagnosed when the above symptoms prevail for over 12 weeks.

EPOS 2012 modification in relation to the agreements of 2007 emphasizes difficulty in making a CRC diagnosis in children, in comparison to criteria adopted for adults. This is connected with the necessity to take into account numerous factors that are important in the development of CRS for the pediatric population. This includes microbiology of infections, especially in the aspect of: diagnosis of viral infections, issues of microbiological testing, as well as increasing drug resistance to commonly used antibiotics [16].

Clinical diagnosis of CRS in children is based on symptoms very similar to those in other childhood diseases, such as: viral upper respiratory tract infections, hypertrophic and chronic

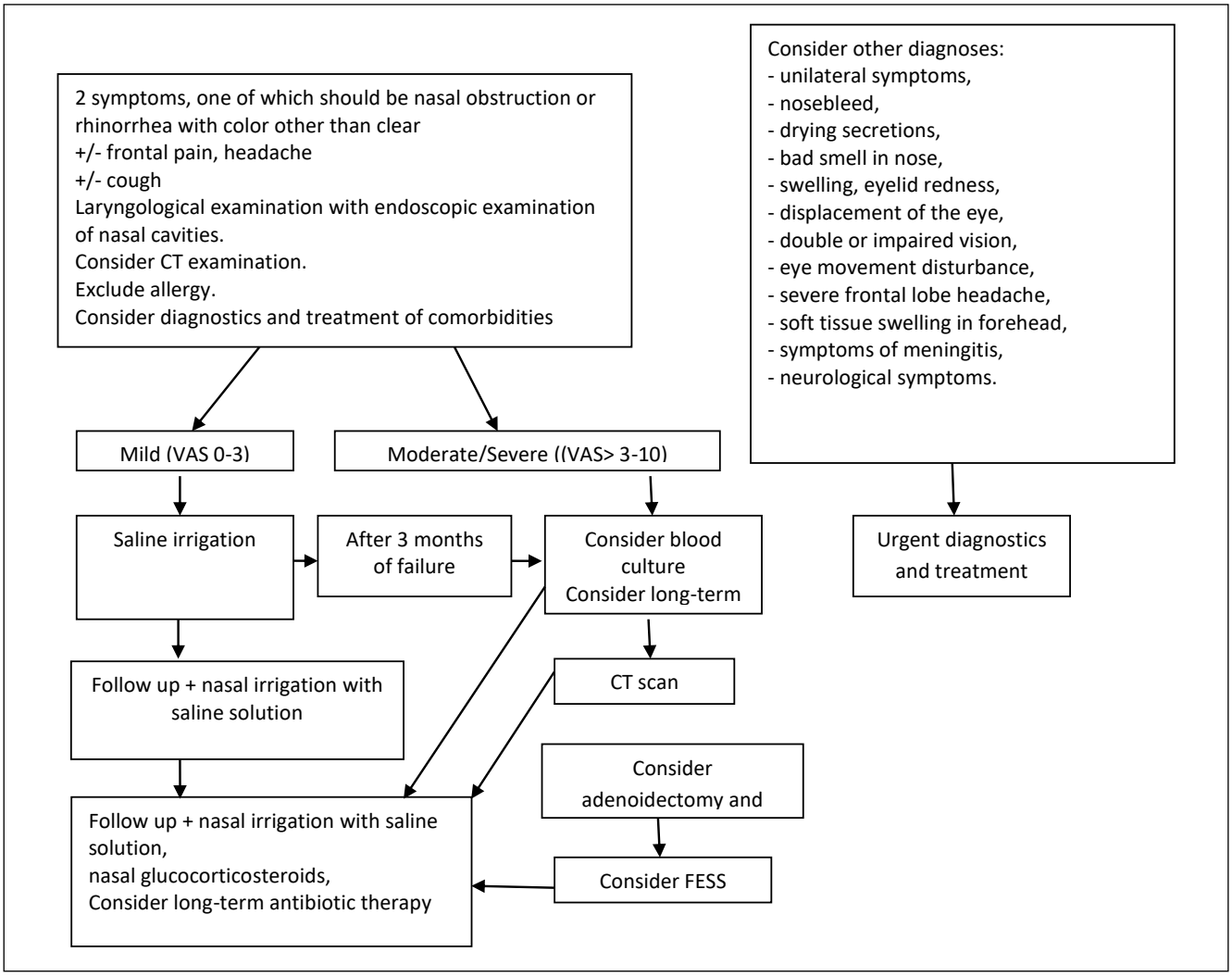

Fig. 2. Model procedure in younger children with CRS as per ESPO 2012 (translation by Dr. M. Zagor in an Otorhinolaryngological Journal of 2013;XIII (2):66).

pharyngitis, as well as allergic rhinitis. In a group of younger children, it is not possible to unequivocally distinguish between CRS and chronic adenoiditis, therefore adenotomy is the recommended initial therapeutic indication. Attention should be paid to the preventive action of vaccines against influenza and Streptococcus pneumoniae in development of CRS in children [17].

Inflammation being a result of an allergic reaction due to virulent allergy, food allergy as well as cross-reaction has a significant meaning in chronic inflammation of the upper respiratory tract [18]. However, it is difficult to establish the cause-and-effect relationship between allergic rhinitis and chronic sinusitis. Research results show a varying frequency of prevalence of allergies in children with diagnosed CRS, some of them match the frequency of prevalence in the general population (approx. 30%) [19]. However, intensified, persisting symptoms of AR may lead to sinus ostial obstruction and lesions in the mucous membrane and periosteum visible in CT images [20]. Prevailing allergic inflammation influences weakening of defense mechanisms which may lead to secondary bacterial infection [21].

Immunodeficiency should be considered in children with CRS who have had past ear inflammations and pneumonia during periods of exacerbation, usually difficult to control. The most common in children are primary hypogammaglobulinemia, selective IgA deficiency, common variable immunodeficiency (CVID) and specific antibody deficiency that is characterized by normal IgG levels but poor response to polysaccharide vaccines [22, 23]. Diagnostic tests should include immunoglobulin level (A, M, G), responses to the polysaccharide pneumococcal vaccine and evaluation of T lymphocytes (particularly Th) [24].

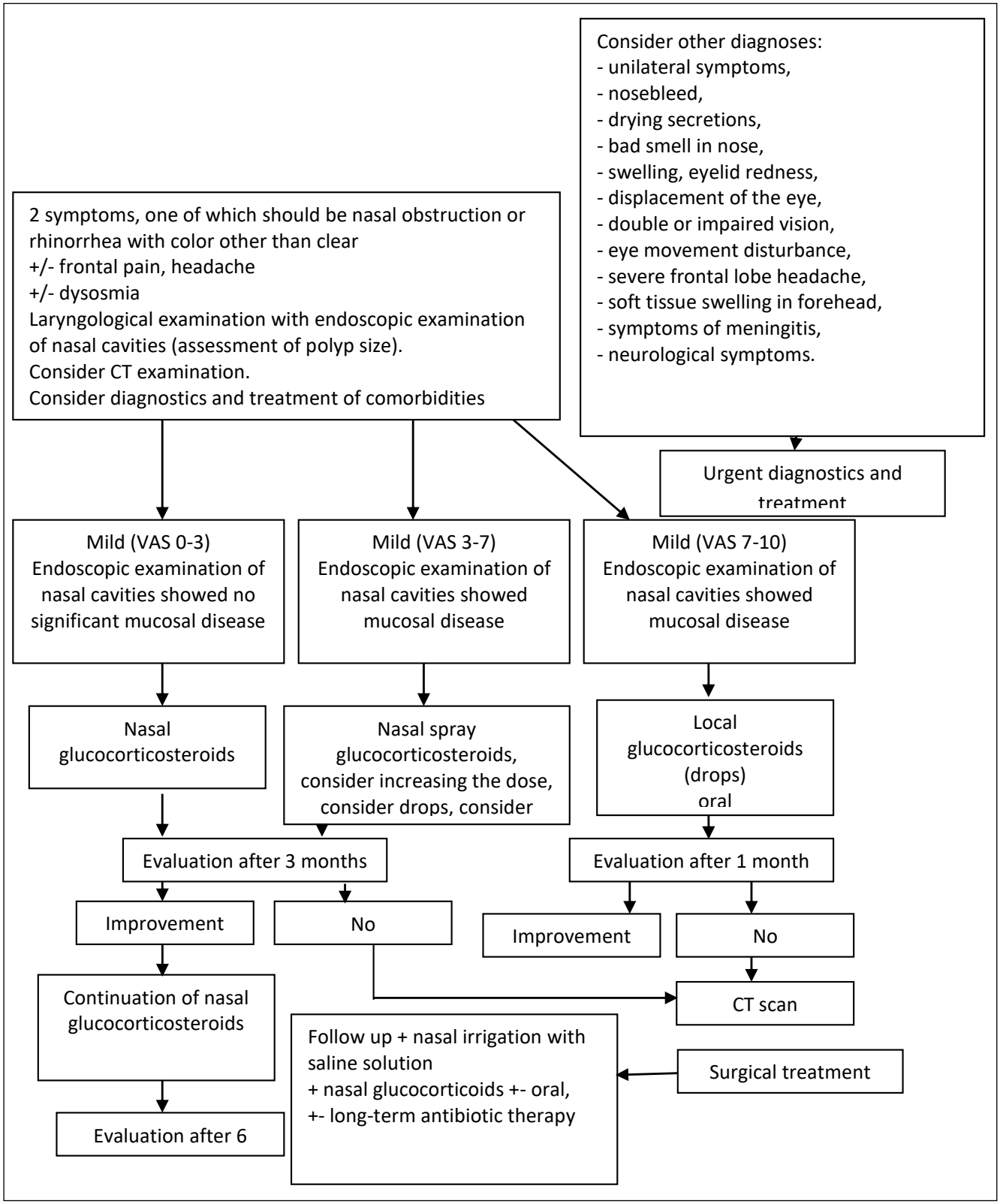

Fig. 3. Model procedure in adults with CRS as per ESPO 2012 (translation by Dr. M. Zagor in an Otorhinolaryngological Journal of 2013;XIII (2):66)

Tab. I. Surgical treatment as per EPOS 2012 and AAO-HNSF 2014.

EPOS 2012	AAO-HNS 2014
In cases of failure of pharmacotherapy and care treatment in line with Recommendations of the European Position Papers on Rhinosinusitis and Nasal Polyps 2012, surgical treatment should be considered.	Clinical Consensus Statement: Pediatric Chronic Rhinosinusitis as per AAO-HNS 2014 RCS in children aged 13 to 18 is similar to the form observed in adults, while below the age of 12, it is different due to developmental anatomy of the sinuses and physiology relevant to age
Adenoidectomy - younger children	Adenoidectomy up to the age of 6 (even up to the age of 12, it is considered as likely to be of significance)
Mini-FESS, FESS.	ESS recommended as a technique not affecting development of the craniofacial region
balonoplasty as proposed treatment	balonoplasty in direct effects is comparable with FESS, whereas its effectiveness is difficult to assess due to the small number of publications
conchoplasty	Conchoplasty: in the inferior concha - lack of an unambiguous opinion, on the other hand, surgery for concha bullosa is recommended
planned surgery is always preceded by CT diagnostics performed in the period free from CRS exacerbation; except for suspicion of complications	

Similarly, assessment of the value of CT-based diagnostic imaging that shows changes in sinuses only in 18-45% cases is consistent with the clinical picture of sinusitis in children. The Lund Mackay Postoperative Endoscopy Score (LMES) applied for chronic rhinosinusitis in adults with respect to children only at the level above 5 confirms CRS [25] (Fig. 2, Fig. 3).

THERAPEUTIC RECOMMENDATIONS

Chronic sinusitis is currently perceived as a result of many factors, of which one are bacteria. [25]. Dlatego antybiotykoterapia, która ze względu na rolę zakażeń bakteryjnych, w ostrym zapaleniu zatok przynosowych jest niepodważalna to jej znaczenie i sposób stosowania w przewlekłym zapaleniu zatok budzi różne wątpliwości.

Nasal steroids hinder inflammation of the nasal mucosa, which has been proven in numerous publications regarding adults, therefore their role in treating CS is unambiguous. On the other hand, due to the small number of publications that fulfill the conditions of assessing efficacy, in the case of children, they are only advised, and not recommended. They are only used as a basic medicine or in combination with antibiotic treatment.

The beneficial role of nasal irrigations in restraining CS symptoms has been proven unquestionably. This also regarded both intensification, in which the beneficial effect was assessed on the basis of life quality assessment and the Lund-Mackay score after 6 weeks of treatment [26], as well as reduction of nasal symptoms, when irrigation was the only recommendation performed in the long term [27]. Basing on the analysis of past examinations, it was proven that irrigation of nasal cavities decreases thickness secretion, improves muco-ciliary transport, facilitates mechanical removal of pathogens and inflammation mediators, and, in particular hypertonic solutions, decreases nasal mucosa swelling [28].

Consideration of treating gastroesophageal reflux as a causal factor of CS in children was not confirmed in published research, therefore empirical management of this treatment is not recommended as per AAO-HNS. While mentioning reflux as a possible cause of CS in children, EPOS does not take an unambiguous stance in regard to empirical treatment.

In conclusion: everyday sinus irrigation as well as use of steroids comprise the basic recommendations in treating CS in children.

Due to the frequency of viral infections and their development in the course of bacterial infections in children, unambiguous diagnosis of chronic sinusitis in children is difficult. As concluded by the authors of a consensus drawn up by AAO-HNS, "many aspects of chronic sinusitis in children remain incorrectly diagnosed." According to Hopp RJ, there are only two studies that asses antibiotic treatment (amoxicillin, erythromycin, clindamycin, cefaclor, trimethoprim-sulfamethoxazole) without surgical treatment, however, none of the assessed are currently recommended [29].

The most investigative study that regards microbiological testing in children with diagnosed CS and choice of antibiotic treatment was done by Brook [30]. In treating CS as an inflammatory process triggered by various factors, and not just a persistent bacterial infection, he emphasizes the significance of diagnostics, but also the need to take into account choice of antibiotics. This includes the need to take into account differences of pathogens present in CS. He underlines, that treatment often includes simultaneous steroid therapy, nasal and sinus irrigation and antibiotic therapy, which according to the assessment of AAO-HNS, are more effective in therapy that lasts 20 days, rather than 10 [31]. Taking into account the fact, that initially antibiotic treatment is empirical, it is necessary to take cognizance of the pathogens of aerobic (S. pneumoniae, H. influenzae, M. catarrhalis) as well as anaerobic bacteria (Fusobacterium nucleatum, Pigmented Prevotella, Porphyromonas, Peptostreptococcus spp.), and MRSA staphylococcus. The recommended drug is amoxicillin with clavulanic acid (45 mg/kg per day or 90 mg per day in areas with proven high S. pneumoniae refractoriness). Clindamycin should be used in patients with hypersensitivity to penicillin or when dealing with

MRSA. Metronidazole is recommended in cases of infections with aerobic gram-positive bacteria and pseudobacteria. It is usually combined with cefuroxime, cefpodoxime, azithromycin, clarithromycin.

When choosing antibiotic therapy, it is necessary to consider the possibility of genetic or metabolic diseases. Patients who suffer from cystic fibrosis or diabetes usually have Pseudomonas spp infections. Treatment and, if necessary, additional recommendation in cases where an odontogenic infection is diagnosed should be consulted with dentists.

Parenteral treatment is applied in patients who present high severity of disease symptoms and threatening complications, including drugs that affect aerobic and anaerobic bacteria, and take into account MRSA. However, it is also always necessary to consider indications for undertaking FESS operative treatment.

RECOMMENDATIONS FOR SURGICAL MANAGEMENT

Recommendations for surgical management of CRS in children concern failure of pharmacotherapy and care treatment in accordance with EPOS 2012 recommendations. Surgical treatment should be considered, which, depending on age, includes adenoidectomy in younger children. In the elderly, proceedings concern successively arrangements depending on irregularities found:

- mini FESS,
- balonoplasty as a suggestion for alternative treatment,
- conchoplasty,
- FESS.

Planned surgery should always be preceded by CT diagnostics performed in the period free from exacerbation of CRS inflammation. This reservation does not apply to suspicion of complications.

Due to difficulties in interpreting radiological images obtained in children with suspected CRS, the need to perform these tests is acknowledged by consensus when considering planned surgical activities due to lack of effects of conservative treatment or in cases of sudden complications [6].

However, the consensus of ESPO 2012, even when significantly expanded, in comparison with that of 2007 in the field of diagnosis and treatment of children, does not solve many diagnostic problems and therapeutic doubts. Current research allows for the expansion of knowledge about this disease and age-related variability, since pediatric patients comprise an age group from infancy to adulthood, i.e., till the age of 18. The document created in the United States as an expert opinion based on the analysis of research and opinions of 22 clinical centers, is the Clinical Consensus Statement: Pediatric Chronic Rhinosinusitis developed on the initiative of the American Academy of Otolaryngology of Head and Neck Surgery [31]. It concerns the analysis of four health problems of children aged from 6 months to 18 years who suffer from CRS. The study excluded children with craniofacial anomalies, diseases associated with disorders of ciliary motility and immunodeficiency disorders, therefore clearly indicating that it is a group that requires individual, disease-dependent therapeutic decisions in the field of CRS. The evaluation covered four main issues: definition of CRS in children and diagnostics, conservative treatment, diagnosis of tonsillitis and necessity of performing adenotomy, as well as surgical treatment - endoscopic surgery of the nose and sinuses (ESS/conchoplasty).

EVALUATION OF THE VALUE OF DIAGNOSTIC TESTS AS PER AAO-HNS

Analysis included CRS ailments (subjective) and symptoms (objective), concluding that CRS in children is diagnosed with the following conditions persisting for 90 days: purulent rhinitis, nasal obstruction, facial pain or cough. The ailments and symptoms mentioned should be confirmed via endoscopy and/or computed tomography. Patients with polyps are a separate group that requires special treatment. It was found that the child's age is a very important factor affecting the course of the disease and treatment decisions. Diseases of the pharyngeal tonsil (independent of its size) are the main factor of CRS in younger children, whereas chronic allergic rhinitis - in older children. Significance of endoscopic examinations in diagnosis was confirmed. However, the relationship between reflux disease and CRS was not confirmed.

EVALUATION OF CONSERVATIVE AND SURGICAL TREATMENT AS PER AAO-HNS

In conservative treatment, the procedure's effectiveness has been established for daily use of nasal steroids as well as nasal and sinus rinse. Antibiotic treatment was not assessed as necessary, whereas when assessing the time of their administration, it was concluded that 20-day treatment brings better clinical results in comparison to treatment of 10 days. Lack of clinical effect of GERD in relation to CRS treatment was established. Treatment with topical antibiotics or antibiotics administered as irrigation were not included in recommendations for disease management.

Inflammation of the pharyngeal tonsils and recommendations for adenoidectomy concern children under 6 years of age. On the other hand, less unambiguous effects and strength of recommendations include the age of 6-12. This operation does not comprise the recommended first-line treatment procedure above the age of 13. Clearly, removal of palatine tonsils without adenotomy was recognized as an ineffective procedure.

ENDOSCOPIC SINUS SURGERY (ESS) AND CONCHOPLASTY

ESS is a procedure recommended for adenoidectomy performed in younger children. It is suggested to perform CT prior to operational qualification. Plastic surgery of the sinuses using balonoplasty that gives an effect comparable to ESS in adults, is rarely done in children. Therefore, its effectiveness (short--term and long-term) cannot be unambiguously assessed and compared with ESS [32]. The committee of experts did not comment on the effects of using this method in treatment of CRS in children. There are no indications to perform conchoplasty of the inferior nasal concha. On the other hand, surgical treatment of the middle concha in concha bullosa is highly recommended (Fig. 4).

FINAL REMARKS

It is important to emphasize the remarks of experts who have issued opinions regarding their treatment as guidelines, with the need for individual inquiring diagnosis of each patient (taking into account age, duration and course of CRS) as well as comorbidities. Treatment failures in CRS should be re-considered in terms of inadequate diagnosis, for example, lack of endoscopic examination of the nose and nasopharynx, as well as abnormal or insufficient laboratory diagnostics (the need to assess the immune status and microbiological tests).

Another very important issue is frequently lack or insufficient control of current treatment resulting from being under the care of many different physicians who have implemented different concepts of treatment. Frequently, there are irregularities in the immunoprophylaxis of bacterial infections, and in particular the time of its application. Many studies confirm the positive effects of such treatment [33]. However, the problem that arises from the so-called persistent immunization applied without monitoring for several years with different formulations is discussed significantly less frequently. Unfortunately, lack of assessment in terms of efficacy and safety may increase the risk of autoimmunity induction and unpredictable immunization [34]. However, the importance of specific immunostimulation is irrelevant. It concerns pneumococcal and influenza vaccination, which is of great importance in the pediatric population due to attendance in children's communities [35].

Analyzing further theories regarding the development of CRS, that is: infections co-existing with anatomical structure disparities of the nasal sidewall, bacterial biofilm adhering to the mucous membrane, staphylococcal superantigens that increase inflammatory reactions in the mucous membrane, the role of fungi in the inflammatory process, and osteitis, the importance of bacteria should be emphasized, however not in the primary sense of an infection. All these theories are connected with another that concerns imbalance of the whole organism's immune response, which can be treated not as the basis of the disease but as its result. In 2014, Hauser et al. proved that the traditional culture is not very useful in assessment of microorganisms inhabiting the paranasal sinuses [36]. In their study "Human microbiome", the authors demonstrated that the composition of microorganisms in the body affects the state of health or disease in the upper and lower respiratory tracts [37].

Importance of the human microbiome in CRS relates to the gastrointestinal microbiome's influence on the regulation of immunotolerance in the human body as well as the influence of the airway microbiome on pathogenesis of CRS.

Results obtained so far regarding changes in the microbiomes of patients suffering from CRS allow to detect small differences between the type of cultured bacteria among the healthy and the sick, while the differences concern concentration of bacteria. The proportion of the most frequently found bacteria was reversed between the healthy and the ill (patients with CRS: Staphylococcus aureus, Staphylococcus epidermidis, Propionibacterium acnes). When assessing the immune response, it was established that the presence of Staphylococus aureus is associated with a Th2-dependant cytokine profile, while demonstration of the presence of Pseudomonas aeruginosa triggers a Th1-dependent cytokine profile [38]. Detailed microbiological research draws attention to deficiencies of lactic acid bacteria in CRS. It was concluded that CRS may be associated with survival of a weakened microbiome. Theoretically, the change may take place through the action of probiotics, prebiotics and symbiotics (filling in gaps in the microbiome). However, nowadays there is emphasis on the significance of including supplementation during childhood, that is before the fixation of adverse changes [39]. Confirmation of the still incomplete knowledge on chronic inflammatory process are studies which have proven that the development and course of the inflammatory process in younger children differs from that in older children and adults, which is illustrated by histopathological examinations [40].

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