LITERATURE REVIEW

Particularities in the management of chronic rhinosinusitis in children

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ABSTRACT

Chronic rhinosinusitis (CRS) is a multifactorial disease which represents a diagnostic and management challenge to ENT specialists as well as to paediatricians. Chronic rhinosinusitis is usually diagnosed in children with predisposing factors, such as recurrent respiratory tract infections, allergic rhinitis, cystic fibrosis, immunodeficiency, ciliary dyskinesia, anatomic abnormalities or gastroesophageal reflux. The optimal management of CRS in children is still controversial. Current therapeutic options include medical treatment ("maximal medical therapy", adjuvant therapy) and surgery, if maximal medical treatment fails. Surgical treatment consists of adenoidectomy as first-line procedure and, when the previous therapies failed, endoscopic sinus surgery (ESS) should be performed in selected cases.

KEYWORDS: chronic rhinosinusitis, cystic fibrosis, immunodeficiency, ciliary dyskinesia, adenoidectomy

INTRODUCTION

Rhinosinusitis is a common respiratory infection in children. Even though this pathology is very common, its diagnosis is often difficult in pediatric practice, either because symptoms are frequently subtle and nonspecific or because of the erroneous belief that paranasal sinuses are not yet developed in a small child[1,2]. Recurrent or chronic cases are usually diagnosed in children with predisposing factors, such as recurrent respiratory tract infections, allergic rhinitis, cystic fibrosis, immunodeficiency, ciliary dyskinesia, anatomic abnormalities or reflux. It is associated with a significant adverse effect on health-related quality of life in children[3]. Despite widespread acceptance of this idea, the proper management of sinusitis in children is controversial[1].

DEFINITION

Rhinosinusitis (RS) is defined as the inflammation of one or more of the paranasal sinuses and the correct term is rhinosinusitis because of the following reasons: sinusitis without rhinitis is rare, inflammation of the contiguous nasal mucosa and obstruction of the ostiomeatal complex play a major role in development of sinusitis.

A proper diagnosis requires a knowledge of the embryologic development of the sinuses. The clinician must identify the child's status of sinus development in order to adequately assess and treat the disease.

The paranasal sinuses develop as diverticula from the lateral nasal wall, extending into the maxilla, ethmoid, frontal, and sphenoid bones. The maxillary sinuses are present at birth and exhibit two phases of growth, between birth and 3 years and again from 7 to 12 years of age. The ethmoid sinuses are present at birth and become visible radiographically at 6 months. The frontal sinuses present an evident radiographically aeration at 6 years, but the frontal disease becomes clinically significant at 10 years. The sphenoid sinuses are absent at birth and develop as an invagination of the spheno-ethmoidal recess. Pneumatization begins at approximately age 7 and continues to adulthood, with a complete aeration at 20 years of age[4].

CLASSIFICATION

Rhinosinusitis is classified depending on the duration of persistent symptomatology: acute RS (ARS)

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with symptoms which last between 10 and 30 days, subacute infection which lasts between 30 and 90 days, recurrent infection which consists of 3 or more episodes of ARS per 6 months or more than 4 per year, chronic RS is defined by the persistence of symptomatology for more than 90 days[5,6].

INCIDENCE OF CHRONIC RHINOSINUSITIS IN CHILDREN

The exact incidence of rhinosinusitis in children is unknown. It is estimated that 6-13% of children will have had one episode of rhinosinusitis by the age of 3 years[6]. Children average between six to eight viral infections of the upper respiratory tract a year, of which 5% to 10% may be complicated by a secondary bacterial infection of the paranasal sinuses[1]. Children with CRS are older than those with acute sinusitis (4-7 years vs. 1-5 years) and are more likely already an antibiotic treatment for a previous sinus infection[1,6,7].

More than 80% of children with CRS have a positive family history of allergic rhinitis and conversely, children with asthma and allergic rhinitis have a higher incidence of CRS[8].

Predisposing factors of CRS in children

CRS is a multifactorial and heterogenous condition induced by the anatomic or acquired obstruction of the ostiomeatal complex caused by local, regional, or systemic factors[1].

The upper respiratory viral infections: Most sinus infections in children develop following a viral upper respiratory infection (URI), most commonly rhinovirus, coronavirus, and *influenzae* virus[1]. Inflammation of sinus ostia causes stasis of secretions and poor ventilation of the affected sinus. This leads to absorption of oxygen and the development of a relative negative pressure or vacuum within the sinus, causing movement of intranasal contents and nasopharyngeal bacteria into the sinus cavity. Viruses also can have a direct inhibitory effect on ciliary function. Finally, there is an increased bacterial growth in the presence of viral infection[1].

It is important to try to differentiate sequential episodes of uncomplicated viral URI from the acutization of CRS with persistent symptoms. The first generally lasts 5-7 days but may last longer; although the respiratory symptoms may not have completely disappeared by the 10th day, they have almost always an improvement. The persistence of respiratory symptoms without any sign of resolution should therefore suggest the presence of a secondary bacterial infection[9].

Bacterial pathogens: The most common bacterial species found in chronic rhinosinusitis are *S. neumoniae, H. influenzae, M. catarrhalis, S. aureus, P. aeruginosa* and anaerobes. The incidence of anaerobic bacteria increases as the infection becomes more chronic. *S. aureus* can survive into nasal mucosa as an intracellular reservoir avoiding host defence and antibiotherapy[10,11]. Fungal sinusitis can take one of three forms: allergic fungal sinusitis, mycetoma or fulminant invasive disease[10].

Adenoids: The adenoids contribute to RS in children by acting as a bacterial and biofilms reservoir, similar to otitis media. 90% of bacterial cultures from middle meatus and from adenoid pad are comparable[1,14], and several studies show that removal of the adenoids will improve RS from 70% to 80% of children[1,12,13,15]. Adenoidectomy has become a first-line surgical intervention in children with CRS. Other authors emphasized the mechanical obstructive role of adenoids in development of CRS[1,15].

Allergy: Allergy represents the second most common factor in CRS, after viral URI in children. However, the role of allergic sensitization in chronic rhinosinusitis in children is currently unclear. Recent data showed that the prevalence of sensitization to aeroallergens in children with CRS is comparable with that of the general paediatric population, as assessed in the Italian arm of the ISAAC study and this doesn't account for routine investigation for allergy in children diagnosed with such disease[16,17]. Allergy can contribute to sinusitis by either nasal congestion and subsequent ostia obstruction, or direct allergic effects on sinus lining cells[18].

Allergy should be considered in all children with the following: a history of allergic signs and symptoms (watery rhinorrhea, pruritus, sneezing, frequent rashes), seasonal patterns of infection, specific allergen reactions (dust, particular foods), and a family history of allergy or asthma. The proper management requires an assessment made by a paediatric allergist who can identify the allergen and prescribe avoidance techniques, targeted drug therapy, and immunotherapy when necessary. Although not IgE mediated, cow's milk protein allergy may be present in very young children with a history of rashes or colic, and can be a contributing factor to RS in these children[1].

CRS and asthma: The relationship between rhinosinusitis and asthma is provided by epidemiologic data. Doubts persist as to whether CRS worsens asthma, or whether these are manifestations in different parts of the respiratory tract of the same underlying disease process. Difficult to control asthma in children requires a review of the diagnosis and evaluation of the different risk factors for exacerbations, including rhinosinusitis. From an epidemiologic point of view up to 80% of patients with asthma have rhinitis and over 50% of patients with sinus disease also have asthma[19,20]. Patients with severe asthma appear to have the more important abnormalities on computed tomography (CT) of paranasal sinuses.

Other mechanisms have been proposed to explain the relationship between asthma and sinusitis, such as the postnasal drip of infectious and inflammatory materials, a naso-bronchial reflex, or a systemic effect of inflammatory mediators released from affected paranasal sinus tissue.

The aggressive medical treatment of CRS in asthmatic children may improve the symptoms, decrease the use of bronchodilators, and normalize the lung function. The effects of concomitant therapy for CRS on asthma and bronchial hyperreactivity (BHR) result from different mechanisms including reduction of aspiration of mucopurulent secretions into the lower airways, reduction of naso-bronchial reflex, reduction of inflammatory mediators, and improvement in beta-adrenergic responsiveness in the lower airways.

Rhinosinusitis is characterized by nasal inflammation, which can play a key role in modulating lower airway responsiveness. CRS may be implicated in the mechanisms of BHR in asthmatic children. The proper treatment of comorbid factors such as CRS could result in less asthma exacerbations, which will greatly improve the quality of life of the patients with difficult to control asthma[21].

Passive smoke: Airway pollutants can have direct irritant effects on the nasal and sinus mucosa. Exposure to passive smoke must be eliminated due to its potential effects on nasal and sinus mucosa. In addition, otitis media and asthma can be prevented by this reasonable intervention[1].

Nasosinusal anatomic abnormalities. Structural anomalies of the sinus and nasal cavity represent risk factors for CRS, and include septal deviation, choanal atresia, lateral nasal wall anomalies (paradoxical middle turbinate, concha bullosa, Haller cells), and maxillary sinus hypoplasia[1,22].

Gastroesophageal reflux disease (GERD): Many authors suggest that recurrent rhinosinusitis might result or be exacerbated by GERD. GERD should be considered in all children with difficult CRS in addition to other suggestive features, including frequent vomiting, unexplained respiratory symptoms such as glottic spasms, early hoarseness, and atypical wheezing or stridor. Empiric therapy with an H2 blocker may be considered in a child with suspected reflux-induced rhinitis[1,23-26]. A positive response to this ''therapeutic trial'' strongly suggests GERD as an etiologic factor. A recent retrospective study[1,26] suggested that GERD therapy could prevent sinus surgery in almost 90% of children with refractory CRS.

Immunologic defects: All young children have a relative immunodeficient state due to a slow rise in immunoglobulin production. In contrast to this self-limited phenomenon, pathologic immune deficiency can cause severe and refractory RS in affected children. Humoral immunodeficiency is the most common disorder in these children, with IgG subclass deficiency being the most common subtype[27,28]. In general, children with immune deficiency present multiple upper and lower respiratory infections in addition to RS, including pneumonia, bronchitis, and otitis media.

Primary ciliary dyskinesia (PCD): Drainage of the paranasal sinuses is dependent on the effectiveness of the mucociliary clearance mechanism. Multiple intrinsic and extrinsic properties can affect the mucociliary clearance mechanism. Intrinsic factors include ciliary dyskinesias that are abnormalities of ciliary form or function, alterations in local nitric oxide production, and cystic fibrosis (CF) which alters the consistency of mucous. Extrinsic factors include exposure to environmental irritants such as tobacco smoke and certain chemicals, as well as infection with viral upper respiratory pathogens[4]. PCD is a rare disorder of ciliary structure or function that can occur alone, or can be a part of the more global Kartagener's syndrome. Functional abnormalities can occur despite normal ciliary architecture, and can be demonstrated by a decrease in ciliary beat frequency[1,29]. As with children who have immunologic defects, children with PCD will have other upper and lower respiratory infections in addition to CRS.

Cystic fibrosis (CF): CF is a genetic, autosomal recessive, multiorgan, chronic disorder which occurs in 1/2500-1/4000 of live births in the United States[30]. Affected children present with chronic upper and lower respiratory infections — most commonly pneumonia and severe refractory RS — often with nasal polyp formation. Other manifestations include malnutrition, intestinal obstruction, and pancreatic insufficiency[1,30]. Altered mucus composition decreases mucociliary clearance with obstruction of paranasal sinus drainage ostia and bacterial colonization (especially *Staphilococcus aureus* and *Pseudomonas aeruginosa*).

- Up to 90% of CF patients have chronic rhinosinusitis (CRS);
- From 8% to 56% nasal polyps;
- Almost 100% reveal upper airway abnormalities on CT scan;
- Nasal polyposis incidence in paediatric age is 0.1%. CF is the main cause (33%).

Immunodeficiency, primary ciliary dyskinesia (PCD), and CF are relatively uncommon, although they should be suspected in children with difficult RS together with a history of frequent upper and lower respiratory infections such as pneumonia and bronchitis. CF and immunodeficiency disease have to be evaluated because of the possibility to treat the patients with IVIG (immunoglobulin iv) or physiotherapy; however, immunodeficiencies are rare diseases and are not the main cause of CRS.

DIAGNOSIS

The best current practice is to establish an accurate diagnosis and prescribe an appropriate therapy[1,27,31]. Diagnosis of CRS in children is difficult because of the following: there is a wide variation in clinical expression of the disease, a discordance between patient symptoms and objective findings, absence of standardised diagnostic criteria. Clinical criteria to diagnose CRS, as well as the predictive value of these criteria, are not well defined, especially in children. The symptomatology is subtle, nonspecific and difficult to evaluate. CRS may be present together with recurrent infections of upper airways, and particularly of middle ear, with persistent cough, post nasal drip, halitosis, poor appetite, slow growth.

Nasal endoscopy is a very important exam, but difficult to perform in infant or preschool children, requiring sedation or anaesthesia.

The diagnosis of CRS in paediatric population should be made first of all clinically, and not on the basis of imaging findings alone. The high incidence of soft tissue abnormalities on CT of paranasal sinuses in infant and children with intercurrent or recent upper respiratory tract infections requires the correlation of clinical and imaging findings. Imaging studies should be restricted to patients in whom the diagnosis of CRS is uncertain or those failing to respond to a maximal medical therapy. Under these special circumstances, CT exam is the evaluation of choice because it provides precise anatomic information that will be helpful when considering a surgical intervention.

CRS is a heterogeneous condition induced by chronic or recurrent infections and by non-infectious inflammatory conditions: allergic fungal sinusitis, chronic hyperplastic eosinophilic sinusitis, aspirin-sensitive asthma. Therefore the role of antibiotics in patients with chronic sinusitis is controversial. CRS can be also associated with other comorbidities such as allergic rhinitis, cystic fibrosis, asthma, immobile cilia syndrome, immunodeficiencies which require specific treatments[7,10].

MANAGEMENT OF CHRONIC RHINOSINUSITIS IN CHILDREN

Medical treatment

The term "maximal medical therapy" is commonly used to describe CRS treatment like as initial trial therapy[1] but there is no consensus on treatment length, organism coverage or which antibiotics are most effective because the bacteriologic exams are variable with polymicrobial aerobic and anaerobic organisms[10]. The role of infection and subsequent antibiotic treatment in CRS is still controversial. This disease may be often due to colonization with a chronic inflammation state or most likely to a non-infectious process such as tissue remodelling with eosinophilic infiltrates, both not requiring antibiotherapy[10,31]. Antibiotic therapy is currently recommended for the treatment of acute exacerbations of CRS in presence of purulent drainage on anterior rhinoscopy or nasal endoscopy[10]. Resistance patterns are important in predicting response to antimicrobial therapy.

The optimal oral treatment consists on amoxicillin/clavulanate, cephalosporin, ampicillin/sulbactam. The studies showed that high-dose amoxicillin/clavulanate (90 mg/kg) covered 94% of *H. influenzae* (including beta-lactamase producing strains), and 98% of *S. pneumoniae*, including more than 90% of the resistant *S. pneumoniae*. This bacteriologic profile makes high-dose amoxicillin/clavulanate an ideal drug for the treatment of CRS, although no scientific studies exist. In case of allergy to these drugs, macrolides are utilized and some patients benefit from their anti-inflammatory properties[10,32-34].

Don et al suggested that intravenous antibiotics such as cefuroxime, ampicillin/sulbactam, ticarcillin, ceftriaxone, vancomycin for more than 14 weeks can be useful to prevent surgery in children with CRS[34].

The same results are confirmed by Adappa et al who supports the long-term efficacy of intravenous antibiotic treatment (ampicillin/sulbactam, clindamycin, piperacillin, tazobactam, metronidazole) and adenoidectomy in children with CRS. According to this author, anatomic remodelling with bone resorption, neogenesis and fibrosis occurred in CRS lead to conditions to bacterial growth in sinus cavity. Bacteria can survive within a polysaccharide matrix called biofilm adherent to sinus. The oral antibiotics fail to eradicate those bacteria while the intravenous antibiotics could have a greater efficacy by reaching sufficient blood concentrations to penetrate into the core of infectious biofilm[31].

A variety of other agents are used in the treatment of CRS, but are considered a second line therapy (oral decongestants, oral corticosteroids, antihistamines, antileukotrienes, mucolytics)[10,35-38]. Successful treatment of CRS in children is critical, because failure usually will lead to surgical therapy.

Adjuvant therapies

Topical treatment modalities are frequently used in paediatric population, even if there is no evidence of the efficacy, excepting topical steroids[39]. Paediatric ENT specialists manage 95% of their patients with CRS with antibiotics while intranasal corticosteroids are used by 90% and use of saline sprays by 68%[40]. Topical nasal steroids typically are used to treat CRS[39]. Mometasone furoate is the only drug approved for children who are 2 years of age or older, based on long term studies that showed no effect on growth. Flutica-

sone propionate is approved for children who are 2-4 years of age, whereas most of the other topical nasal sprays, such as budesonide and triamcinolone, can be used in children older than 6 years. Nasal saline irrigation with different osmotic pressures improves the symptomatology, especially post nasal drip.

Surgical therapy

Surgery is indicated for children with CRS who have failed maximum medical therapy. Current surgical options for the treatment of CRS in children include adenoidectomy, endoscopic sinus surgery (ESS) or both. Most authors agree that adenoidectomy should be the first-line surgical procedure to remove the adenoid pad as a reservoir of bacterial pathogens[1]. The expected rate of improvement is 70% to 80%[1,12]. Endoscopic sinus surgery (ESS) should be performed only when children have failed previous therapies[41,42]. In contrast to older traditional techniques of sinus surgery, ESS consists on enlarging the natural ostia of the maxillary and ethmoid sinuses, while preserving most or all of the sinus mucosa. The typical procedure is a ''mini ESS" consisting of uncinectomy plus limited anterior ethmoidectomy. In properly selected children, the results are good, with an expected improvement of 80% to 100%[1]. Preoperative CT scan is essential in defining the specific diseased sinuses, and in looking for anatomic abnormalities including septal deviation, concha bullosa, and paradoxical middle turbinate. The surgery should be performed only by an otolaryngologist experienced in paediatric ESS[1]; when properly performed, the incidence of major complications is less than 1%[1]. Some authors suggest that the surgical procedures on paranasal sinuses in children <6 years could have adverse effects on facial growth[43-45]. Ramadan demonstrated that adenoidectomy alone initially is recommended for children who are 6 yr of age or younger, have no asthma and a low CT score. Children older than 6 years of age with high CT score benefit from an ESS at the time of adenoidectomy[13]. The children with cystic fibrosis, immunodeficiency or ciliary dyskinesia represent a very difficult challenge to the surgeon.

CONCLUSIONS

The successful management of RS in children requires careful diagnosis, recognition of predisposing factors, and adequate medical therapy. Refractory cases require surgical therapy, with adenoidectomy as the firstline intervention and ESS reserved for refractory cases. This overall approach improves quality of life and prevents complications in children with CRS.

REFERENCES

1. Goldsmith A.J, Rosenfeld R.M. – Treatment of pediatric sinusitis. Pediatr Clin N Am, 2003;50:413–426.
2. Lack G. - Pediatric allergic rhinitis and comorbid disorders. J Allergy Clin Immunol, 2001;108:S9-15.
3. Cunningham M.J., Chiu E.J., Landgraf J.M., Gliklich R.E. - The health impact of chronic rhinosinusitis in children. Arch Otolaryngol Head Neck Surg, 2000;126:1363 –8.
4. Hepworth E., Mitchell R.B. - Diagnostic workup for pediatric rhinosinusitis, Pediatric sinusitis and sinus surgery, edited by Ramzi T. Younis, 2006,;29-42.
5. American Academy of Pediatrics. Clinical practice guideline; management of sinusitis. Pediatrics, 2001;108:798-808.
6. Taylor A. - Sinusitis. Pediatrics in Review., 2006;27: 395-7.
7. Steele R.W. - Chronic sinusitis in children. Clin Pediatr, 2005;144: 465-71.
8. Nelson H.S. - Advances in upper airway disease and allergen immunotherapy. J Allergy Clin Immunol, 2006;117:1047-53.
9. Esposito S., Bosis S., Bellasio M., Principi N. - From clinical practice to guideline: how to recognize rhinosinusitis in children. Pediatr Allergy Immunol, 2007;18:53-55.
10. Novembre E., Mori F., Pucci N., Bernardini R., Vierucci A., De Martino M. - Systemic treatment of rhinosinusitis in children. Pediatr Allergy Immunol, 2007;18(Suppl.18): 56-61.
11. Clement S., Vaudaux P., Francois P. et al. - Evidence of an intracellular reservoir in the nasal mucosa of patients with recurrent S. aureus rhinosinusitis. J Infect Dis. 2005;192:1023-8.
12. Vandenberg S.J., Heatly D.G. - Efficacy of adenoidectomy in relieving symptoms of chronic sinusitis in children. Arch Otolaryngol Head Neck Surg, 1997;123: 679-88.
13. Ramadan H.H. - Adenoidectomy vs.endoscopic sinus surgery for the treatment of pediatric sinusitis. Arch Otolaryngol Head Neck Surg, 1999;125:1208-11.
14. Lee D., Rosenfeld R.M. - Sinonasal symptoms and adenoid bacteriology. Otolaryngol Head Neck Surg, 1997;116:301–7.
15. Tuncer U., Aydogan B, Soylu L, et al. - Chronic rhinosinusitis and adenoid hipertrophy in children. Am J Otolaryngol, 2004;25:5-10.
16. Leo G., Piacentini E., Incorvaia C., Consonni D., Frati F. - Chronic sinusitis and atopy: a cross-sectional study. Allergol Immunol, 2006;38:361-3.
17. Leo G., Piacentini E., Incorvaia C., Consonni D., Frati F. - Chronic rhinosinusitis and allergy. Pediatr Allergy Immunol, 2007;18:19-21.
18. Di Domenicantonio R., De Savio M., Sammarro S. et al. - Asthma and allergies in childhood in the city of Rome. The Italian contribution to the International study on asthma and allergies in childhood (ISAAC). Phase II. Epidemiol Prev, 2003;27:226-33.
19. Leynaert B., Neukirch F., Demoly P., Bousquet J. - Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol, 2000;106:S201-5.
20. Peroni D.G., Piacentini G.L., Ceravolo R., Boner A.L. - Difficult asthma: possible association with rhinosinusitis. Pediatr Allergy Immunol, 2007;18:25-27.
21. Tosca M., Cosentino C., Pallestrini E. et al. - Medical treatment reverses cytokine pattern in allergic and nonallergic chronic rhinosinusitis in asthmatic children. Pediatr Allergy Immunol, 2003;14: 238-41.
22. Walke M., Shankar L., Hawke M., Takeno S. - Maxillary sinus hypoplasia, embryology, and radiology. Arch Otolaryngol Head Neck Surg, 1993;119:1353– 7.
23. Phipps C.D., Wood E., Gibson W.S., Cochran W.J. - Gastroesophageal reflux contributing to chronic sinus disease in children. Arch Otolaryngol Head Neck Surg, 2000;126:831–6.

24. Contencin P., Narcy P. - Nasopharyngeal monitoring in infants and children with chronic rhinopharyngitis. Int J Pediatr Otorhinolaryngol, 1991;22:249–56.
25. Beste D.J., Conley S.F., Brown C.W. - Gastroesophageal reflux complicating choanal atresia repair. Int J Pediatr Otorhinolaryngol; 1994;29:51 – 8.
26. Bothwell M.R., Parsons D.S., Talbot A., Barbero G.J., Wilder B. - Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngol Head Neck Surg, 1999;121:255– 62.
27. Lund V.J., Neijens H.J., Clement P.A. - The treatment of chronic sinusitis: a controversial issue. Int J Pediatr Otorhinolaryngol, 1995;32(Suppl):521– 32.
28. Shapiro G.G., Virant F.S., Furukawa C.T., Pierson W.E., Bierman C.W. - Immunologic defects in patients with refractory sinusitis. Pediatrics, 1991;87:311– 6.
29. Chapelin C., Coste A., Reinert P., Boucherat M., Millepied M.C., Poron F., et al. - Incidence of primary ciliary dyskinesia in children with recurrent respiratory diseases. Ann Otol Rhinol Laryngol, 1997;106:854– 8.
30. Rosenstein B.J., Cutting G.R. - The diagnosis of cystic fibrosis. J Pediatr. 1998;132:589– 95.
31. Adappa N.D., Coticchia J.M. - Management of refractory chronic rhinosinusitis in children. Am J Otolaryngol, 2006;27:384-9.
32. Leiberman A., Dagan R., Leibovitz E., Yagupsky P., Fliss D.M. - The bacteriology of the nasopharynx in childhood. Int J Pediatr Otorhinolaryngol, 1999;49(Suppl 1):S151– 3.
33. Stankiewicz J. - Chronic sinusitis. In: De Souza C., Stankiewicz J. eds. - Textbook of Paediatric Otorhinolaryngology- Head and Neck Surgery, 1998:vol I and II;pp.350-60.
34. Don D.M., Yellon R.F., Casselbrant M.L. et al. - Efficacy of a stepwise protocol that includes intravenous antibiotic therapy for the management of chronic sinusitis in children and adolescents. Arch Otolaryngol Head Neck Surg, 2001;127:1093-8.
35. Palmer J.N., Kennedy D.W. - Medical management in functional endoscopic sinus surgery failures. Curr Opin Otolaryngol Head Neck Surg, 2003;11:6-12.
36. Lusk R. - Pediatric chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg, 2006;14:393-6.
37. Tanner S.B., Fowler K.C. - Intravenous antibiotics for chronic rhinosinusitis: are they effective? Curr Opin Otolaryngol Head Neck Surg, 2004;12:3-8.
38. Brook I. - Chronic sinusitis in children and adults: role of bacteria and antimicrobial management. Curr Allergy Asthma Resp, 2005;5:482-90.
39. Clement P.A.R., Bluestone C.D., Gordts F., Lusk R.P., Otten F.W.A., Goossens H., et al. - Management of rhinosinusitis in children. Int J Pediatr Otorhinolaryngol, 1999;49(Suppl 1):S95–100.
40. Fiocchi A., Sarratud T., Bouygue G. R., et al. - Topical treatment of rhinosinusitis. Pediatr Allergy Immunol, 2007;18: 62-67.
41. Hebert R.L., Bent J.P. - Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. Laryngoscope, 1998;108:796– 9.
42. Walner D.L., Markey R., Jain V., Myer C.M. - Clinical outcome of pediatric endoscopic sinus surgery. Am J Rhinol, 2002;16:151– 4.
43. Mair E.A., Bolger W.E., Breisch E.A. - Sinus and facial growth after pediatric endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg, 1995;121:547– 52.
44. Senior B., Wirtschafter A., Mai C., Becker C., Belenky W. - Quantitative impact of pediatric sinus surgery on facial growth. Laryngoscope, 2000;110:1866–70.
45. Bothwell M.R., Piccirillo J.F., Lusk R.P., Ridenour B.D. - Long-term outcome of facial growth after functional endoscopic sinus surgery. Otolaryngol Head Neck Surg, 2002;126:628– 34.