

REVIEW ARTICLE

Pediatric Chronic Sinusitis and Asthma: A Review

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Rhinosinusitis and asthma are common conditions associated with significant morbidity and health care costs. Recent studies in adults have suggested that rhinosinusitis and asthma may be manifestations of an inflammatory process within a continuous airway rather than fully separate diseases that only act locally; and, in fact, the presence of upper airway disease may influence lower airway disease. Controlling upper airway infection, inflammation, and symptoms may improve signs and symptoms of asthma. Pediatric studies regarding this matter are few, but the impact of rhinosinusitis and asthma is still immense and significant in children. This article discusses several pediatric studies regarding medical or surgical management of sinusitis and asthma outcome. These studies show that aggressive treatment of sinusitis when present can significantly improve asthma symptoms and quality of life in children, indicating that sinusitis may play an important role in initiating or exacerbating asthma. These findings have important implications for the physician treating a child with chronic asthma.

Keywords asthma, sinusitis, pediatrics

INTRODUCTION

The importance of discovering and treating hidden factors that exacerbate asthma has been overshadowed by the emphasis of pharmacologic treatment. An aggressive evaluation of all potential factors that may contribute to asthma is essential to optimal, efficient, and cost-effective asthma care (1). One of the potential factors that has been shown to be prevalent and may contribute to asthma morbidity includes sinusitis.

The 1998 US National Health Interview Survey reports that sinusitis affected approximately 16% of the US population (2). Overall costs in 1998 had been estimated to be \$5.8 billion annually, and \$1.8 billion of this was spent on patients younger than 12 years (3). However, sinusitis may be underestimated and underrecognized during childhood and adolescence. Its health impact on the quality of life in children is significant (4), particularly if there is concomitant asthma. Sinusitis may be present in as many as 20% to 30% of children with asthma based on supportive radiographic changes (5, 6).

A consensus conference among various specialties, including allergy-immunology, otolaryngology, infectious disease, and radiology, recently convened to develop a precise definition for sinusitis (predominately in adults). The report states that the term *rhinosinusitis* more accurately describes the spectrum of infectious and inflammatory conditions regarding *sinusitis* because sinusitis is almost always accompanied by concurrent nasal airway inflammation and is preceded in many cases by rhinitis symptoms. (7) Thus, the terminology *rhinosinusitis* has been used interchangeably with *sinusitis* throughout current literature.

PATHOPHYSIOLOGY OF RHINOSINUSITIS

Rhinosinusitis most often is classified according to duration of symptoms and the mechanism of the disease. Acute rhinosinusitis is an inflammatory condition involving the paranasal sinuses and nasal passages and lasts up to 4 weeks (7). Twelve or more weeks of symptoms are considered under the category of chronic rhinosinusitis (7).

Subacute rhinosinusitis is defined by nasal and sinus symptoms lasting longer than 4 weeks and fewer than 12 weeks (8), whereas recurrent rhinosinusitis are episodes of nasal and sinus symptoms, each lasting less than 30 days, separated by intervals of at least 10 days and with complete resolution between episodes (9).

Acute rhinosinusitis in an immunocompetent person is presumed to be viral in nature for the first 10 to 14 days and does not require antibiotics unless the patient shows signs of regression, severe headaches or facial pain, high fever, or impending or actual complications to the eye, lung, or brain. After 10 or 14 days, bacteria are presumed to be dominant and antibiotics are beneficial at this time (7). The bacterial species most encountered in childhood acute and subacute rhinosinusitis include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Hemophilus influenzae*, whereas coverage to *Pseudomonas aeruginosa*, Group A streptococcus, *Staphylococcus aureus*, and anaerobes such as *Bacteroides* spp., *Fusobacteria*, and *Propionibacterium acnes* may need to be considered in chronic rhinosinusitis (10).

Various mechanisms in the development of rhinosinusitis have been proposed. The key to pathology in the sinus area involves the ostia of the paranasal sinuses (11). The ostia of the maxillary sinuses have a diameter of 2.5 mm. The diameter of the ostium of each individual ethmoid air cell that drain independently into the middle meatus measures 1 to 2 mm. The narrow caliber of each of these ostia predisposes easily and frequently to obstruction. Factors leading to ostial obstruction usually are divided into those that cause mucosal swelling and those caused by mechanical obstruction (11).

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The various causes of mucosal swelling may include viral upper respiratory infection, allergic inflammation, cystic fibrosis, immune deficiency, primary ciliary dyskinesia, and rhinitis medicamentosa. Mechanical obstruction may be due to choanal atresia, severe deviated nasal septum, nasal polyps, foreign body, tumor, or ethmoid bullae. But, by far the most frequent and most important conditions leading to ostial obstruction are viral rhinosinusitis and allergic inflammation (11).

Rhinosinusitis in adults has been further identified by either an "infectious" or "inflammatory" driven status (7, 12). "Infectious rhinosinusitis" results from obstruction of normal drainage from the sinus ostia, which is produced by inflamed tissue in acute viral rhinosinusitis or allergic rhinitis or by structural abnormalities, such as polyps and severe deviated nasal septum. The stasis of mucus in the sinuses created by the obstruction allows for bacterial growth, which further promotes inflammation and perpetuates the chronic process (12). In contrast, "inflammatory rhinosinusitis" develops primarily from an inflammatory process involving cytokines (interleukin-4, tumor necrosis factor- α , etc.) and inflammatory cells (i.e. eosinophils) that cause damage to local tissue, such as epithelia denudation, allowing bacterial superinfection as a secondary process (12). It is likely that there is considerable overlap between infection-driven and inflammation-driven rhinosinusitis (13). Whether the "inflammatory" mechanism can be extended into pediatric sinusitis is unclear and will require further studies.

RELATIONSHIP BETWEEN RHINOSINUSITIS AND ASTHMA

The observation that asthma and rhinosinusitis coexist in patients at a higher frequency than would be expected from the prevalence of each in the general population provides a strong connection between the upper and lower airways. (14) Various explanations for the observed asthma-rhinosinusitis association have been presented. These include the nasobronchial reflex, pharyngobronchial reflex, postnasal drainage of inflammatory mediators from the upper to lower airway, inhalation of dry, cold air and environmental pollutants, and the "shared pathogenesis" or common mucosal susceptibility between the lower and upper airway (12, 15).

The latter concept above of a "one-airway" or "united-airway" disease has been the subject of investigation and debate over the years. The idea behind this concept lies with the evidence that the upper and lower airways share similarities in histology and physiology, immune and clinical response, and allergic and nonallergic cofactors. Therefore, rhinosinusitis and asthma may exist as part of a systemic inflammatory disease. The systemic and bidirectional integration of the upper and lower airways are facilitated mostly by the circulatory system and amplified by the bone marrow precursor cells; cytokines, particularly IL-4, IL-5, and IL-13; and various adhesions molecules, such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1) (14–17).

To further support the idea of this "united-airway", studies have found that stimulation of one organ system by an allergen may trigger a systemic inflammatory response affecting the other organ (18–20). For example, nasal provocation induces lower airway inflammatory responses, whereas

bronchial provocation may induce nasal inflammation in allergic individuals. A major player in the systemic signaling effects includes IL-5 on the proliferation and mobilization of eosinophils from the bone marrow to the tissues. Eosinophils were found to extensively infiltrate the sinus tissue from adolescents and adults with sinusitis and chronic asthma and/or allergy (21). Additionally, there was a strong association between the extracellular deposition of major basic protein and damage to the sinus mucosa similar to that in bronchial asthma (21).

MEDICAL TREATMENT OF SINUSITIS IN PEDIATRIC ASTHMA

Another way to demonstrate the link between sinusitis and asthma is to treat one disease and observe the effect on the other. There have only been a few studies focusing on children with respect to asthma outcome when sinusitis is treated pharmacologically.

A study by Cummings et al. in 1983 compared the effects of antibiotics, nasal corticosteroids, and oral decongestants versus placebo in children with asthma who had opacified or markedly thickened maxillary sinuses on plain radiographic studies. The children who had active treatment showed improvement in asthma symptoms and less bronchodilator and corticosteroid use. However, there was no significant change in pulmonary function or bronchial hyperresponsiveness in either group (22).

Rachelefsky et al. reported the treatment of 48 children ages 4 to 13 years of age with sinusitis and asthma (23). All of the children presented with wheeze, cough, and abnormal sinus radiographs. All children were receiving oral bronchodilators 10 were receiving cromolyn sodium; and 6 were receiving oral steroids. Pulmonary function testing in 30 children showed an forced expiratory volume in 1 second (FEV₁) and forced expiratory flow (FEF_{25–75%}) of less than 70% of predicted for age. Most children also had nasal discharge, sore throat, headache, and earache. Antimicrobial agents and in some cases antral lavage allowed 79% of the children to discontinue their anti-asthmatic therapy. At follow-up 79% had normal findings on Waters radiographs; and 71% showed clinical improvement in rhinosinusitis symptoms. Furthermore, pulmonary function testing returned to normal in 67% of the 30 children who underwent testing before treatment (23).

Friedman et al. conducted a small study on eight asthmatic children with exacerbation of asthma despite bronchodilator therapy and who had concurrent maxillary sinusitis confirmed by plain radiographs (24). All had cough, wheezing, nasal stuffiness, and rhinorrhea. Among the maxillary sinus aspirates that were obtained, bacterial cultures were positive in five. All patients received bronchodilators, and four of eight patients received steroids. All the children were treated with antibiotics for 14 to 28 days. All five children who kept symptom-diary cards showed improvement. Pulmonary-function tests improved in five of seven patients. Sinus radiographs cleared in three, improved in three, and were unchanged in two patients after antibiotic therapy (24).

In a more recent study, Oliveira et al. (25) showed improvement of bronchial hyperresponsiveness in asthmatic children treated for concomitant sinusitis. Methacholine PC₂₀ (provocative concentration of methacholine required to cause

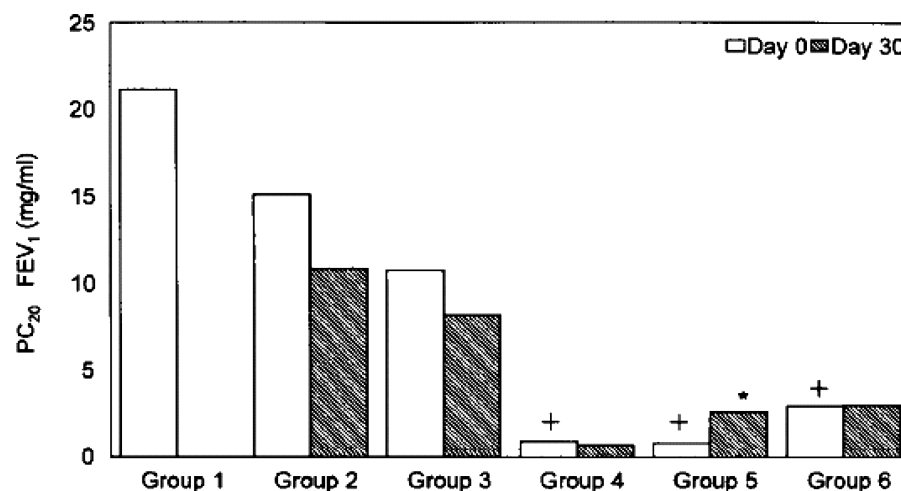


FIGURE 1.—Normal children (group 1) and atopic children (groups 2, 3, 4, 5, and 6), according to methacholine PC₂₀ FEV₁ (mean, mg/mL) on day zero (0) and after 30 days of treatment (30). Kruskal Wallis day 0 (groups 1 $\times$ 2 $\times$ 3 $\times$ 4 $\times$ 5 $\times$ 6). Group 1 > groups 4, 5, and 6. Group 2 > groups 4 and 5 + P < .05 Wilcoxon day 0 < day 30 * P < .05. Group 1 = normal children (n = 20); Group 2 = children with perennial allergic rhinitis with normal radiographs before and after treatment with intranasal saline (n = 12); Group 3 = children with perennial allergic rhinitis with opacification of the maxillary sinuses and normalization after clinical treatment (n = 6); Group 4 = children with perennial allergic rhinitis and asthma with normal radiographs before and after treatment with intranasal saline (n = 13); Group 5 = children with perennial allergic rhinitis and asthma with opacification of the maxillary sinuses and normalization after clinical treatment (n = 8); and Group 6 = children with perennial allergic rhinitis and asthma with opacification of the maxillary sinuses before and after clinical treatment (n = 7). Adapted with permission (25).

a reduction in FEV₁ by 20%) was measured before and 30 days after treatment with nasal saline, antibiotic, antihistamine/decongestant, and 5 days of prednisone. Only patients with opacified maxillary sinuses that had cleared at the end of the treatment period had increased PC₂₀ values (Figure 1) (25).

Another study looking at the effect of treatment of sinusitis on bronchial hyperresponsiveness was conducted by Tsao et al. (26). They enrolled 61 children with mild asthma and concurrent allergic rhinitis and 10 healthy children with no clinical history of allergic rhinitis, chronic coughing, asthma, or sinusitis who served as the control group. Forty-one of the 61 children with mild asthma and concurrent allergic rhinitis had clinical and radiographic evidence of sinusitis. The children were enrolled sequentially and divided into four groups: group A included 20 of 41 children with concurrent asthma, allergic rhinitis, and sinusitis; group B included 21 of 41 children with concurrent asthma, allergic rhinitis, and sinusitis; group C included 20 children with asthma and allergic rhinitis only; and Group D, included the 10 healthy children. Group A received sinusitis treatment (amoxicillin-clavulanate 40 mg/kg/d and intranasal saline irrigation every week), while group B received only weekly intranasal saline irrigation for the first 6 weeks. During the second 6 weeks, group B received sinusitis treatment and group A received weekly intranasal saline irrigation. groups C and D received only weekly intranasal saline irrigation throughout both treatment periods. Clinical symptoms of sinusitis (e.g., mucopurulent rhinorrhea, postnasal drainage, nasal congestion, sore throat, and nocturnal cough), but not FEV₁, demonstrated a significant improvement in those children with concurrent mild asthma, allergic rhinitis, and sinusitis after antibiotic treatment. The treatment of sinusitis in children with concurrent mild asthma, allergic rhinitis, and sinusi-

tis (groups A and B) resulted in a significantly higher PC₂₀ (26).

Richards et al. conducted a retrospective review of 34 children who were referred to their allergy service for protracted (more than one month) and debilitating symptoms of allergic rhinitis and/or asthma. The main symptoms consisted of cough (94%), nasal congestion (97%), rhinorrhea (85%), and worsening asthma (87% of asthmatics). All of the children had marked discomfort and incapacitation from their symptoms and may also complain of severe sleep disturbance, irritability, and impaired appetite. Antibiotic therapy was administered previously to 27 (79%) of the patients often more than once but for no more than 10 days. Twelve of 15 asthmatic children who had exacerbation of their asthma were subsequently found to have sinusitis as identified by history, physical examinations, and sinus re-radiographs. These patients had improvement in their symptoms once medical treatment, including longer courses (3 to 4 weeks) of antibiotics, was instituted (27).

Tosca et al. evaluated the effects of treating concomitant chronic rhinosinusitis on respiratory symptoms and function in asthmatic children (28). Eighteen poorly controlled moderate asthmatic children (ages 5 to 12 years) had chronic rhinosinusitis based on nasal symptoms (mucopurulent rhinorrhea, nasal obstruction), postnasal drip and cough, and evidence of endoscopic signs of rhinosinusitis. They were all treated with oral amoxicillin-clavulanate (20 mg/kg/d), fluticasone propionate aqueous nasal spray, and a short course of oral corticosteroids. All children showed a significant decrease in asthma and nasal symptoms (rhinorrhea, nasal obstruction, wheezing, dyspnea, and cough) and a significant increase in FEV₁ (28).

Despite the significant improvement of symptoms and bronchial hyperresponsiveness of asthmatic children with

rhinosinusitis, it could be possible that the treatment of sinusitis did not improve asthma, but rather, the anti-inflammatory effect of medical treatment of sinusitis resulted in improved asthma. Macrolide antibiotics have been shown to have a systemic anti-inflammatory action by several studies (29–31). Furthermore, the concurrent use of intranasal steroids can also result in improvement of asthma symptoms by reaching the lower airways (32). Additionally, in the studies by Tosco et al., oral steroids were administered concomitantly with the antibiotics and intranasal steroid (24, 28). Although difficult to perform, it will require double-blinded studies to potentially resolve the issue of local versus systemic effects.

SURGICAL TREATMENT OF SINUSITIS IN PEDIATRIC ASTHMA

Functional endoscopic sinus surgery (FESS) has mostly replaced other surgical procedures for the treatment of sinusitis. However, few studies regarding the use of FESS of pediatric patients with asthma have been accomplished. One of the earlier findings included a retrospective study of 52 asthmatic children from 7 months to 17 years of age who were treated with FESS for chronic sinusitis refractory to medical therapy. They used a comprehensive parental questionnaire and a review of the medical charts to analyze the results from these children with a mean follow-up time of 21.8 months postoperatively. The authors observed that 89% of these children had a reduction in chronic cough, and 96% had a decrease in their asthma symptoms. Furthermore, the monthly asthma exacerbations reduced from 6.7 to 2.5 with a 79% decrease in emergency room visits (33).

Manning et al. enrolled 14 pediatric patients 3.5 to 13 years of age with severe asthma requiring at least intermittent systemic steroid therapy. All the children had a history of sinusitis aggravating asthma with computed tomographic evidence

of chronic sinus disease, and all patients underwent endoscopic sinus surgery. Although no significant difference was found for pulmonary function test results, 11 of 14 patients had a significant reduction in hospitalization and school days missed, whereas 12 of 14 patients experienced a reduction in glucocorticoid requirements. Almost all patients experienced a significant improvement in asthma and sinusitis symptom scores (34).

These studies strongly suggest that rhinosinusitis in children may have a detrimental effect on asthma and that FESS may have some benefit in the management of children with concurrent asthma and rhinosinusitis. However, studies to date are uncontrolled, without a non-surgical treatment group.

MANAGEMENT OF ASTHMATIC CHILD WITH CHRONIC RHINOSINUSITIS

Given the association of pediatric sinusitis with asthma severity and excessive symptomatology, successful management of chronic childhood asthma must adequately address upper airway disease. Sinusitis should be suspected in a child with asthma that is difficult to manage, and aggressive treatment for sinusitis can be a way to achieve significant improvement in asthma symptoms (35). Figure 2 is a recommendation of how to approach a child with asthma that is difficult to control.

A child presenting to the office with poorly controlled asthma should be evaluated for upper airway disease. If the history and physical is suggestive of rhinosinusitis symptoms (such as nasal congestion, rhinorrhea, sneezing, pruritis, and/or headaches), allergy testing is recommended to identify an allergy that can be reduced, such as environmental control (e.g., dust mites, pet dander, cockroaches) and/or for

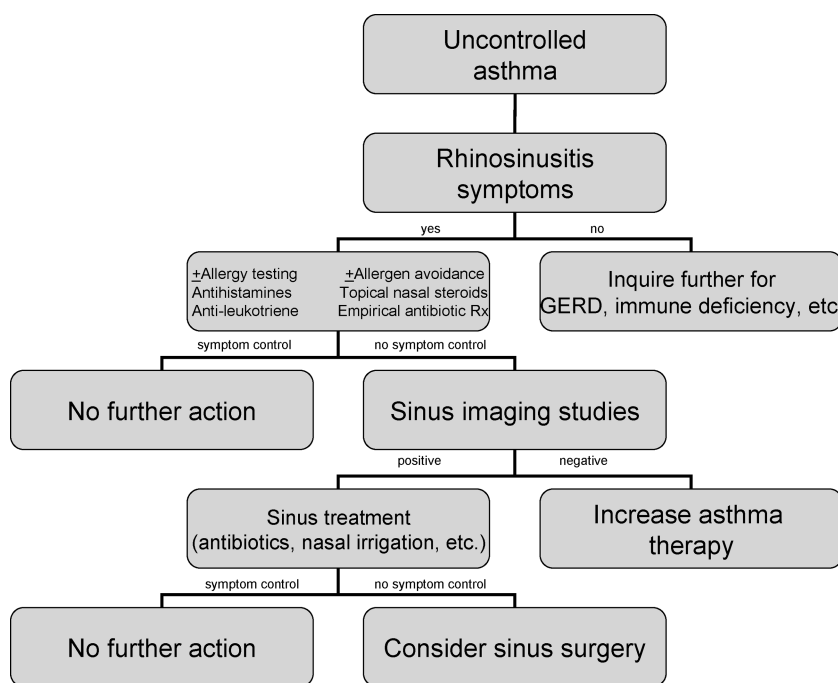


FIGURE 2.—Algorithm: possible approach to a child with difficult-to-manage asthma.

consideration of additional medications (e.g., antihistamines, leukotriene receptor antagonist, topical nasal steroids, and/or empirical antibiotic treatment for suspected sinusitis). If the symptoms do not improve with allergy treatment or empirical antibiotics, radiographic imaging is indicated (35).

Radiographic imaging is an important aspect in the treatment of chronic sinusitis and asthma in children. Attention should be made particularly to the anatomy and developing sinuses of young children. The maxillary and ethmoid sinuses develop in utero, are present at birth, and are visible on radiographs (computed tomography [CT] scans) during infancy (36). The frontal sinuses appear at 7 to 8 years of age but are not completely developed until late adolescence (9). The sphenoid sinuses develop by the third year of life but are not seen radiographically until the ninth year. However, there is great variation in the shape and size of the sinuses at all ages (36).

Plain radiographs are often used to screen for sinus disease because they are inexpensive and widely available (37). However, opacification and thickening of the sinuses may be due to other causes (e.g., upper respiratory tract infections and possibly allergies) rather than sinusitis. Furthermore, paranasal sinuses vary in shape, size, and pneumatization in children, making interpretation of plain radiographs in very young children difficult (37). McAlister et al. conducted a prospective study of 70 infants and children with recurrent sinusitis. They compared plain radiographs with coronal CT scans of the sinuses to determine whether plain radiographs can accurately reveal residual sinus disease, which is thought to be important in recurrent sinusitis. They found that plain radiographs do not correlate with CT scans of the sinuses, and sinusitis in infants and children may be underdiagnosed or overdiagnosed with the use of plain radiographs (38).

Computed tomography scans of the sinuses are superior to plain radiographs when assessing anatomy and disease or planning surgical approaches of the sinuses (39). Computed tomography scans can reliably demonstrate chronic sinus disease when it is present with a sensitivity of more than 80% (40). Lazar et al. compared plain radiographs, CT scans, and intraoperative findings for 300 pediatric patients with chronic or recurrent sinusitis. The authors demonstrated that CT was better than plain radiographs in diagnosing chronic sinusitis and evaluating patients for surgery (41). In infants and children with recurrent sinusitis, approximately 45% of the patients who had normal findings on plain radiograph had an abnormality on CT scan, and almost 35% of the patients who had an abnormality on plain radiograph had normal sinuses on CT (38).

There are few studies regarding sinus cultures in children in relation to clinical symptoms or imaging. Wald et al. revealed that 77% of the children they studied who had symptoms of acute sinusitis and abnormal sinus radiographs had positive sinus cultures obtained from sinus aspirates (42). There are no studies examining sinus cultures in children with asthma or in children with abnormal CT scans. In either case, cultures of sinus aspirates or endoscopically guided nasoantral specimens are not routinely performed in clinical practice in a pediatric setting (37). However, there is information that now shows good correlation between middle meatus swab culture and maxillary sinus aspiration (43).

Another modality in the diagnosis of sinusitis has been introduced in children recently and consists of rigid nasal endoscopy. Tosca et al. evaluated rigid nasal endoscopy in 145 mild to severe asthmatic children (2 to 15 years of age) to help identify any upper airway disease that may be treated to aid in asthma management. They found that most asthmatic children tolerated the procedure without complications and that it correlated with clinical symptoms of rhinosinusitis. They concluded that endoscopy of the nasal cavity and rhinopharynx may be proposed as an appropriate routine diagnostic tool in children because it is well tolerated, easily and quickly performed, cost-efficient, and useful in diagnosing rhinosinusitis (44). However, flexible nasal endoscopy is better tolerated than rigid endoscopy, particularly in younger children, and the size and status of the adenoids can be assessed during the same examination.

Surgical treatment of pediatric sinusitis should be reserved for those patients who have failed medical therapy (45). The surgical options include antral puncture and lavage, adenoidectomy, endoscopic sinus surgery (ESS), or combined adenoidectomy and ESS. Nasal antral windows were shown not effective for the long-term treatment of sinusitis in children (46).

Adenoidectomy is performed because adenoid tissue may act as a reservoir for pathogenic bacteria, interfere with nasal mucociliary clearance (47), and/or narrow air flow. Ramadan et al. demonstrated that asthmatic children who were exposed to tobacco smoke benefited the least from adenoidectomy alone, but the asthmatic children who were exposed to tobacco smoke had the best outcome with adenoidectomy in conjunction with ESS (48, 49).

Endoscopic sinus surgery has been widely accepted as a treatment modality in adults (50). The role of ESS in children has been controversial owing to the small anatomy and developmental immaturity of the sinuses in children. The implications it may have to the growing midface may be a concern, but a recent study by Bothwell et al. found no evidence that ESS affected facial growth (51). Nevertheless, many physicians opt to take a more conservative approach. Some physicians perform adenoidectomy first. However, ESS may be a treatment option for the older children who fail medical management or who have orbital and central nervous system complications (52). The role ESS plays in the treatment of pediatric rhinosinusitis with concurrent asthma still requires further studies.

Despite the modalities mentioned to aid in treating difficult-to-manage asthma with concomitant rhinosinusitis, those children with persistent symptoms should also be evaluated for gastroesophageal reflux disease, immunodeficiency, including cystic fibrosis, primary ciliary dyskinesia, hypogammaglobulinemia, and/or fungal disease. One must consider other pharmacological or therapeutic treatments that may play a role in controlling allergic asthma and rhinitis symptoms, such as immunotherapy and/or anti-immunoglobulin E.

CONCLUSION

Rhinosinusitis is a common disease that may be present in the pediatric population and may influence the clinical course of asthma by a variety of mechanisms. There is a

growing body of evidence supporting the concept that rhinosinusitis and asthma are closely linked. For this reason, it may be beneficial to determine the presence of sinusitis in a child with difficult-to-manage asthma, particularly in a child with upper airway symptoms. Infection may not be the sole cause of pediatric chronic sinusitis, and inflammation may be an aggravating, etiological factor, which has been shown in adult studies. The development of chronic sinusitis may be influenced by other factors, such as allergies, immune deficiencies, gastroesophageal reflux, or anatomical defects. And, all confounding conditions need to be addressed by the clinician. Sinus imaging may aid in the clinical suspicion of sinusitis. Sinus plain radiographs have been shown to be inaccurate compared with sinus CT scans. Computed tomography scans should be required when considering surgery. Pharmacological treatment is the preferred modality of therapy for rhinosinusitis. Surgery is considered for those pediatric patients in whom all other conservative treatments failed.

Although most studies regarding the relationship between rhinosinusitis and asthma have been in adults, the few studies observed in the pediatric population have prompted the need for further investigation with randomized, double-blinded, controlled studies to discover new approaches to the evaluation and treatment of rhinosinusitis in relation to asthma in children. More studies, particularly in children, are needed to further define the pathology and mechanism underlying rhinosinusitis and asthma and the link that bring these diseases together. The relevance of such findings would greatly benefit the pediatric population from the burden of such chronic conditions.

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