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Fernando M. de Benedictis and Andrew Bush

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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Rhinosinusitis and Asthma*

Epiphenomenon or Causal Association?

Fernando M. de Benedictis, MD, FCCP; and Andrew Bush, MD

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Key words: asthma; children; rhinitis; sinusitis

Abbreviations: BHR = bronchial hyperresponsiveness; EAHR = extrathoracic airway hyperresponsiveness; IL = interleukin

It has long been recognized that diseases of upper and lower airways may coexist. Indeed, as many as 80% of patients with asthma have rhinitis,¹ and up to 15% of patients with allergic rhinitis have asthma.² Sinusitis and asthma are also frequently associated in the same patient, but doubts still remain as to whether a causal relationship exists wherein sinusitis worsens bronchial asthma, or whether they are manifestations in different parts of the respiratory tract of the same underlying disease process.

According to a recent consensus document,³ the term of rhinosinusitis should be preferred in children, because (1) rhinitis and sinusitis in children are often a continuum of the same disease, and (2) it is not possible to differentiate these two conditions on clinical grounds alone. Indeed, there are many similarities in anatomic, physiologic, and pathologic characteristics of the nose and paranasal sinuses. The following definitions are recommended:

Acute rhinosinusitis is a sinus infection in which complete resolution of symptoms without intermittent upper respiratory tract infection may take up to 12 weeks.

Chronic rhinosinusitis is a sinus infection with low-grade symptoms and signs that persist for longer than 12 weeks, although acute exacerbations can occur in chronic infection.

Recurrent acute rhinosinusitis consists of multiple acute episodes in which symptoms and signs resolve completely between episodes.

The diagnosis of rhinosinusitis in children is usually made on clinical grounds alone, and imaging studies are not universally necessary in the diagnosis

of sinus disease.³ Although sinus radiographs may be misleading in assessing the ethmoid sinuses or the sphenoid and frontal sinuses in small children, they can be helpful in diagnosing maxillary sinusitis in older children.⁴ CT scans may be required in specific cases, *ie*, when symptoms persist despite appropriate medical management, when suppurative complications are present, and if endoscopic sinus surgery is being considered. However, because the prevalence of sinus abnormalities in asymptomatic children may be as high as 50%, the interpretation of CT scanning should always be done within the context of history and clinical findings.⁵

Interactions Between Upper and Lower Airways: Experimental Studies

In the 2nd century, Galen noted the association between nasal symptoms and asthma, and advocated purging the nostrils of secretions in order to relieve the lower breathing passages.⁶ After this historical observation, the relationship between asthma and nasal disease remained obscure for several hundred years, and it re-emerged only at the beginning of this century when studies demonstrated that bronchoconstriction was provoked by applying irritants or electrical stimulation in the nose of animals.^{7,8} Consequently, Sluder⁹ first hypothesized a sinonasal-bronchial reflex, *ie*, a reflex bronchoconstriction by activation of a trigeminal afferent–vagal efferent neural arc. Subsequent studies have provided evidence for and against the existence of such a sinonasal-bronchial reflex. In fact, after placing an irritant or allergic stimulus in the nose of nonatopic and atopic patients, respectively, some authors were able^{10–13} and others unable^{14–18} to provoke an increase in lower airway resistance. However, there were some important differences between trials; the populations in the studies with negative results were usually evaluated when asymptomatic, whereas the populations with positive results had active disease when they were investigated.¹⁹ The pathophysiologic significance of such differences is unknown, but a critical threshold of nasal disease severity may be required to provoke reflex changes in the lower airways as a response to nasal challenge.

Interestingly, Hoehne and Reed¹⁴ demonstrated airway resistance increased only if the allergic stim-

*From the Pediatric Department (Dr. de Benedictis), University of Perugia, Perugia, Italy; and the Royal Brompton Hospital (Dr. Bush), London, United Kingdom.

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Correspondence to: Fernando M. de Benedictis, MD, *Clinica Pediatrica, Policlinico Monteluce; 06100 Perugia, Italy*

ulus was placed at the base of the tongue, thus suggesting that the sensory arc of this reflex might originate in the oropharynx rather than in the nose. Recently, an elegant series of experimental studies by Irvin²⁰ in animal models has partially confirmed this original hypothesis. After inducing granulocytic sinusitis with the use of a modified complement fragment C5a des arg, lung mechanics and bronchial reactivity to inhaled histamine were measured. Although there were no changes in baseline pulmonary function, histamine responsiveness increased with the presence of upper airway inflammation. These changes in reactivity were blocked by strategies, such as positioning the animal's head down, that prevented the exudate from draining beyond the pharynx, but were maintained when the animals were intubated. Irvin suggested that airway hyperresponsiveness in sinusitis may be caused by the activation of a pharyngobronchial reflex by the inflammatory process with no cell migration into the lower airways.

Silent dripping of infected material from the nose into the bronchial tree has been proposed in the past as a possible link between sinusitis and asthma.²¹ Despite several early studies supporting the concept that sinus material can be aspirated into the lower airways,²²⁻²⁴ this mechanism was strongly questioned in a recent report. After placing radionuclide in the sinuses of patients with sinusitis and asthma, Bardin et al²⁵ could not demonstrate any form of pulmonary aspiration and concluded that seeding of the lower airways by secretions from the nose is unlikely to account for coexistent pulmonary disease.

The Link Between Sinusitis and Asthma

Over the years, important clinical data that link sinusitis and asthma have emerged. First, radiographic findings of sinus abnormalities, such as mucosal thickening, air fluid levels, and total opacification of the paranasal sinuses, have been shown to be common (40 to 60%) in adults and school-age children with asthma.²⁶⁻²⁹ Second, treatment of sinusitis, whether medical or surgical, improves asthma in most patients to such an extent that the amount and type of antiasthma medication can be reduced. Indeed, Rachelefsky et al³⁰ and Friedman et al³¹ evaluated 48 and 8 children, respectively, with asthma and sinusitis, and found an improvement in subjective asthma symptoms, decreased use of bronchodilators, and normalization of pulmonary function after antibiotic treatment in the majority of their patients. A significant improvement in asthma symptoms has been also obtained after surgery for sinusitis, using standard procedures such as the Caldwell-Luc operation^{32,33} or the newer endoscopic techniques.³⁴ Unfortunately, these studies can be

faulted for the lack of control subjects and even lack of accurate description of severity of asthma, so that the results are difficult to interpret.

In an attempt to throw some light on the problem, Zimmerman et al³⁵ examined the prevalence of radiographic abnormalities in the paranasal sinuses in 138 children with asthma of differing severity and in control subjects. They hypothesized that if sinusitis really is an aggravating factor for asthma, the prevalence of radiographic abnormalities would be higher in the more severe asthmatic patients. The overall prevalence of abnormalities was significantly greater in the patients with asthma (31.2%) than in control subjects (0%). However, no relationship was found between the percentage of patients with sinus abnormalities and the severity of asthma; thus, the hypothesis that sinusitis, as identified on radiographs, aggravates asthma and creates a need for increased medication was questioned strongly. The authors emphasized that the lack of correlation between prevalence of sinus abnormalities and the severity of asthma might depend on one or more of the following possibilities: (1) the grading system did not reflect the severity of asthma; (2) the sinus radiograph did not properly detect underlying sinusitis, as compared with sinus tap; or (3) the abnormalities found on radiographs did not necessarily reflect infection. Indeed, at a time when data on inflammation in asthma were preliminary, the authors were the first to suggest that in asthmatic patients, radiographically detected sinus abnormalities probably reflect inflammation associated with asthma rather than sinus infection.

Over the years, the theory of a common inflammatory involvement of paranasal sinuses and bronchi in patients with sinusitis and asthma has been supported by several studies. Indeed, observations in patients who underwent surgery for chronic sinusitis suggest that the eosinophil, which plays a pivotal role in the pathogenesis of asthma, may act as an effector in chronic inflammatory disease of the paranasal epithelium. Harlin et al³⁶ first found that sinus tissue from patients with sinusitis and asthma or allergic rhinitis is extensively infiltrated with eosinophils, while biopsy samples from subjects with chronic sinusitis alone have no eosinophils. There was a strong association between the presence of extracellular deposition of major basic protein and sinus mucosa damage, and in most patients the histologic abnormalities of the paranasal epithelium appeared similar to those seen in patients with bronchial asthma. Newman et al³⁷ demonstrated that the extension of sinus involvement, as documented by CT scan in a selected population of patients with chronic sinusitis, strongly correlates with the presence of peripheral and tissue eosinophilia. It was

therefore hypothesized the abnormalities in the sinonasal mucosa seen on CT scans may reflect immunologically active soft tissue in an environment where constant exposure to irritant/allergic stimuli is the rule.

Baroody et al³⁸ also found significantly more eosinophils in the sinus tissues of children with chronic sinusitis than in normal sinus mucosa. Allergy status did not affect the degree of tissue eosinophilia, which suggests that IgE-dependent interactions are not the only mechanism to attract eosinophils into sites of inflammation in chronic sinusitis. However, since a significant positive correlation between severity of disease on CT scan and serum levels of both total and specific IgE was found by the same authors in another study, the inflammatory response to precipitating events such as viral or bacterial infections or IgE-mediated allergic reactions may be an important contributing factor for sinusitis.³⁹ Interestingly, the levels of leukotrienes C₄, D₄, E₄, prostaglandin D₂, and histamine in maxillary sinus lavage fluid were significantly increased in patients with chronic sinusitis compared with control subjects, but no difference emerged between sinusitis and allergic rhinitis.⁴⁰ The authors conclude that mast cell/basophil activation does occur in chronic sinusitis and may contribute to the persistence of inflammation.

Several clinical observations suggest that different mechanisms of eosinophilia may exist in patients with allergic vs nonallergic sinusitis. Demoly et al⁴¹ found that both allergic and nonallergic rhinosinusitis were associated with significant increases in eosinophils in biopsy specimens and in eosinophil cationic protein in sinus lavage fluid, but an increased number of intraepithelial mast cells and lymphocytes was found only in allergic patients. Hamilos et al⁴² also demonstrated that eosinophilia was prominent both in atopic and nonatopic adults with chronic sinusitis, but cytokine expression and T lymphocyte population differed in these two groups of patients. Finally, al Ghamdi et al⁴³ recently demonstrated the number of cells expressing interleukin-4 (IL-4) and IL-13 transcripts was significantly higher in atopic subjects with chronic sinusitis compared with normal control subjects. In contrast, the numbers of IL-13 but not IL-4 messenger RNA-positive cells were increased in nonatopic subjects with chronic sinusitis, indicating that IL-4 and IL-13 are under differential regulation. All previous data indicate that tissue eosinophilia is characteristic of chronic sinusitis and that inflammation is an important factor in its pathogenesis. The inflammatory changes in chronic sinusitis are similar to those seen in chronic asthma and could possibly contribute to sinus osteomeatal obstruction and mucosal thickening.

An important contribution to explaining the mechanisms linking sinusitis and asthma comes from a study by Bucca et al,⁴⁴ who investigated the relationship between extrathoracic airway hyperresponsiveness (EAHR) and bronchial hyperresponsiveness (BHR) in adult patients with chronic sinusitis during exacerbation of the disease and after a course of treatment with antibiotics and intranasal steroids. In most patients, exacerbation of sinusitis was associated with an increase in EAHR and BHR, which significantly decreased after treatment. Since both EAHR and BHR were strongly associated with the presence of clinical pharyngitis, the authors speculate that airway hyperresponsiveness in patients with sinusitis may be sustained by a pharyngobronchial reflex triggered by seeding of the inflammatory process into the pharynx from affected sinuses.

Finally, an interesting new pathogenetic hypothesis has been proposed by Baraldi et al,⁴⁵ who demonstrated that nasal nitric oxide concentrations largely decrease during acute maxillary sinusitis and return to normal levels after appropriate medical treatment. Since nitric oxide is believed to have a modulating effect on the bronchial tone, the authors speculate that a reduction in nitric oxide in the upper airways of patients with sinusitis and the resulting reduction in physiologic autoinhalation may have a role in increasing bronchial reactivity. Indeed, patients with Kartagener's syndrome (a triad consisting of situs inversus, sinusitis, and bronchiectasis) have extremely low nasal nitric oxide levels⁴⁶ and also demonstrate some increase in bronchial hyperreactivity.⁴⁷

The Link Between Allergic Rhinitis and Asthma

The association between allergic rhinitis and asthma has been extensively studied in terms of pathophysiology, epidemiology, and treatment.^{48,49} As our understanding of the role of inflammation in airway disease evolves, the classical perspective that allergic rhinitis and asthma are distinct entities is being displaced by the increasing evidence that they are a manifestation of a continuous inflammation within one common airway.⁵⁰ Of particular interest to clinicians are the studies showing that control of nasal inflammation by topical steroids in patients with asthma and allergic rhinitis improves the asthma symptoms and also reduces bronchial hyperreactivity.

Welsh et al⁵¹ compared the effect of intranasal flunisolide, beclomethasone, cromolyn, and placebo on nasal and chest symptoms in patients with ragweed hay fever and seasonal asthma. Rhinitis scores improved among patients receiving active treatment, and intranasal steroids were more effective than

cromolyn. In addition, asthma symptoms were virtually eliminated in the two groups receiving intranasal steroids, but not in subjects taking cromolyn or placebo.

Corren et al⁵² evaluated the effect of intranasal beclomethasone on chest symptoms, pulmonary function, and bronchial hyperreactivity to methacholine in patients with seasonal allergic rhinitis and asthma. Despite the lack of difference between the active-therapy and placebo groups in terms of asthma symptoms, peak expiratory flow rates, and spirometric indexes, bronchial responsiveness increased in a statistically significant way at the peak of the pollen season in patients receiving placebo but did not change in those receiving active treatment.

More recently, Foresi et al⁵³ studied the effect of intranasal fluticasone on nasal symptoms, circulating eosinophils, and nasal inflammation in patients with seasonal allergic rhinitis, and also examined its efficacy in preventing the increase in bronchial responsiveness to methacholine during the pollen season. Compared with placebo, fluticasone decreased nasal symptoms and eosinophil inflammation and partially prevented the increase in bronchial responsiveness during the pollen season.

In another study, 4 weeks of intranasal budesonide treatment significantly reduced respiratory symptoms and exercise-induced bronchospasm in asthmatic children with concomitant perennial rhinitis.⁵⁴ In addition, intranasal delivery of beclomethasone for 2 weeks caused a marked improvement in bronchial responsiveness to carbachol, whereas intrabronchial (by means of oral inhalation) administration had no effect in adults with perennial rhinitis and no asthma.⁵⁵

Finally, in a crossover study involving young patients with perennial allergic rhinitis and asthma, Watson et al⁵⁶ demonstrated that airway responsiveness to methacholine was significantly reduced after 4 weeks of treatment with intranasal beclomethasone but not after placebo treatment. The investigators also performed a radiolabeled deposition study of the corticosteroid aerosol and found that less than 2% of the drug was deposited into the chest area, suggesting that the improvement of asthma is due to better nasal function and not to a direct effect of the drug on the lower airways.

All these data support the concept that nasal inflammation plays a key role in modulating lower airway responsiveness. Long-term studies involving patients with perennial rhinitis and bronchial hyperreactivity will help determine whether asthma can be prevented in some patients by means of early treatment with intranasal steroids.

Rhinitis, Sinusitis, and Asthma: A Common Link?

Important information on the relationship between rhinitis, sinusitis, and asthma are provided by epidemiologic data. In their large study on children enrolled at birth, the Tucson group evaluated the prevalence and the natural history of physician-diagnosed sinusitis and also studied the relationship of sinusitis to allergic rhinitis, atopy, and asthma.⁵⁷ The authors found that the prevalence of sinusitis was quite high (13%), and sinusitis was independently associated with allergic rhinitis and sensitivity to grass pollen. Children with sinusitis were also more likely to have current asthma than were children without sinusitis, but after the investigators stratified for allergic rhinitis, sinusitis was no longer significantly associated with asthma. Some limitations are present in this study, since sinusitis was diagnosed clinically with a questionnaire that had not been validated as a measure of sinusitis. However, based on these results, the association of sinusitis and asthma is most likely dependent on the link between allergic rhinitis and asthma.

Evidence of interactions between upper and lower airways is also provided by the results of a recent study by Oliveira et al,⁵⁸ who evaluated the effect of a combined treatment with antibiotics and systemic steroids on bronchial reactivity in different groups of children with complete opacification of maxillary sinuses. A significant improvement in bronchial hyperreactivity was achieved only in patients with allergic rhinitis and asthma whose sinuses were normalized by treatment, while no difference was seen in the other groups of subjects whose sinuses remained abnormal despite therapy.

Where do we stand on the relationship between asthma and sinusitis, at the present time? Although the mechanisms behind these diseases have not been completely defined, in light of current knowledge it seems that rhinosinusitis and asthma are linked by a common process that is mainly inflammatory in nature. Central to the pathogenesis are the eosinophil and its interaction with the airway epithelium. Eosinophils could contribute to epithelial damage by releasing preformed basic proteins and newly synthesized mediators, and also by secreting proinflammatory cytokines and chemokines. Epithelial cells can release cytokines and chemokines, which in turn attract eosinophils, thus setting up a cycle of events that could establish ongoing inflammation.⁵⁹ Environmental irritants or infection alone may be sufficient to initiate the inflammatory process through epithelial damage, and may also enhance the response of the airways to inhaled allergens.

It is likely that inflammation worsens airway hyperreactivity by a reflex mechanism due to dripping

of nasal secretions into the oropharynx, but nasal obstruction caused by tissue swelling and retained secretions may also cause predominant mouth breathing, which is recognized to adversely affect airway responsiveness.⁶⁰ Inflammation may in turn facilitate sinus infection by provoking mucosal edema and decreasing ciliary beat frequency, both of which interfere with the natural drainage of secretions (Fig 1).

The relationship between rhinosinusitis and asthma is not only academically interesting, but also has important diagnostic and therapeutic implications. In our view, the use of the term *sinusitis* for a disorder that is most probably caused by an inflammatory process does not appear to be fully suitable. Has the time come to change the definition of sinusitis in asthmatic patients? Might it not be better to speak of *inflammatory rhinosinusitis* or *inflammatory rhinosinopathy*? Whatever the name, the most suitable treatment of sinus disease in asthmatic patients mainly relies on clinical judgment.

Management of the Asthmatic Child With Rhinosinusitis

The key to treatment of rhinosinusitis is the relief of nasal obstruction and the control of superinfection, when it is suspected.⁶¹ A sinus infection should always be taken into account and adequate antibiotic therapy considered in individual cases. Since bacterial infection may contribute to epithelial damage, thereby increasing inflammation, the control of infection is mandatory.

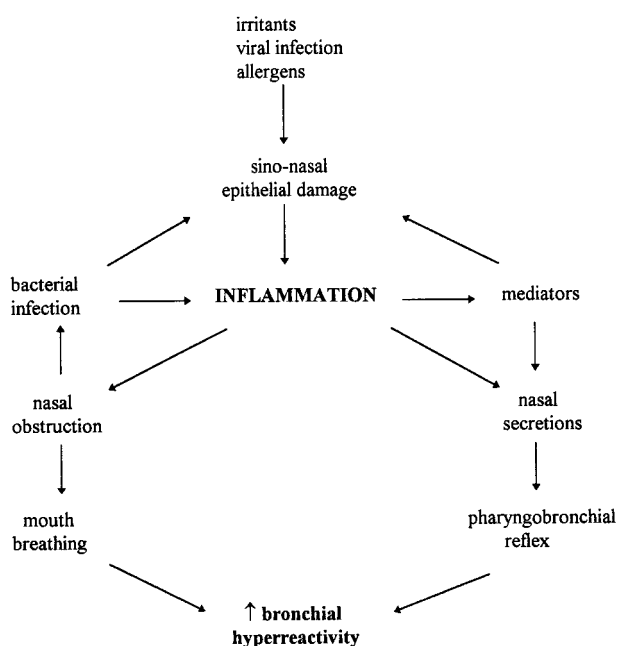


FIGURE 1. Possible pathogenetic mechanisms linking rhinosinusitis and asthma.

Local administration of steroids can control mucosal inflammation, reduce nasal congestion, and possibly improve bronchial hyperreactivity. Indeed, intranasal steroids are recommended by many experts for treatment of rhinosinusitis,⁵ and their effect in reducing bronchial hyperreactivity may be particularly useful in patients with concomitant asthma. When compared with placebo, intranasal steroids as an adjunct to antibiotic therapy improve nasal symptoms, lower the number of local inflammatory cells, and help resolve radiographic abnormalities of the paranasal sinuses in patients with both chronic⁶² and acute sinusitis.⁶³

Allergen avoidance and adequate pharmacologic management of allergies are also crucial strategies in the control of sinus mucosal inflammation. Antihistamines have been shown to improve nasal symptoms when added to standard treatment in acute sinusitis,⁶⁴ and may also slightly improve pulmonary symptoms in patients with concomitant asthma.^{65,66} Whether decongestants speed the resolution of rhinosinusitis is debatable, but their use can be considered for short periods to alleviate nasal obstruction.⁶⁷ Ipratropium bromide, a topical anticholinergic agent, is effective in reducing glandular hypersecretion and sneezing in patients with rhinitis, but no studies have been done to validate its efficacy in children with rhinosinusitis.⁶¹ Mast cell stabilizers and, possibly, immunotherapy may also be effective for selected patients.⁶¹

Finally, functional endoscopic sinus surgery must be considered for those children in whom appropriate medical therapy fails to clear sinus disease.⁶⁸ However, although endoscopic sinus surgery in patients with sinusitis and concomitant asthma improved asthmatic symptoms, it failed to produce significant changes in lung function at 1-year follow-up when patients who underwent surgery were compared with normal control subjects.⁶⁹

For clinical practice, a suggested algorithm for patients with asthma and suspected rhinosinusitis is shown in Figure 2. Specifically, a trial of aggressive sinus therapy with inhaled steroids and antibiotics should be provided, if imaging investigations are suggestive for concomitant sinusitis. The utility of this algorithm needs to be confirmed in a clinical setting, however.

Furthermore, one other point must be emphasized: patients with rhinosinusitis and asthma need to realistically accept the natural history of their diseases and understand that, at present, the main goals of therapy can only be better control of nasal symptoms and eventually a reduction in asthma medications.

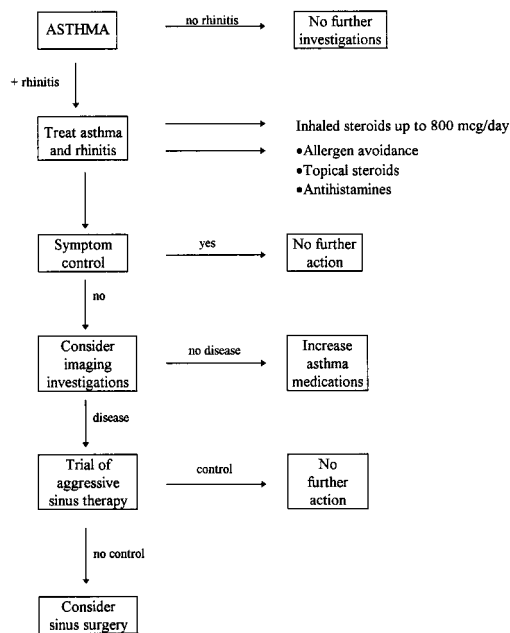


FIGURE 2. A clinical algorithm for patients with asthma and suspected sinusitis. The dosage of inhaled steroids is arbitrary and is based on the British Thoracic Society Guidelines for asthma severe enough to be referred to a respiratory pediatrician.

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Fernando M. de Benedictis and Andrew Bush

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