Allergic rhinitis, rhinosinusitis, and asthma: one airway disease

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Asthma and allergies, including rhinoconjunctivitis and atopic dermatitis, are common throughout the world, with a high burden of morbidity and cost. The nasal and bronchial mucosa present similarities, and most patients with asthma also have rhinitis [1,2], suggesting the concept of “one airway, one disease.” Not all patients with rhinitis present with asthma, however, and there are differences between rhinitis and asthma.

Chronic rhinosinusitis is defined on the basis of history, clinical examination, nasal endoscopy, and sinus CT scanning according to the criteria established by Lund et Kennedy [3]. There are differences in severity and pattern of symptomatology, nasal endoscopy, and magnitude of CT-scan changes between the diseases; nasal polyposis generally presents as a more severe disease (with the exception of headache and facial pain) [4]. For this article, the authors differentiate between chronic rhinosinusitis and nasal polyposis based on the presence of polyps in the nasal cavity or the sinuses during clinical examination or surgery. This approach

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neglects an ill-defined group of chronic hyperplastic sinusitis, which might represent a transition phase.

**Pathophysiology of rhinitis, rhinosinusitis, and nasal polyposis**

*Similarities and differences between nasal and bronchial inflammation in asthma*

In normal subjects, the structure of the airways mucosa presents similarities between the nose and the bronchi. Nasal and bronchial mucosa are characterized by a pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane. In the submucosa, vessels and mucous glands are present with structural cells, some inflammatory cells, and nerves.

There are also differences between the nose and the bronchi. In the nose, there is a large supply of subepithelial capillaries, an arterial system, and venous cavernous sinusoids. The high degree of vascularization is a key feature of the nasal mucosa, and changes in the vasculature may lead to severe nasal obstruction. Smooth muscle is present from the trachea to the bronchioles, explaining the presence of bronchoconstriction in asthma (for review, see [5]).

The progresses achieved in the cellular and molecular biology of airways diseases has documented that inflammation has a critical role in the pathogenesis of asthma and rhinitis. The same inflammatory cells seem to be present in the nasal and bronchial mucosa. A growing number of studies show that the inflammation of nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate. The same proinflammatory mediators, T helper cell type 2 (Th2) cytokines, chemokines, and adhesion molecules seem to be involved in nasal and bronchial inflammation in patients with rhinitis and asthma [6,7].

There are major differences between the sites, however. Although the nasal and bronchial mucosa are exposed to the same noxious environment (and the nose has even greater exposure), epithelial shedding is more pronounced in the bronchi than in the nose of patients with asthma and rhinitis [8]. The magnitude of inflammation may not be identical. In patients with moderate-to-severe asthma, eosinophilic inflammation is more pronounced in the bronchi than in the nose [8], whereas in patients with mild asthma, the degree of inflammation seems to be similar in both sites. Eosinophilic inflammation of the nose exists in asthmatics with or without nasal symptoms [9]. Features of airways remodeling seem to be less extensive in the nasal than in the bronchial mucosa.

**Bronchial inflammation in rhinitis**

Studies have examined the bronchial mucosa in atopic nonasthmatic patients and in patients with allergic rhinitis. They indicate that there was a slight increase in inflammation of the basement membrane [10] and a moderate increase in eosinophilic inflammation, respectively [11]. Natural exposure to pollen during a
season can provoke an increase in airway responsiveness in nonasthmatic subjects with seasonal allergic rhinitis and induce inflammatory cell recruitment and IL-5 expression, leading to bronchial inflammation [12].

**Inflammation in sinusitis**

The pathology of sinusitis has been studied in recent years. The mucosal lining in chronic sinusitis is characterized by goblet cell hyperplasia, subepithelial edema, and mononuclear cell infiltration. Activated eosinophils commonly are found in biopsies taken from the sinus of allergic and nonallergic patients [13–16]. Among patients with untreated chronic sinusitis, those without nasal polyps have less eosinophils (mean, 2%) than do those with nasal polyposis (mean of inflammatory cells, 50%) [17]. These observations suggest that there are major differences in the pathophysiology of sinusitis with and without nasal polyposis.

Numbers of other cells, including mast cells, lymphocytes, macrophages, and to a lesser extent neutrophils, are increased, releasing proinflammatory mediators, cytokines, and growth factors [15,18]. IL-8, a highly potent chemoattractant for neutrophils, has been demonstrated in chronic sinusitis tissues [19] and nasal secretions obtained from patients with chronic sinusitis [20]. In a study measuring cytokine protein concentrations in tissue homogenates, IL-8 was found to be significantly increased in acute sinusitis, and IL-3, but not IL-5, was increased in chronic sinusitis mucosa compared with inferior turbinate samples [21]. IL-3 might be involved in the local defense and repair of chronically inflamed sinus mucosa by supporting various cell populations and contributing to fibrosis and thickening of the mucosa [22]. In patients with perennial allergic rhinitis, however, expression of intercellular adhesion molecule 1 was found to be low in the sinus mucosa compared with expression in the nasal mucosa [23].

Analysis of the lavage fluid from patients with chronic rhinosinusitis reveals high concentrations of histamine, cysteinyl leukotriene (CysLT), and prostaglandin D2 that are similar to levels obtained after challenge with antigen in patients with allergic rhinitis [24]. These high concentrations may indicate mast cell and basophil stimulation [23].

**Inflammation in nasal polyposis**

Although a large heterogeneity exists between polyps, there are common structures in bilateral eosinophilic polyposis, including pseudocyst formations, a thickened basement membrane, and edematous-to-fibrotic stromal tissue, with a reduced number of vessels and glands but virtually no neural structures [25,26].

Among the inflammatory cells, eosinophils are a prominent and characteristic feature in about 80% of polyps [27]. They are localized around the vessels, glands, and directly beneath the mucosal epithelium [25]. It is likely that chronic mucosal eosinophilia in nasal polyps involves a self-sustaining mechanism [28,29] through the local release of inflammatory mediators, cytokines, and chemokines. The presence of eosinophils in nasal polyps has been associated with increased levels
of IL-5 [30–33] and other cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF). The key role of IL-5 was supported by the finding that in vitro treatment of eosinophil-infiltrated polyp tissue with neutralizing anti–IL-5 monoclonal antibody (mAb), but not anti–IL-3 or anti–GM-CSF mAbs, resulted in eosinophil apoptosis and decreased tissue eosinophilia [34]. No difference in the amounts of cytokines was detected in polyps from allergic or nonallergic patients [35]. The highest concentrations of IL-5 were found in polyps from patients with nonallergic asthma and aspirin intolerance [36]. Other studies have shown that nasal polyps also express high levels of RANTES and exotoxin [26,31,37,38].

Increased release of inflammatory mediators contributes to the development of nasal polyps, determining edema and an increased recruitment of inflammatory cells. Besides eosinophils, mast cells also have a key role in this process [39]. Transforming growth factor $\beta$ (TGF-$\beta$) is found in low levels in tissue homogenates from nasal polyps. Corticosteroid treatment significantly reduces IL-5, eosinophil cationic protein (ECP), and albumin concentrations, whereas the level of TGF-$\beta_1$ is increased [26]. TGF-$\beta_1$ is a potent fibrogenic growth factor that stimulates extracellular matrix formation and acts as a chemoattractant for fibroblasts, but inhibits the synthesis of IL-5 and abrogates the survival-prolonging effect of hematopoietins (IL-5, GM-CSF) on eosinophils [40]. The relative lack of TGF-$\beta$ and the overexpression of metalloproteinase 9 and metalloproteinase 7 in nasal polyposis without up-regulation of the tissue inhibitor of matrix metalloproteinase 1 may account for the tissue destruction, recognized as pseudocyst formation [41].

The number of CysLTs is increased in chronic hyperplastic sinusitis [42]. Among patients with chronic rhinosinusitis, an elevated number of nasal inflammatory leukocytes expressing the CysLT1 receptor was found in patients with aspirin intolerance as compared with those without aspirin sensitivity [43].

**Rhinitis and asthma**

*Epidemiologic relationship between rhinitis and asthma*

Epidemiologic studies have consistently shown that asthma and rhinitis often coexist [44,45].

*Prevalence of rhinitis in asthma*

Most patients with asthma present seasonal or perennial allergic rhinitis symptoms. It has been shown, however, that perennial rhinitis is a factor that is independent of allergy in the risk for asthma. Rhinitis usually occurs in more than 75% of patients with allergic asthma and in more than 80% of patients with nonallergic asthma (for review, see [1]). In many instances, however, symptoms predominate in
one of the organs and may be hidden in the other, although the symptoms may exist. The Copenhagen Allergy Study [46] showed that than more than 99% of subjects with allergic asthma also had allergic rhinitis. The results observed in developing countries may differ from those observed in western populations. One study showed that allergic rhinitis is far less common among asthmatic subjects in rural China than in asthmatic subjects in industrialized countries with a western lifestyle [47]. In Costa Rica, rhinitis and asthma were found to be common comorbidities [48].

The age of onset of atopy may be an important confounding factor for the development of asthma and rhinitis or rhinitis alone. In an Australian study, atopy acquired at an early age (before age 6 years) was an important predictive factor for the continuation of asthma into late childhood, whereas atopy acquired later in life was associated strongly only with seasonal allergic rhinitis [49,50].

**Nonspecific bronchial hyperreactivity in rhinitis**

Many patients with allergic rhinitis have unique physiologic behavior that separates them from patients with asthma and normal subjects. They have increased bronchial sensitivity to methacholine or histamine [51], especially during and slightly after the pollen season [52]. There are large differences in the magnitude of airway reactivity between asthmatics and people with rhinitis that are not explained by the allergen type or degree of reactivity.

**Prevalence of asthma in rhinitis**

The prevalence of asthma in patients with rhinitis usually ranges between 15% and 40% [53]. It seems that patients with seasonal rhinitis or with intermittent rhinitis present with asthma in about 10% to 15% of cases, whereas patients with perennial and seasonal rhinitis or patients with severe persistent rhinitis have asthma in 25% to 40% of cases (DREAMS [Etude Descriptive des Rhinites Allergiques et des Modifications du Sommeil] study).

**Rhinitis as a risk factor for asthma**

Allergic rhinitis was proposed to be a risk factor for asthma. The Children’s Respiratory Study [54] showed that the presence of physician-diagnosed allergic rhinitis in infancy was associated independently with a doubling of the risk for asthma by age 11 years. In adults, allergic rhinitis was shown to be a risk factor for asthma in a 23-year follow-up of college students [55]. This study was confirmed by two other studies in Sweden [56] and the United States [57]. In both studies, the onset of asthma was associated with allergic and nonallergic rhinitis. Patients with persistent and severe rhinitis had the highest risk for asthma. The authors concluded that rhinitis is a significant risk factor for adult-onset asthma in atopic and
nonatopic subjects. It is not clear whether allergic rhinitis represents an earlier clinical manifestation of allergic disease in atopic subjects who eventually develop asthma or if the nasal disease itself is causative for asthma.

Causative agents in rhinitis and asthma

Among the causative agents inducing asthma and rhinitis, some (eg, allergens and aspirin) [58] are well known to affect the nose and bronchi. Most inhaled allergens are associated with nasal [59] and bronchial symptoms, but in epidemiologic studies, differences have been observed. Although there are some concerns, the prevalence of IgE sensitization to indoor allergens (house dust mites and cat allergens) is correlated positively with the frequency and severity of asthma. *Alternaria* and insect dusts have been found to be linked with asthma, but pollen sensitivity has not been found to be associated with asthma in epidemiologic studies [5].

Occupational diseases represent an interesting model for studying the relationships between rhinitis and asthma. All of the most common triggers of occupational asthma can induce occupational rhinitis (for review, see [5]). Rhinitis caused by many occupational agents often develops into occupational asthma, highlighting the importance of cessation of allergen exposure in occupational allergic rhinitis to prevent asthma.

Bronchial challenge of patients with rhinitis leads to bronchial symptoms and inflammation

Endobronchial allergen challenge was performed in patients with seasonal rhinitis who previously had not presented with asthma. These patients developed bronchoconstriction, and lavage performed serially after challenge demonstrated the occurrence of proinflammatory mediators and cytokines and the recruitment of inflammatory cells [60]. Pulmonary inflammation after segmental ragweed challenge was examined in allergic asthmatic and nonasthmatic subjects with rhinitis [61]. A marked inflammatory response that was measured in bronchoalveolar lavage fluid 24 hours after challenge was seen only in subjects who demonstrated a late airway reaction after whole-lung antigen challenge.

These studies indicate that patients with rhinitis only can react if the allergen is administered properly into the lower airways. A greater dose of allergen may reach the lower airways in thunderstorm-induced asthma [62], which has been associated with grass pollen allergy [63]. The aerodynamic size of pollen grains ranges from 10 to 100 μm, and only a fraction of these grains can be deposited into the bronchi under normal conditions. When exposed to water, pollen allergens are released in submicronic particles (starch granules), which can reach the lower airways and induce asthma [64].

There may be differences in bronchial reactivity to allergens in patients with rhinitis and asthma. Provocation concentration (PC)20 methacholine and provoca-
tion dose (PD)\textsubscript{20} allergen in patients with rhinitis and asthma were reduced significantly in comparison with those in patients with rhinitis alone [65].

**Clinical consequences**

Most atopic and nonatopic asthmatics have rhinitis. Although some studies have attempted to link the severity of nasal and bronchial symptoms, there are insufficient data to make a firm conclusion. In one study, patients with severe persistent rhinitis had more asthma symptoms and more severe nonspecific bronchial hyperreactivity than did those with intermittent or mild persistent rhinitis (DREAMS study). In another study [66], patients with severe asthma had more severe nasal symptoms than did those with moderate asthma.

Quality of life has been found to be impaired in patients with asthma and in patients with allergic rhinitis. The relative burden of these diseases has been studied using the generic SF-36 questionnaire in the European Community Respiratory Health Survey, a population-based study of young adults [67]. Patients with asthma and allergic rhinitis experienced more physical limitations than did patients with allergic rhinitis alone, but no difference was found between the groups for concepts related to social and mental health. Patients with asthma and without rhinitis could not be studied, because their number was too low. It seems that impairment in social life in asthmatics may be attributable to nasal symptoms.

**Therapeutic consequences**

Although asthma and allergic rhinitis commonly occur together, treatments for one condition may alleviate the coexisting condition.

**Efficacy of treatments in rhinitis and asthma**

Medications for asthma and rhinitis can be administered by way of local, oral, and parenteral routes. There are advantages (and some drawbacks) to administering the drug directly into the target organ [1]. Some drugs, like cromoglycate or nedocromil, are not absorbed when given orally and are only effective when administered locally. In patients with asthma and rhinitis, local administration of drugs requires that they are given nasally and bronchially.

The links between rhinitis and asthma in terms of treatment should be reported using an evidence-based model. Using the strength of evidence from Shekelle et al [68], which provides evidence levels from A to D, the following considerations can be proposed:

- The intranasal treatment of rhinitis using corticosteroids was found to improve asthma moderately at best in some but not all studies. Pulmonary function tests and bronchial hyperreactivity were improved moderately at best [69,70]: Evidence A
Only one study examined the effect of inhaled (intrabronchial) corticosteroids in seasonal rhinitis [71]. Although the treatment was found to reduce nasal symptoms and inflammation, more studies are needed to support this finding.

Drugs administered by the oral route may have an effect on nasal and bronchial symptoms. Oral H₁ antihistamines represent the first-line treatment for allergic rhinitis. Although studies have found some effect on asthma symptoms at the recommended dose in the treatment of seasonal asthma [72,73], these drugs are not recommended for the routine treatment of asthma [74]: Evidence A.

The combination of oral H₁ antihistamines and decongestants was found to be more effective on asthma symptoms compared to antihistamine alone [75]. More studies are needed for support.

Leukotriene modifiers were shown to be effective in controlling symptoms of mild-to-moderate asthma and seasonal allergic rhinitis [76]: Evidence A.

Oral and intramuscular corticosteroids are found by physicians to be highly effective in the treatment of rhinitis and asthma, but randomized, controlled trials are lacking (Evidence D), and side effects are common.

The indications for specific immunotherapy in allergic asthma and rhinitis have been separated in some guidelines. Specific immunotherapy should be considered that is based on the allergen sensitization rather than on the disease itself, because most patients with allergic asthma also present with rhinitis or rhinoconjunctivitis [77]. Immunotherapy is effective in rhinitis and asthma caused by several pollen species and house dust mites when the optimal dose is administered intracutaneously and sublingually: Evidence A.

Immunotherapy can alter the atopic phenotype by restoring the normal equilibrium between T₈₁ and T₈₂ lymphocytes. This form of therapy is under investigation in subjects with allergic rhinitis as a means of prevention of secondary asthma, and initial results are encouraging [78]: Evidence B.

The anti-IgE antibody omalizumab has been shown to be effective in separate populations of patients with seasonal and perennial allergic rhinitis [79] and in children and adults with moderate-to-severe allergic asthma [80]: Evidence A.

Treatment of rhinitis reduces asthma severity

Two studies showed that treating allergic rhinitis reduces healthcare use for comorbid asthma. A retrospective cohort study was performed in 4944 patients with allergic rhinitis and asthma (age range, 12 to 60 years) who were enrolled continuously and had no evidence of chronic obstructive pulmonary disease [81]. The risk for an asthma-related event (hospitalizations, emergency department visits) for the treated group was about half that for the untreated group. Another retrospective cohort study was performed in 13,844 asthmatics (age, > 5 years) who were part of a managed care organization [82]. Patients who received intranasal corticosteroids had a reduced risk for emergency department visit compared with those who did not receive this treatment (Evidence B).
Rhinitis and asthma: a continuum of disease?

It seems that most if not all asthmatics have rhinitis, and it is possible that the few asthmatics without demonstrable signs of rhinitis have a particular phenotype. Only a fraction of patients with rhinitis have clinically demonstrable asthma, even though a greater number of patients with persistent rhinitis has increased non-specific bronchial hyperreactivity.

There are similarities and differences between the nasal and bronchial mucosa in rhinitis and asthma. It seems that the epithelial–mesenchymal trophic unit exists from the nose to the bronchiolar–alveolar junction and that the same inflammatory cells are present throughout the airways, suggesting a continuum of disease. There are also major structural differences between the nasal and the bronchial mucosa: In the former there is a large vascular supply, whereas in the latter there is smooth muscle. Airway smooth muscle is of paramount importance in asthma because of its contractile properties, and it may contribute to the pathogenesis of the disease by increased proliferation and by the expression and secretion of proinflammatory mediators and cytokines.

It is speculated that the difference between rhinitis and asthma is caused by the fact that there is an epithelial–mesenchymal trophic unit in rhinitis [83] but an epithelial-mesenchymal–muscular trophic unit in asthma (Fig. 1). Other difference

![Fig. 1. Continuum of the epithelial–mesenchymal trophic unit from the nose to the small airways. In the nose, smooth muscle is absent.](image-url)
may be related to the embryologic origin of the airways, the development of the nose from the ectoderm, and the lower airways from the endoderm.

**Sinusitis and lower airways diseases**

Sinusitis often has been associated with allergy and asthma [45,84]. In several diseases, such as the immotile cilia syndrome [85], some immunoglobulin deficiencies [86], cystic fibrosis [87,88], and diffuse panbronchiolitis [89,90], there are comorbid associations between the bronchial tree and the sinuses.

**Relationship between allergy and rhinosinusitis**

The maxillary, anterior ethmoidal, and frontal sinuses drain by way of the ostium of the maxillary sinuses and middle meatus, collectively known as the ostiomeatal complex. Swelling of the mucous membranes, whether caused by allergy, infection, or other causes, may obstruct the drainage and aeration of the sinuses, and one might expect allergy to increase the risk for acute and chronic sinusitis [91,92].

Some studies suggested that rhinosinusitis is a common complication of allergic rhinitis [93–95]. In one study, 43% of cases of acute rhinosinusitis were seasonal, of which 25% were allergic [96]. In another study, allergy was considered to be the cause of acute maxillary rhinosinusitis in 25.0% of young adults compared with 16.5% of healthy controls [97]. There is no evidence that ostial patency changes or that the incidence of purulent rhinosinusitis increases during the pollen season [98]. Sinusitis is present in similar proportions of patients with or without allergic rhinitis [99]. Although one study has shown an increase in sinus involvement in allergic patients [98], two other studies [100,101] found no significant difference on CT scans of allergic and nonallergic adults with chronic rhinosinusitis.

It has been suggested that allergens may enter the sinuses, resulting in a similar allergic inflammation as in the nasal mucosa [98]. Experimentally, nasal instillation of allergens can produce mucosal edema and sinus opacification [102]. Using radiolabeled pollens, investigators have found no evidence that allergens deposited in the nose can reach the sinus cavities [103]. There is an increased incidence of immediate-type hypersensitivity reactions in patients with chronic rhinosinusitis [15], and IgE-mediated reactions, confirmed by challenge with nasal allergens [104], are found in 78% of patients with chronic rhinosinusitis [98]. Investigators found that only a small percentage of subjects with chronic rhinosinusitis had increased IgE antibody concentrations in tissue homogenates of sinus mucosa (Bachert, unpublished data).

Although allergy may be expected to result in inflammation and swelling of the nasal mucosa, leading to obstruction of the sinuses and acting as a precursor for acute and chronic rhinosinusitis, evidence is still conflicting. Allergic sinusitis does not seem to exist, and one should use the term “rhinosinusitis in atopic subjects.”
Relationship between asthma and rhinosinusitis

For more than 70 years, the coexistence of asthma and paranasal rhinosinusitis has been noted in the medical literature [94,105,106]. The debate remains as to whether rhinosinusitis is a precipitating factor for bronchial asthma. It seems that rhinosinusitis and asthma are linked by a common process that is mainly inflammatory, and central to the pathogenesis is the role of eosinophils and airway epithelium. Chronic rhinosinusitis associated with asthma and allergy seems to be restricted to the asthmatic population with an extensive sinonasal disease, and the presence of peripheral eosinophilia in patients with rhinosinusitis indicates a high likelihood of extensive disease [107]. Mucosal thickening in the nasal passages, sphenoidal, ethmoidal, and frontal sinuses, but not the maxillary sinuses, was found to be more common in subjects with acute asthma than in control subjects [108]. Sinusitis may contribute to the severity of the bronchial symptoms [109].

In a study comparing patients with mild-to-moderate asthma with corticosteroid-dependent asthmatics, the proportion of patients with symptoms of rhinosinusitis was similar in both groups (74% in the corticosteroid-dependent group and 70% in mild-to-moderate asthma group) [66]. All corticosteroid-dependent asthmatics versus 88% of patients with mild-to-moderate asthma had abnormal CT scans. The clinical and CT-scan scores were higher in corticosteroid-dependent asthmatics. In both groups, the CT-scan scores were correlated to the clinical scores and the absolute number of eosinophils.

In another study of severe asthmatics, CT scans showed abnormalities in 84% of patients [110], and some of these subjects may have had nasal polyposis rather than chronic rhinosinusitis. Extensive sinus disease was found in 24% of patients. There was a significant positive correlation between CT-scan scores and eosinophils in peripheral blood and induced sputum and the level of exhaled nitric oxide. CT-scan scores were related positively to functional residual capacity and related inversely to diffusion capacity, particularly in patients with adult-onset asthma. The results show a direct relationship between sinonasal mucosa thickness and bronchial inflammation in severe asthma, particularly in patients with adult-onset disease. Whether sinus disease directly affects the intensity of bronchial inflammation is still an unanswered question.

Nasal polyps

Polyps are smooth, grape-like structures that arise from the inflamed mucosa lining (paranasal sinuses) and may obstruct the nasal cavity. Nasal polyps occurring in association with cystic fibrosis may be neutrophilic in nature [111], whereas in polyps associated with asthma and aspirin-sensitive asthma [112], infiltrating cells are eosinophils [21,113,114]. Although the degree of cellular infiltration may vary, some patients with cystic fibrosis may have allergic rhinitis, and the distinction between neutrophilia and eosinophilia may not be clear cut [115,116].
**Relationship between allergy and polyposis**

For many years, an allergic origin has been presumed [117] but never firmly demonstrated in nasal polyposis. The prevalence of nasal polyposis in allergic patients is low (usually less than 5%) [118–120]. In a series of 249 patients undergoing nasal polypectomy, Wong and Dolovich [121] found that 66% had at least one positive allergy skin prick test when tested to 14 inhalants and five food allergens. Positive skin tests were found in 74% of control patients undergoing non-polyp nasal surgery. Skin tests may not identify all possible allergens that could have a role in nasal polyposis [122], and there may be a local production of IgE [123–125].

Drake-Lee [126] found no correlation between a positive skin prick test and the number of repeated polypectomies. Wong and Dolovich [121], in the previously mentioned study, found no association between the number of polypectomies in patients with at least one positive allergy skin test. An increased number of polypectomies was found in patients with asthma, and there was a positive association between the blood eosinophil count and the number of previous polypectomies.

**Relationship between aspirin intolerance and polyposis**

Aspirin intolerance often is observed in nasal polyposis [127], and many patients present asthma, nasal polyposis, and sinusitis [128–130]. Of 500 patients registered at the European Network on Aspirin-Induced Asthma, almost 80% had symptoms of rhinosinusitis and complained of nasal blockage accompanied by rhinorrhea [58]. Loss of smell was present in 69% of these patients. Significant abnormalities in almost all paranasal sinuses were detected in 75% of patients. Any combination of air-fluid levels, mucosal thickening, or opacification was a characteristic finding in one or more paranasal sinuses. Nasal polyps were diagnosed in 62% of patients at a mean age of 33 years. The polyps had a tendency to recur, and multiple polypectomies were common [58]. Eosinophils seem to be a link between nasal polyps, asthma, and aspirin intolerance [17]. Decreased apoptosis of inflammatory cells in nasal polyps from patients with aspirin intolerance reflects a distinct mechanism of local inflammation and may be related to persistence and severity of the disease [36].

**Relationship between asthma and polyposis**

Nasal polyposis commonly is found in association with lower tract respiratory disorders, such as asthma and nonspecific bronchial hyperreactivity [131–133]. Patients with nasal polyposis and asymptomatic bronchial hyperreactivity have an eosinophilic bronchial inflammation similar to that observed in asthmatic patients with nasal polyposis, whereas patients with nasal polyposis without bronchial hyperreactivity do not show eosinophilic lower airways inflammation [134]. The significance of asymptomatic bronchial hyperreactivity associated with nasal polyposis is unknown, but it may represent an indication of potential asthma.
The clinical relevance of these results requires careful follow-up to determine whether eosinophilic inflammation in these patients precedes and is responsible for the development of obvious asthma.

The presence of asthma does not correlate with increased levels of CysLT in the nasal polyp mucosa of patients with chronic sinusitis [135]. In another study, IL-5 was found to be involved in bronchial eosinophilia and in the pathogenesis of asymptomatic bronchial hyperresponsiveness, whereas IL-5 and eotaxin were found to be involved in asthma associated with nasal polyps [136].

**Impact of the treatment of sinusitis and nasal polyps in asthma**

It is impossible to discriminate between the treatments of sinusitis and nasal polyps in their impact on asthma, so they are discussed together. The treatment of nasal polyposis and sinusitis may be involved in the control of asthma. It consists of medical or surgical management [137–140]. Topical steroid therapy has a well-established role in the management of nasal polyp, because it has proven efficacy on symptoms and size of polyps and may help prevent the recurrence of nasal polyposis after surgery [141–146].

A study of 205 patients attempted to determine whether nasal and sinus surgery had a beneficial or deleterious effect on the asthma of patients with nasal polyps and aspirin intolerance [147]. A classification system was devised to provide a means of determining the severity of asthma before and after surgery. The data indicated that surgery improves asthma for relatively long periods of time. Conflicting opinions exist concerning the evolution of asthma and asymptomatic bronchial hyperreactivity in patients with nasal polyposis [147–162]. Some studies have indicated that polypectomy and sinus surgery may induce worsening of asthma severity [163]. Few authors have evaluated the consequences of sinus surgery in nasal polyposis, relying on objective criteria such as lung-volume measurements and evaluation of nonspecific bronchial hyperreactivity, and no prospective studies have been published.

The initial response of nasal polyposis to corticosteroids may be of importance in the relationships between asthma and nasal polyposis. Lamblin et al [134] reported an enhancement of nonspecific bronchial hyperreactivity and a significant, but modest, decrease in forced expiratory volume in 1 second (FEV₁) over 12 months in 23 nonresponders to intranasal corticosteroids who underwent intranasal ethmoidectomy; no change was observed in 21 responders. No change in pulmonary symptoms and asthma severity was observed in steroid responders. In another study, the same investigators studied the long-term changes of pulmonary function and bronchial hyperreactivity over a 4-year period in 46 patients with nasal polyposis [164]. Patients were treated first with intranasal corticosteroids for 6 weeks (600 μg/d of beclomethasone). Eighteen patients were treated successfully with intranasal corticosteroids (corticosteroid responders). Ethmoidectomy was performed in 28 patients who did not improve with intranasal corticosteroids alone (corticosteroid nonresponders). Bronchial hyperreactivity
did not change significantly in the two groups during the 4-year follow-up period. No change in pulmonary symptoms or asthma severity occurred, but nonreversible airflow obstruction appeared in corticosteroid nonresponders only and required surgery. A more critical approach might be necessary to determine the effect of nasal polyp treatment on the lower airways.

**Links between the upper and lower airways**

Epidemiologic studies show a link between the upper and the lower airways, and mechanistic studies suggest a cause-and-effect rather than a coexistence [165]. Several nonexclusive possibilities can be proposed.

**Allergy as a systemic disease**

In one study, endobronchial allergen challenge induced nasal and bronchial symptoms and reductions in pulmonary and nasal function [166]. The number of eosinophils increased in the challenged bronchial mucosa, in the blood, and in the nasal mucosa 24 hours after bronchial challenge. Eotaxin-positive cells in the nasal lamina propria and enhanced expression of IL-5 in the nasal epithelium also were found 24 hours after bronchial challenge. Braunstahl et al [167] found that nasal challenge increased eosinophils in the bronchial mucosa.

There has been an increasing appreciation of the important contribution of bone-marrow–related, hemopoietic mechanisms to allergic diseases [168,169]. In patients with allergic diseases, allergen provocation can activate a systemic response that provokes inflammatory cell production by the bone marrow [170]. After release and differentiation of progenitor cells, eosinophils, basophils, and mast cells typically are recruited to tissues in atopic individuals [171]. Studies that support the critical involvement of the bone marrow in the development of eosinophilic inflammation of the airways point out the systemic nature of these conditions. In nasal polyps, there may be a systemic involvement, because immunoreactive, mononuclear CD34 cells are present in the lamina propria of all nasal polyps [172]. In situ hemopoiesis [173] depends on the production of hemopoietic cytokines by inflamed tissues from patients with allergic rhinitis [174], which, generating a particular local microenvironment, promotes the differentiation and maturation of eosinophil progenitors that populate the nasal or bronchial mucosa [175]. It is likely that a truly systemic response to the application of inflammatory stimuli to the nasal (or bronchial) mucosa should be associated with an activation of the aforementioned mechanisms.

**Links between the upper and lower airways**

Several theories have been proposed to explain the links between the upper and lower airways [165]. A nasobronchial reflex may exist, inducing bronchial obstruction during nonspecific [176] or allergen-specific challenge of the nose [177]. Mouth breathing caused by nasal obstruction is another possible mechanism [178],
but more data are needed to confirm these hypotheses. Pulmonary aspiration of nasal contents may occur [179,180], and the proinflammatory mediators and cytokines that are released during rhinitis may act on the lower airways; however, conflicting results have been published [181].

**Staphylococcus aureus enterotoxins: a possible link between upper and lower airways**

*Staphylococcus aureus*-derived enterotoxins (SAEs) are a family of structurally related, high-molecular-weight proteins that act as superantigens. They possess a potent stimulatory activity for T lymphocytes by cross-linking the V\(_b\)-chain of the T-cell receptor with major histocompatibility complex class II molecules on accessory or target T cells, outside the peptide-binding groove area [182]. *Staphylococcus* -derived protein A and toxic shock syndrome toxin 1 have been demonstrated to possess B-cell superantigen moieties, inducing polyclonal IgE synthesis [183].

SAEs have been related to eosinophilic inflammation in nasal polyposis [38]. In approximately 50% of the polyp homogenates, IgE antibodies specific to SAE A or SAE B could be demonstrated, which were linked to high total-tissue IgE levels and a local polyclonal IgE antibody formation against various inhalant allergens. In SAE-specific IgE antibody-positive polyp samples versus controls,
the eosinophilic inflammation was significantly more severe in terms of synthesis of IL-5, eotaxin, ECP, and CysLT, and SAE-IgE positive patients mostly also had asthma and aspirin hypersensitivity.

There is circumstantial evidence that SAEs may trigger T-cell activation in poorly controlled asthma in humans, as the expression of corresponding T-cell receptor (TCR)-V\textsubscript{8} on T cells in bronchoalveolar lavage is increased significantly compared with controls [184]. IgE antibodies to SAEs are increased in patients with severe persistent asthma [185] and are related to ECP and FEV\textsubscript{1}. Because most patients with severe asthma also have rhinitis symptoms, it could be speculated that the source of SAEs may be the nose and sinuses and that droplets from the nose containing SAEs would be inhaled [186]. Further research needs to be done to clarify the pathophysiologic link between SAE-specific IgE and bronchial inflammation.

SAEs may link allergic rhinitis and mild, atopic asthma (Fig. 2). In one study 41% of patients with mild asthma versus 13% of controls had serum anti-SAE–IgE antibodies [185]. Also, 25.0% of patients with allergic rhinitis versus 6.3% of controls had serum anti-SAE–IgE antibodies [187]. The rate of nasal carriage in \textit{S. aureus} in patients with perennial allergic rhinitis (44%) was significantly higher than that in the control subjects in another study (20%), and the rate of nasal carriage of superantigen-producing \textit{S. aureus} in patients (22%) was significantly higher than that of the control subjects (6.7%) [188].

The studies in rhinitis, rhinosinusitis, nasal polyps and lower airway diseases suggest that the upper and lower airways always should be considered in patients with signs at one site of the airways (nose, sinuses, or lower airways) (Box 1).

References


