Introduction

Rhinitis and asthma are very common diseases that often present concurrently. The high prevalence of these diseases is associated with high morbidity and elevated health costs. Both diseases have a number of characteristics in common, but they also differ substantially in certain aspects.

In 2001, the Allergic Rhinitis and Its Impact on Asthma (ARIA) Workshop Group published an international consensus statement. The statement extensively reviewed asthma classification, epidemiology, genetics, triggers, pathophysiological mechanisms, coexistence with rhinitis, diagnosis, and treatment. Evidence-based treatment guidelines were also presented, and the need for research into allergic rhinitis was highlighted. In the wake of the ARIA statement, several studies on the relationship between asthma and rhinitis have been published. This article provides an updated review of how the upper and lower airways may be interrelated. The anatomy and main aspects of nasal physiology are described, with particular emphasis on the importance of the nose for conditioning inspired air.

Anatomy and Physiology

In healthy people, the structure of the nasal mucosa is similar to that of the bronchial mucosa. Both mucosae are characterized by the presence of a ciliated pseudostratified columnar epithelium, and both submucosae contain mucous glands, blood vessels, connective tissue, nerves, and inflammatory cells. However, the 2 structures also differ in that the nose has a large network of subepithelial capillaries, an arterial system, and venous sinuses. This extensive vascularization is an important characteristic of the nasal mucosa because changes in this vascular network can lead to severe nasal blockage. The bronchi, unlike the nose, contain smooth muscle, which is responsible for bronchoconstriction in asthma (Figure 1).

Human noses can vary greatly in shape and size, but the anatomy and function of the basic structures are similar (Figure 2). The highest airflow occurs in the nostrils—the most anterior part of the nose. After passing through the nostrils, the air enters the nasal vestibule before the nasal fossa constricts to form the nasal valve, the narrowest part of the nasal fossa located 1.5 cm downstream from the nostrils. The function of the nasal valve is to generate resistance to disrupt laminar airflow. The nose is responsible for half the total resistance of the airway and 60% to 70% of this resistance is generated in the nasal valve. The resulting turbulence helps bring the air into contact with the nasal mucosa, in turn favoring suitable temperature and humidity conditioning and filtration of solid particles, which are then expelled by mucociliary clearance. The flow of inspired air can largely be modulated by changes in the erectile tissue of turbinate mucosa of the nasal septum. This segment accounts for 30% to 40% of nasal resistance.

The nose provides not just a physical but also an immunological barrier, as it is the first organ encountered by microorganisms that penetrate the airway. Smell is another function of the nose. Sensory activity is transmitted via branches of the olfactory nerve, which cross the roof of the nasal cavity through the cribiform plate of the ethmoid bone.

Epidemiology

Epidemiological studies have clearly shown that rhinitis and asthma are frequently concurrent. Most patients with asthma have rhinitis, which presents in
more than 75% of the patients with allergic (extrinsic) asthma and in more than 80% of those with nonallergic (intrinsic) asthma. However, patients may often only report the most bothersome and annoying symptoms, which are usually bronchial manifestations. According to Gaga et al., nasal inflammation was present in a group of asthmatic patients who did not report any symptoms of rhinitis. Therefore, although such patients consider themselves free of symptoms, nasal involvement is almost always present.

On the other hand, the prevalence of asthma in patients with rhinitis ranges from 15% to 40%. Particularly noteworthy is the fact that asthma is present in 10% to 15% of the patients with seasonal rhinitis and in 25% to 40% of those with severe persistent rhinitis. Moreover, the severity of rhinitis is directly related to asthma severity.

Several studies have suggested that allergic rhinitis is an important risk factor for the development of asthma. Diagnosis of allergic rhinitis in childhood is independently associated with a twofold increase in the risk of suffering from asthma at the age of 11 years.8 Findings from studies of young people and adults with long-term follow-up were similar, and also revealed that asthma was associated with both allergic and nonallergic rhinitis.9,10 This suggests that the 2 diseases are interrelated regardless of whether or not they are atopic.

The age of onset of atopy may have a strong influence on whether asthma and/or rhinitis develop. In an Australian study,11 onset of atopy at an early age (before the subjects were 6 years old) was an important predictor of the development of asthma in late
childhood, whereas onset during adult life was strongly associated only with the development of rhinitis. Although the frequency of asthma and rhinitis differs between developing and developed countries, the frequency with which the 2 diseases present concurrently is similar. In short, these studies suggest that asthma and rhinitis coexist frequently and that rhinitis is directly related to the development of asthma.

**Pathophysiology**

**Effects of Poorly Conditioned Air**

The effects on the lower airway of breathing poorly conditioned air have been clearly described in experiments of exercise-induced bronchial provocation. Strohl et al. assessed the changes in airway resistance after breathing first cold dry air and then warm humid air through the mouth. They found that airway resistance increased 84% with exercise while breathing cold dry air but was unchanged with exercise while breathing warm humid air. Likewise, Shtruman-Ellstein et al. found that the bronchoconstrictive response in patients with asthma was greater when breathing through the mouth than through the nose.

An important observation is that a large number of subjects who practice elite competitive winter sports develop asthma. In an interesting study, Wilber et al. assessed the presence of exercise-induced bronchospasms among the members of the United States team during the Winter Olympics of 1998. The overall incidence of exercise-induced bronchospasm was 23% but as high as 50% among cross-country skiers. Karjalainen et al. also found (mainly neutrophilic) inflammatory bronchial infiltration and a thicker basement membrane in another group of skiers. These findings contrast with a study of the Summer Olympics of 2000, in which the incidence of asthma among Italian athletes participating in the games was reported to be 15%. These findings can, in turn, be compared with the overall prevalence of asthma according to the Global Initiative for Asthma, which reports an overall prevalence of asthma of between 5% and 10%. Therefore, practice of elite competitive sports could be associated with a higher incidence of asthma (Figure 3). We do not know why this is so, but it may be that these athletes are exposed to unconditioned air for much of the day because they inhale through the mouth when training. They would therefore be more susceptible to bronchial hyperreactivity. Studies have shown that the switch from nose to mouth breathing comes when a minute volume of 30 L to 40 L is reached—a threshold easily exceeded by elite athletes in their daily training.

In short, these findings suggest that repeated and prolonged exposure of airways to poorly conditioned air may lead to functional and inflammatory disorders and even induce airway remodeling.

**Figure 3.** Presence of asthma in elite athletes and in the general population (GP). SOA indicates Summer Olympics athletes; WOA, Winter Olympics athletes (cross-country skiers).

**Similarities and Differences Between Nasal and Bronchial Inflammation**

In patients with rhinitis or asthma, the inflammatory infiltrate is similar, with the same mediators, T-helper (Th) 2 lymphocyte derived cytokines, and adhesion molecules. Nevertheless, the extent of inflammation may vary. In patients with moderate to severe asthma, eosinophilic infiltration is more pronounced in the bronchi than in the nose, whereas patients with mild asthma have a similar degree of inflammation at both sites. As mentioned earlier, nasal eosinophilic inflammation is present in asthmatic patients with or without nasal symptoms, but airway remodeling seems to be less extensive in the nasal mucosa than in the bronchial mucosa. Patients with asthma have a thicker basement membrane, smooth muscle hypertrophy, and greater epithelial desquamation, whereas the nasal epithelium of those with rhinitis alone is less damaged.

**Nasal Inflammation and Bronchial Response**

A number of clinical and experimental studies have investigated the link between rhinitis and the presence of inflammation and functional disorders in the lower airway. Bronchial hyperreactivity and changes in lung function occurred in patients with allergic rhinitis after nasal provocation with allergen. Other studies have described the presence of systemic allergic inflammation after nasal provocation in both animal models and in humans. McCusker et al. used ovalbumin for nasal provocation in a murine model, and showed that inflammatory changes, as indicated by elevated interleukin 5 and eosinophils in bronchoalveolar lavage, occurred in both the nasal and bronchial mucosae. Braunstahl et al. studied the
expression of adhesion molecules in nasal and bronchial biopsies taken before and 24 hours after nasal provocation with allergen in patients with seasonal rhinitis. They found a significant increase in eosinophils in the epithelium and the nasal lamina propria, and in the bronchial epithelium at 24 hours. This increase was directly related to expression of adhesion molecules. They also detected a significant increase in the number of eosinophils and concentration of interleukin 5 in blood samples obtained at 24 hours. Beeh et al\(^{28}\) studied inflammatory markers in induced sputum and in plasma before and 24 hours after nasal provocation with pollen extracts in allergic patients outside the season for allergies. Inflammatory markers (eosinophil cationic protein and intercellular adhesion molecules) were found to be elevated in sputum. This increase was related to an increase in interleukin 5 in plasma.

Other studies have shown bronchial inflammatory response in nonasthmatic patients with allergic rhinitis after natural exposure to pollen and after repeated provocation at low doses.\(^{29-32}\)

**Bronchial Inflammation and Nasal Response**

Braunstahl et al\(^{33,34}\) have also taken the opposite approach and studied nasal inflammatory response after segmental bronchial provocation with allergens in nonasthmatic patients allergic to pollen. They found that this procedure induced nasal and bronchial symptoms, and increased peripheral blood eosinophils and eosinophilic and basophilic infiltration of the nasal and bronchial mucosae.

**Response to Exercise (Figure 4)**

The nose and bronchi respond differently to exercise. Forced expiratory volume in 1 second decreases in 40% to 90% of asthmatic patients during exercise testing. Some authors suggest that this bronchoconstriction may be mediated by mast cell degranulation resulting from the higher osmolarity of the fluid coating the airways.\(^{35}\)

Unlike the bronchi, the nose is always dilated after exercise. Several studies done both in healthy subjects and in those with a range of respiratory diseases (nasal septal deviation, rhinitis, asthma, cystic fibrosis)\(^{36-41}\) have shown that exercise lowers nasal resistance and increases nasal volume. These changes occur immediately after exercise and basal values are usually recovered within 30 or 40 minutes.\(^{36,39}\) Nasal response to exercise is thought to occur through decreased volume of the venous sinuses as a result of vasoconstriction, which in turn is due to an increase in sympathetic activity. This hypothesis is supported by the fact that stellate ganglion block and local application of phentolamine have been shown to impede nasal vasoconstrictive response during exercise.\(^{36}\)

In asthmatic patients, bronchoconstriction after exercise is much more pronounced when subjects breathe through the mouth (probably because of the lack of conditioning of inspired air),\(^{14}\) whereas nasal dilatation occurs regardless of whether the patients are breathing through the nose or through the mouth,\(^{13}\) and even when their noses are blocked.
Effect of Chronic Rhinosinusitis and Polyposis on Asthma Severity

The main pathologic findings of chronic sinusitis are goblet cell hyperplasia, presence of subepithelial edema, and infiltration by mononuclear cells and activated eosinophils.42,43 Eosinophil infiltration is more extensive in patients with polyps (50% of the inflammatory infiltrate) than in those with no polyposis (2% of the inflammatory infiltrate).44 This type of inflammatory infiltrate is similar to that found in asthmatic patients.

The counts of other inflammatory cells such as, for example, mast cells, lymphocytes, macrophages, and, to a lesser extent, neutrophils, are also increased, and this contributes to the release of proinflammatory mediators, cytokines, and growth factors.

Some studies suggest that asthma is more prevalent and severe in those with severe rhinosinusitis.3 Brescia et al45 compared the incidence of rhinosinusitis in patients with mild to moderate asthma with that in patients with severe corticosteroid-dependent asthma. The proportion of patients with nasal symptoms was similar in both groups, whereas abnormalities of the paranasal sinuses detected by computed tomography were present in all patients with severe asthma and in 88% of those with mild to moderate asthma. Scores on clinical and tomographic scales were higher in those with severe asthma.

Acetylsalicylic acid intolerance, which is present in 10% of asthmatic patients46 and which possibly affects up to 40% of patients with concurrent chronic rhinosinusitis or nasal polyposis,47 is another important issue related to disease of the paranasal sinuses, and therefore, to asthma severity. Asthmatic patients with chronic rhinosinusitis or nasal polyposis, and acetylsalicylic acid intolerance are said to suffer from the Widal or acetylsalicylic acid triad and, in such cases, asthma is usually hard to control.

Otitis Media With Effusion as Part of Respiratory Allergic Disease

Otitis media with effusion is a chronic inflammatory disease in which fluid accumulates in the middle ear. Previous studies have indicated that the effects of inflammatory mediators derived from Th2 lymphocytes are largely responsible for its appearance in atopic patients. In an interesting study by Nguyen et al,48 cell infiltrates and the cytokine profile were studied in fluid samples taken from the middle ear and adenoid tissue in 45 patients with otitis media with effusion, 11 of whom (24%) were atopic. The authors found that the eosinophil and T-lymphocyte counts in the fluid from the atopic patients were significantly higher than those from nonatopic patients, whereas the neutrophil count was significantly lower. Similarly, immunohistochemical study showed a significant increase in cells containing messenger RNA for interleukin 4 in atopic subjects. Analysis of biopsies taken from nasopharyngeal (adenoid) tissue showed similar patterns of inflammatory response. The investigators concluded that allergic inflammation occurs at both ends of the eustachian tube, that is, in the nasopharynx and in the middle ear, a finding that explains involvement of the middle ear in atopic patients.

Interrelationship Mechanisms

The following mechanisms have been proposed to explain the interrelationship between the nose and the bronchi in allergic respiratory disease:

Nasobronchial reflex. This reflex was first observed in animals then later in humans when increased bronchial resistance was observed after nasal provocation with an aerosol of silica crystals.49 The existence of the reflex was confirmed when it was found that the increase in bronchial resistance disappeared in 5 individuals who had undergone unilateral resection of the trigeminal nerve.50 Although the sensory nerves of the nose are more activated in patients with allergic rhinitis, evidence of increased activation of this reflex in patients with rhinitis is inconclusive. Further investigation should aim to determine whether neural interactions between the nose and the bronchi are the cause of chronic cough suffered by many patients with allergic respiratory syndrome.51

Drainage of inflammatory mediators. It has been hypothesized that aspiration of mediators present in secretions may occur. These mediators then reach the lower airway in inspired air, particularly at night, leading to a deterioration in lung function, increased bronchial hyperreactivity, and symptoms on waking.51 However, the only study in humans to date that has attempted to clarify this possibility was unable to provide confirmation. In that study, Bardin et al52 injected technetium 99 into the maxillary sinuses of patients with chronic sinusitis and moderate to severe asthma and assessed bronchial reactivity over 24 hours. The authors found no traces of radioactive material in any of the lung fields, even though such material was recovered from the gastrointestinal tract. Nevertheless, several inflammatory substances produced during allergic reactions have been known to enter the gas phase or be present in aerosols that can be distributed throughout the bronchial tree.53 This hypothesis should therefore not be definitively rejected.

Systemic dissemination of mediators. Probably the most relevant and most recent information on the mechanism by which the upper and lower airways are linked comes from one of the studies done by Braunstahl et al.27 These investigators studied a group of patients with allergic rhinitis. Biopsies were taken from the nasal and bronchial mucosae before and 24 hours after nasal provocation with allergen. The investigators found that eosinophils increased 24 hours after provocation, and expression of adhesion
molecules (intercellular adhesion molecule 1 and vascular adhesion molecule 1) was also greater in both mucosae (Figure 5). In view of these findings and the fact that nasal provocation with allergen induces eosinophilia and leukocyte activation in peripheral blood, systemic propagation of inflammation from the nasal mucosa to the bronchial mucosa has been proposed as one of the main mechanisms whereby rhinitis and asthma are interrelated. Furthermore, this phenomenon has been shown to be not just 1-way. As mentioned earlier, Braunstahl et al also found an increase in inflammatory markers in the nasal mucosa after bronchial provocation with allergens.

Finally, Magnusson et al took biopsies from the duodenum of 9 patients with allergy to birch tree pollen at the end of the allergy season and repeated the procedure 6 months later. Eosinophils were significantly increased in the first sample, with presence of major basic protein and cells positive for immunoglobulin E compared to the second sample. These findings constitute important evidence of the interrelationship between immunologically active cells of the airways and the intestine.

Taken together, the observations discussed in this section point to the existence of an allergic inflammatory cascade that originates at a mucosal surface, but that tends to propagate systemically.

**Therapeutic Aspects of the Interrelationship Between Rhinitis and Asthma**

**Effect of Nasal Corticosteroids on Asthma**

The interrelationship between rhinitis and asthma has also been described in studies that have assessed the effect of topical nasal corticosteroids on bronchial inflammation and lung function. Sandrini et al reported that intranasal administration of triamcinolone acetonide lowers the levels of exhaled nitric oxide in patients with rhinitis and asthma, but they did not find any changes in lung function parameters. Other studies have found a moderate improvement in lung function and bronchial hyperreactivity. It has also been reported that appropriate treatment of rhinitis with these drugs decreases the frequency of visits to the emergency room for asthma exacerbations and the number admissions to hospital.
On the other hand, Pinto et al.\(^4\) recently reported that intranasal administration of budesonide to asthmatic patients was associated with a decrease in conditioning of inspired air among nonsmokers. Conditioning was assessed by determining the overall water gradient between the air prior to inspiration and on its passage through the nasopharynx. In asthmatic smokers, no changes in this gradient were observed. The authors highlighted the following important points: a) the presence of nasal inflammation favors nasal conditioning of air; b) smoking probably interferes with the antiinflammatory effects of budesonide, a possible explanation for the lack of effect of this drug on nasal conditioning in smokers; c) the nose can influence the lower airways and it is important to determine and extensively investigate the physiological and molecular processes of nasal conditioning; and d) the aforementioned possible benefits of treating nasal inflammation.

**Effect of Antihistamines on Asthma**

Antihistamines are 1 of the main therapeutic options for treatment of allergic rhinitis. Some of these drugs have been studied for antiinflammatory effects, because such effects could provide additional benefit, particularly for controlling nasal congestion. Previous studies suggest that loratadine and cetirizine might, to a greater or lesser extent, improve asthma symptoms in patients with allergic rhinitis.\(^6\) Continuous treatment with cetirizine has also been reported to reduce the frequency and severity of bronchial symptoms.\(^6\) A recent comparative study found that desloratadine and montelukast were equally effective at reducing asthma symptoms and use of bronchodilators in patients with seasonal allergic rhinitis and asthma.\(^6\) It has also been reported that use of combined treatment (antihistamines and an antileukotriene) in patients with asthma and rhinitis seems to be more effective than use of a single agent on its own. In accordance with the findings presented in this review, and bearing in mind that antihistamines are not considered asthma drugs, these beneficial effects on bronchial symptoms can probably be explained by reduced nasal inflammation.

**Immunotherapeutic Effect on the Development of Asthma**

Immunotherapy has been shown to be effective in the management of rhinitis and allergic asthma, both in clinical trials and according to recent systematic Cochrane reviews.\(^6\) The World Health Organization considers this type of therapy effective and has published a position paper on its correct use.\(^6\) Such therapy should be administered at optimal doses, regardless of whether the route is subcutaneous or sublingual. The decision to resort to immunotherapy should be based on allergic sensitization findings rather than on whether rhinitis or asthma is present, as both diseases coexist in most patients. The immunological effect of such therapy works by restoring the normal equilibrium between Th1 and Th2 lymphocytes. Moreover, this is the only treatment available that can modify the natural course of the disease. Moller et al.\(^6\) in a randomized, double-blind, placebo-controlled study, aimed to assess whether administration of specific immunotherapy could prevent the development of asthma and decrease bronchial hyperreactivity in children with seasonal allergic rhinoconjunctivitis. They found that bronchial hyperreactivity had significantly improved in the patients on active treatment after 3 years. The incidence of asthma among these patients was also significantly lower.

**Anti-Immunoglobulin E Monoclonal Antibodies**

In a multicenter, randomized, double-blind, placebo-controlled study, Vignola et al.\(^7\) evaluated the efficacy of omalizumab in 405 patients with moderate to severe asthma and persistent concurrent allergic rhinitis. Patients were randomized to receive conventional treatment and omalizumab or placebo every 4 weeks for 28 weeks. The results of the study showed that the patients treated with omalizumab had significantly lower scores on rhinitis and asthma symptoms scales than those treated with placebo. Moreover, use of omalizumab was associated with better control of rhinitis symptoms, a decrease in the number of asthma exacerbations, and an improvement in quality of life. At present, however, omalizumab is only indicated for use by patients with moderate or severe persistent allergic asthma whose symptoms are inadequately controlled by patients with moderate or severe persistent allergic asthma whose symptoms are inadequately controlled with conventional treatment, or who have adverse reactions to or who fail to comply with such treatment. Further studies are needed to demonstrate the benefit of joint treatment of rhinitis and asthma.

In short, previous observations suggest that management of patients with respiratory allergies should be integrated and appropriate for the overall severity of the syndrome (Figure 6).\(^7\)

**Contributions From the Allergic Rhinitis and Its Impact on Asthma Publication**

In order to raise awareness of the theory of “one airway, one disease,” the ARIA publication proposes 3 considerations for patients with allergic respiratory disease (Table).

### TABLE

**Recommendations of the Allergic Rhinitis and Its Impact on Asthma (ARIA) Workshop Group**

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<th>Condition</th>
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antihistamines. Immunotherapy seems to alter the natural course of allergic respiratory disease and prevent the appearance of asthma in subjects with rhinitis. Other treatments such as anti-immunoglobulin E monoclonal antibodies (omalizumab) appear to be the most promising options for management of patients with concurrent asthma and rhinitis. These findings reinforce the epidemiological and pathophysiological data on the interrelationship of asthma and rhinitis and serve to highlight the need for an integrated management of allergic respiratory disease.

REFERENCES


**Figure 6. Schematic diagram of the “integrated” therapeutic approach in patients with rhinitis and asthma. The broken line shows the potential effect of treatment of the nose on the bronchi. AL indicates antileukotrienes; IgE, immunoglobulin E. (Adapted from Passalacqua and Canonica.)**

**Conclusions**

Asthma and rhinitis are highly prevalent diseases that are often present side by side. Allergic rhinitis is a major risk factor for the development of asthma. Other conditions of the paranasal sinuses such as polyposis and chronic sinusitis are also often associated with asthma, and also influence the severity of asthma.

The nose is an organ with several functions, but the single most important one is probably conditioning inspired air, and impairment of this function is related to the presence or severity of asthma.

Nasal and bronchial mucosae share many characteristics, but they differ in a single important aspect, namely, that venous sinuses are present in the nose whereas smooth muscle is present in the bronchi. This difference is responsible for the different clinical repercussions.

Several studies have shown that bronchial inflammation occurs after nasal exposure to an allergen, and that nasal inflammation is present before bronchial provocations.

Bronchial and nasal response to exercise is very different. Most asthmatic patients suffer decreased forced expiratory volume in 1 second after exercise, whereas all healthy subjects or those with other respiratory diseases experience an increase in this parameter and a reduction in nasal resistance.

Systemic dissemination of inflammatory response is the most likely mechanism by which the nose and bronchi are interrelated. Aspiration of mediators, particularly in the gas phase, might be of importance, but this has not been clearly demonstrated.

Several studies have shown clinical improvement and decreased bronchial inflammation after treatment of rhinitis with corticosteroids, antileukotrienes, and antihistamines. Immunotherapy seems to alter the natural course of allergic respiratory disease and prevent the appearance of asthma in subjects with rhinitis. Other treatments such as anti-immunoglobulin E monoclonal antibodies (omalizumab) appear to be the most promising options for management of patients with concurrent asthma and rhinitis. These findings reinforce the epidemiological and pathophysiological data on the interrelationship of asthma and rhinitis and serve to highlight the need for an integrated management of allergic respiratory disease.
SERRANO C, ET AL. RHINITIS AND ASTHMA: ONE AIRWAY, ONE DISEASE


