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# Upper airway disorders and asthma: a syndrome of airway inflammation

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**Objective:** This article presents recent evidence of an upper and lower airway link. After reading this article, readers should have an understanding of the evidence for the pathologic relationship between asthma and upper airway disorders such as rhinosinusitis and allergic rhinitis.

**Data Sources:** Epidemiologic, pathophysiologic, and treatment outcomes studies were used. Only literature in the English language was reviewed.

**Study Selection:** Material was taken from academic/scholarly journals.

**Results:** Epidemiologic data indicate that asthma and allergic rhinitis frequently coexist, with rhinitis symptoms reported among 19 to 94% of asthma patients, and asthma reported among 19 to 38% of those with allergic rhinitis. Allergic rhinitis often precedes asthma symptomatology and has been shown to be a risk factor for the development of asthma. The severity of one's allergic rhinitis also has been shown to be directly correlated with asthma severity. Patients with allergic rhinitis exhibit increased eosinophil activity in both upper and lower airways. In these patients, nasal allergen challenge can induce increased bronchial hyperresponsiveness, suggesting that upper and lower airway disorders share common inflammatory features. Treatment of rhinitis symptoms has been shown to produce better asthma symptom control and, in a few studies, the improvement of airway function in patients with concomitant asthma.

**Conclusions:** Evidence suggests that upper respiratory disorders such as allergic rhinitis and rhinosinusitis are different facets of a larger systemic inflammatory syndrome involving both the upper and lower airways. Several important questions remain to be answered before the nature of the relationship between lower and upper airway disorders is fully understood.

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## INTRODUCTION

A link between upper and lower airway diseases has been suspected for more than 80 years,<sup>1</sup> but the nature of this relationship has remained a subject of debate. Because the upper and lower airways share common histopathologic features, including contiguous ciliated columnar cell epithelial lining, extensive mucinous glands, vasculature, and innervation, at least some link between upper and lower respiratory tract diseases would be expected. Indeed, upper airway diseases, including sinusitis and allergic rhinitis (AR), can precipitate or exacerbate lower airway inflammatory diseases such as asthma.<sup>2</sup>

A clear temporal relationship also exists between upper respiratory disorders and asthma. Approximately 80% of patients with asthma have accompanying symptoms of rhinitis, and up to 60% of the patients with asthma have sinusitis.<sup>3</sup>

AR and rhinosinusitis are related disorders; they coexist in up to 80% of the patients who undergo endoscopic sinus surgery.<sup>4</sup> Although the hallmark symptoms of AR, (sneezing, rhinorrhea, eye and nasal itching, and congestion) are triggered by allergens, the nasal obstruction, facial pain, headache, and purulent discharge characteristic of rhinosinusitis can result from infectious as well as noninfectious causes.<sup>5</sup> Nevertheless, allergy has been

implicated as a pathogenic factor in up to 67% of the chronic rhinosinusitis cases.<sup>6</sup>

The body of evidence strengthening the pathologic relationship between asthma and upper airway disorders such as rhinosinusitis and AR has grown in recent years. Derived primarily from epidemiologic, pathophysiologic, and treatment outcomes studies, the evidence suggests that upper respiratory allergic disorders and asthma may represent facets of a single inflammatory airway syndrome.

## EPIDEMIOLOGIC EVIDENCE OF AN UPPER AND LOWER AIRWAY LINK

Epidemiologic evidence for the coexistence of upper and lower respiratory symptoms extends back more than 80 years. In 1920, Keller<sup>1</sup> reported that among 100 case histories of patients with chest symptoms, 86 presented with concomitant nasal pathology. Keller hypothesized that predominant mouth breathing secondary to persistent nasal congestion may have prevented the proper moistening, warming, and filtering of the air, thus triggering asthma symptomatology. Since then, numerous studies have bolstered the epidemiologic link between asthma and the upper respiratory disorders, AR, and rhinosinusitis. Generally, these studies indicate that rhinitis is present in 28 to 94% of patients with asthma, compared with approximately 20% of the general population. Conversely, 19 to 38% of the patients with rhinitis present with coexisting asthma symptomatology.<sup>7-10</sup>

### *Temporal Relationship*

In a study that included adolescents 13 to 17 years of age with both rhinitis and asthma, 59% either had rhinitis symptoms first or had symptoms ap-

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pear during the same year.<sup>11</sup> Similar results have been observed in college students with both asthma and AR. In these students, 64% experienced rhinitis symptoms before asthma symptoms, and in 21% the onset of these diseases was concurrent.<sup>12</sup> In 7,662 patients who consulted a physician for AR or asthma over a 1-year period, 48% of the asthma patients sought a physician's care because of AR, whereas 17% with AR consulted a physician because of their asthma symptoms.<sup>8</sup> In 25% of the patients, the onset of both diseases occurred within the same year, whereas in 35% the onset of asthma occurred first, and in 40% AR occurred first. These findings support the hypothesis that rhinitis often precedes, and occurs concomitantly with, asthma. However, these studies all have limitations, as they were based on data from questionnaires that were not standardized, and information was based solely on patient recall.

More recently, these limitations were addressed in an analysis of asthma patients involved in three asthma studies at Johns Hopkins University. Their asthma was well characterized, and all underwent skin testing, pulmonary function testing, and methacholine challenge. In addition, standardized questionnaires were used. Across the three databases, coexisting AR occurred in 85 to 94% of the 641 asthmatic patients enrolled.<sup>10</sup> Together, the results of these studies affirm that rhinitis and asthma frequently coexist.

#### Disease Severity

Data suggest that asthma severity is related to the presence of comorbid AR and rhinosinusitis. An analysis of Blue Cross/Blue Shield prescription claims data in New England from 1990 to 1994 found a higher utilization of typical asthma medications such as inhaled corticosteroids, inhaled albuterol, prednisone, and cromolyn, among those patients with coexisting asthma and AR versus those with asthma and no AR. (Fig 1).<sup>13</sup> Similarly, in 1,261 patients with coexisting asthma and AR, there was an apparent

association between the severity of asthma and AR (Table 1). Those whose AR was severe or poorly controlled had worse asthma control and tended to have more persistent asthma than those with mild or well controlled rhinitis.<sup>14</sup>

#### Risk Factors

A longitudinal study estimated the long-term risks for developing asthma and AR in 1,836 college students at Brown University. The students were evaluated for asthma and perennial and seasonal AR during their freshman year in 1963. In the original cohort, asthma, seasonal, and nonseasonal AR were diagnosed in 5.3, 21.1, and 5.2% of the students, respectively. At the 23-year followup, when the subject's age was approximately 40 years, increases of 0.7, 9.8, and 4.3% were noted in the frequency of asthma, seasonal, and nonseasonal AR respectively. Additionally, of the 162 participants who had AR, 10.5% subsequently developed asthma. In contrast, only 3.6% of the participants without previous evidence of AR developed asthma. These findings not only suggest that the prevalence of these atopic diseases continues to increase with age, but also that those with AR were three times more likely to subsequently develop asthma.<sup>15</sup>

At the 28-year followup of the same patients, among the 70 asthmatic participants with AR, asthma was active in 75% with worsening AR, 66% with

unchanged AR, 53% with improving AR, and only 20% with asymptomatic AR. Conversely, AR was active in 92% with coexisting active asthma and 65% with asymptomatic asthma. Asthma symptom control correlated with severity of AR. In parallel, good AR symptom control was related to improvements in asthma.<sup>16</sup> These data illustrate a direct relationship between AR severity and active asthma and therefore suggest that the effective treatment of one condition may improve the other.

#### Rhinosinusitis and Asthma

A recent study showed that rhinosinusitis is often associated with asthma and asthma severity. Chronic rhinosinusitis was evaluated in 69 adults with asthma (35 patients with steroid-dependent asthma and 34 patients with mild-to-moderate asthma) using coronal computed tomography (CT) and clinical scores. The percentage of patients with rhinosinusitis was comparable in both groups: 74% in patients with steroid-dependent asthma and 70% in patients with mild-to-moderate asthma. The CT scans were abnormal in all steroid-dependent asthmatic patients and in 88% of the patients with mild-to-moderate asthma. A significant correlation was shown between clinical and sinus CT scan severity scores in both the severe steroid-dependent group ( $r = 0.8$ ;  $P < 0.0001$ ) and the mild-to-moderate asthma group ( $r = 0.47$ ;  $P < 0.006$ ).

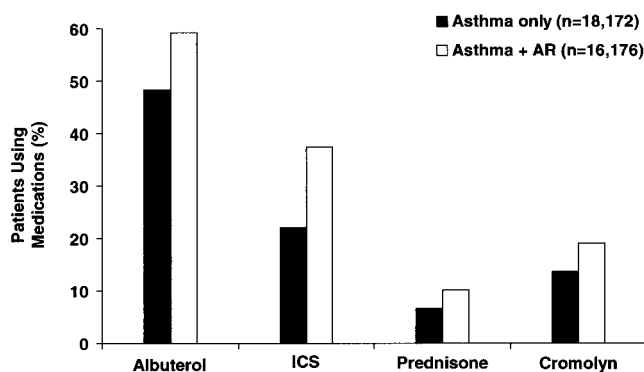


Figure 1. Asthma severity related to AR. An analysis of Blue Cross/Blue Shield prescription claims data from 1990 to 1994 in New England found a higher use of inhaled corticosteroid, inhaled albuterol, prednisone, and cromolyn among patients with coexisting asthma and AR. From reference 13.

Additionally, significant elevations were detected in clinical ( $P < 0.05$ ) and CT scan ( $P < 0.0005$ ) severity scores for patients with severe steroid-dependent asthma versus those with mild-to-moderate asthma.<sup>17</sup> This study demonstrates that rhinosinusitis is common in patients with asthma and the risk for sinonasal involvement appears enhanced in patients with more severe asthma.

Collectively, the epidemiologic data, although far from establishing a definitive cause-and-effect relationship, highlight an important association between upper respiratory disorders and asthma. The data demonstrate that rhinitis and asthma frequently occur together, that asthma severity is directly related to the presence and control of coexisting AR and/or rhinosinusitis, that the onset of asthma and rhinitis may be temporally related, and that rhinitis may be a precursor for asthma in some patients.

## **PATHOPHYSIOLOGIC EVIDENCE OF AN UPPER AND LOWER AIRWAY LINK**

Although there are important differences between upper airway disorders and asthma, strong pathophysiologic parallels occur between these diseases, principally in their histopathologic and immunologic features. Proposed mechanisms for such a pathologic link include

Table 1. Asthma Severity Related to Allergic Rhinitis (N = 1,261)

| Asthma symptom            | Severe allergic rhinitis | Mild or no allergic rhinitis |
|---------------------------|--------------------------|------------------------------|
| Attacks at least weekly   | 64.0%                    | 44.3%                        |
| Awakening nightly         | 19.6%                    | 11.8%                        |
| Any related work loss     | 24.2%                    | 12.1%                        |
| Moderate-to-severe asthma | 60.3%                    | 51.2%                        |

Adapted from data in reference 14.

the propagation of inflammation systemically or through contiguous pathways, loss of nasal protective function, the potentiation of allergens by the nasal mucosa, and the presence of a nasal-bronchial reflex (Fig 2).

### *Shared Inflammation*

AR, rhinosinusitis, and asthma may represent aspects of the same chronic inflammatory syndrome but with different patterns of onset and symptoms. Recent articles have proposed operative definitions and reviewed evidence from scientific literature to support and expound on this concept. Terms introduced included united airways disease, allergic rhinobronchitis, and chronic allergic airways syndrome.<sup>10,18,19</sup>

One such study that illustrated the association between inflammation in the nose and in the airways evaluated whether cellular infiltration was present in the nasal mucosa of asthmatic patients even in the absence of rhinitis symptomatology. It measured

nasal and lung eosinophil counts in asthmatic patients with and without AR and in healthy control subjects. The results showed that activated eosinophil counts, EG2<sup>+</sup> in the lung, were significantly ( $P < 0.01$ ) higher in both asthma groups when compared with the control group. Asthmatic patients, with or without rhinitis, also had elevated EG2<sup>+</sup> positive eosinophils in the nasal mucosa compared with controls. Further, there was a significant correlation ( $r = 0.85$ ;  $P = 0.001$ ) between elevations in both nasal and lung eosinophil counts (Fig 3).<sup>20</sup> This demonstrates that inflammatory cells are present in the nasal mucosa of asthmatic patients even in the absence of rhinitis symptoms.

That asthma and AR share important inflammatory features was further supported by a study in which eight non-asthmatic grass-sensitive patients with AR and eight healthy control subjects underwent segmental bronchial provocation (SBP) with grass pollen extract. Blood samples and bronchial biopsies were taken before and 24 hours after SBP. There was a significant increase in blood ( $P = 0.03$ ) and bronchial mucosa ( $P < 0.05$ ) eosinophil counts in the AR group 24 hours after SBP, as compared with controls, and there was a significant correlation between the two ( $r = 0.49$ ;  $P = 0.05$ ). A significant correlation was also seen between total nose symptom scores and total lung symptom scores ( $r = 0.57$ ;  $P = 0.02$ ). An SBP challenge produced nasal and bronchial symptoms as well as a diminution in pulmonary and nasal function in the AR group.<sup>21</sup> The allergic inflammatory response in the lower airways of nonasthmatic AR patients after SBP challenge, and concomitant increase in inflammatory cells in the nasal mucosa,

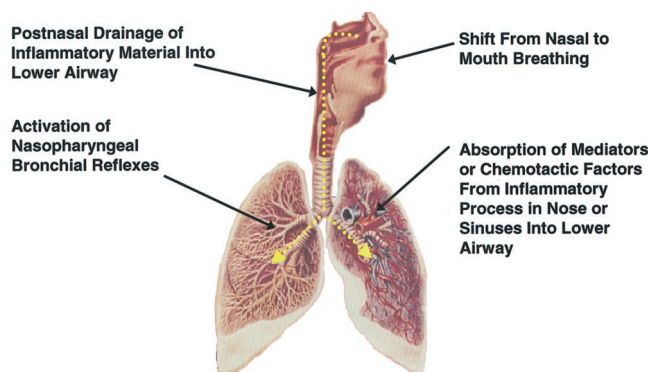


Figure 2. Proposed mechanisms for pathologic link between upper and lower airway diseases. The proposed mechanisms for a pathologic link between upper and lower respiratory diseases include propagation of inflammation systemically or through contiguous pathways, loss of nasal protective function, the potentiation of allergens by the nasal mucosa, and the presence of a nasal-bronchial reflex. (Source pending)

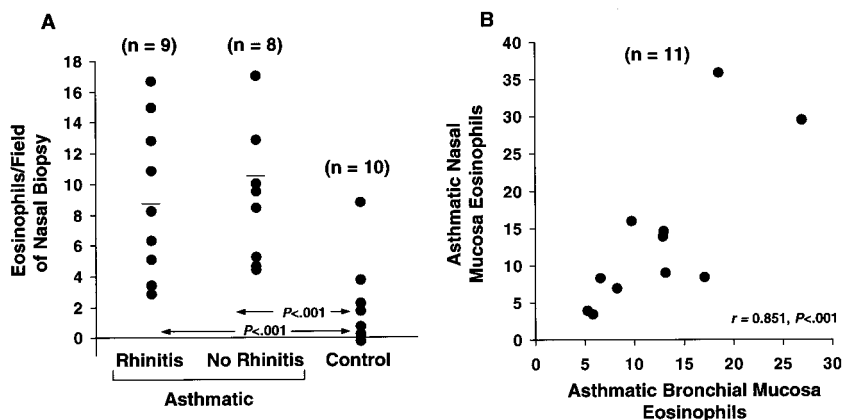


Figure 3. Patients with asthma have nasal inflammation regardless of rhinitis symptoms. Evaluation of cellular infiltration of nasal mucosa biopsies of asthmatic patients with or without AR and in control subjects. (A) Activated eosinophil counts (EG2<sup>+</sup>) were significantly ( $P < 0.01$ ) higher in both asthma groups versus controls. (B) A significant correlation ( $r = 0.85$ ;  $P = 0.001$ ) was found between nasal mucosa and bronchial mucosa eosinophil counts in asthmatic subjects. From reference 20.

underscore the pathophysiologic link between AR and asthma through common inflammatory processes, possibly through a systemic pathway.

Other studies have shown that nasal challenge can induce an increase in bronchial hyperresponsiveness (BHR). A double-blind, placebo-controlled, crossover study explored the relationship between AR and lower airway dysfunction using randomized nasal challenges with either allergen or placebo in 11 subjects with a history of asthma exacerbations associated with seasonal symptoms of AR. The technique used a nasal provocation that limited allergen (timothy grass extract) delivery only to the nose. After the induction of a marked nasal allergic response, no changes were observed in forced expiratory volume in 1 second ( $FEV_1$ ), specific conductance, lung volumes, or peak expiratory flow rates (PEFRs). Yet when compared with placebo, allergen nasal provocation resulted in a significant increase in BHR to methacholine at 30 minutes ( $P = 0.011$ ) and 4.5 hours ( $P = 0.0009$ ) after the challenge.<sup>22</sup> These results demonstrate that although a nasal allergic response may not cause airflow limitation, it can enhance BHR in patients with asthma and AR.

#### Loss of Nasal Protection

The loss of nasal protective function and the development of asthma symptomatology was examined in patients with exercise-induced asthma. Patients underwent exercise-challenges under three conditions: spontaneous breathing, nasal breathing, and mouth breathing. After exercise,  $FEV_1$  decreased 5, 17, and 20% for the patients in the nasal, spontaneous, and mouth-breathing groups, respectively (Fig 4). Mouth breathing secondary to nasal obstruction increased the intensity of exercise-

induced bronchospasm, whereas nasal breathing reduced it.<sup>23</sup> The authors concluded that AR, by consequence of blocking the natural warming and moistening of the air that occurs with nasal breathing, may induce bronchial responsiveness associated with asthma.

More recent studies, however, dispute these conclusions. Two prospective studies were performed in patients with AR. In the first study, the nasal conditioning capacity (NCC), or the ability of the nasal passage to warm and humidify the air, was measured and compared before and during allergy season in 10 patients with seasonal AR. During their allergy season, these patients, when challenged with cold, dry air, demonstrated a significant ( $P < 0.01$ ) increase in NCC versus preseason baseline levels. In the second study, 20 patients with seasonal AR underwent nasal allergen challenge outside their allergy season; NCC was measured before and 24 hours after the challenge. For these patients, there was a significant ( $P = 0.01$ ) increase in NCC 24 hours after allergen challenge compared with their prechallenge baseline. Even with increased nasal epithelial inflammation induced by either seasonal exposure to allergens or antigen challenge, the ability of the nose to condition inspired air remained intact and even increased. According to the

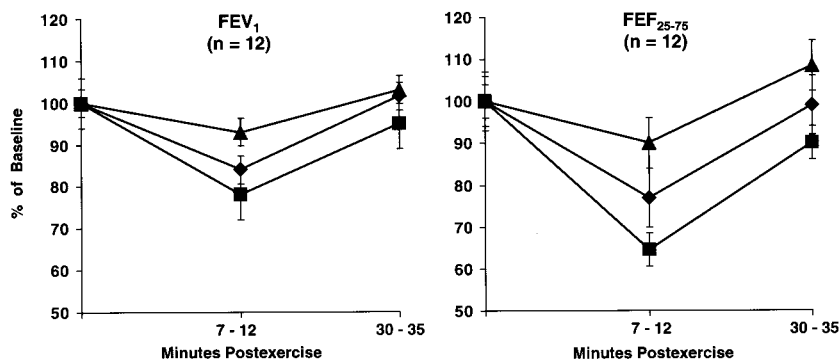


Figure 4. Nasal protective function and asthma. Patients with exercise-induced asthma underwent exercise-challenge testing under three conditions: spontaneous breathing (◆), nasal breathing (▲), and mouth breathing (■). After exercise,  $FEV_1$  decreased 5, 17, and 20% for patients in the nasal, spontaneous, and mouth-breathing groups, respectively. Mouth breathing secondary to nasal obstruction increased the intensity of exercise-induced bronchospasm, whereas nasal breathing reduced it. From reference 23.

authors, increased local inflammation of the nose produces increased amounts of secretions, and thus more water to humidify inspired air and increased heat. Another resultant effect was the increased surface area of contact between inspired air and the nasal mucosa. The resultant effects of AR on the lower airways are probably mediated primarily through other mechanisms other than disruption of airway mechanics.<sup>24</sup>

#### *Allergen Potentiation*

It has been proposed that the nasal mucosa may process allergens into a form more capable of inducing nasal and bronchial reactions. In one study, Phl p 5, a major allergen in timothy grass that can cause rhinitis and bronchial asthma symptoms, was converted to smaller molecular forms by proteolytic enzymes found in nasal secretions. In allergic patients, skin prick testing with the fragmented protein ranging in sizes between 10 and 20 kD induced a significantly greater allergic response, as measured by wheal area and histamine release assays, than the parent protein. In contrast, pancreatic secretions completely degraded the Phl p 5 and almost completely eliminated its allergenicity. Thus, proteolytic degradation of Phl p 5 in the nasal mucosa may result in peptide fragments of a size more allergenic than the parent compound.<sup>25</sup> More studies are needed to replicate these results and elucidate on the mechanisms of increased antigen immunogenicity and its clinical implications.

#### *Nasal-Bronchial Reflex*

More than 30 years ago, the existence of a nasal-bronchial reflex was proposed as a possible basis for a physiologic connection between upper and lower respiratory tract disorders. In this paradigm, nasal stimulation promotes bronchoconstriction through a reflex arc with the afferent arm located in the pharyngolaryngeal area, a central locus possibly in the hypothalamic area and vagal efferents. The study that highlighted this theory included six patients without lung disease who underwent unilateral tri-

geminal nerve resection for trigeminal neuralgia. Subsequently, lung volume and resistance were evaluated before and after 10 to 15 minutes of nasal challenge with silica particles. This natural irritant is known to induce nonspecific bronchoconstriction. Upon insufflation in the nares on the side where the trigeminal nerve was intact, a decrease in lung function and bronchoconstriction was effected, whereas no bronchoconstriction was effected upon insufflation in the nares on the resected side. Bronchoconstriction in response to nasal silica was inhibited by previous topical atropine administration, suggesting that the bronchoconstriction could have resulted from activation of a cholinergic reflex arc.<sup>26</sup> Since that early study, however, no definitive studies have been able to define and identify the exact components of this reflex arc and its physiology. Further, the clinical implications of this theory have not been realized or shown.

Overall, there are growing data that the pathophysiologic link between AR and asthma could be explained mainly by systemic inflammatory processes. Several key questions need to be answered to shed clarification on this paradigm, however.

#### **THERAPEUTIC EVIDENCE OF AN UPPER AND LOWER AIRWAY LINK**

Therapeutic response studies have provided further evidence buttressing the link between upper respiratory disorders and asthma. Generally, when one of these disorders responds to treatment, the other shows improvement as well, thus pointing to a common pathologic mechanism.

In a randomized, double-blind crossover study, 21 patients (mean age 10 years) with perennial AR and asthma and documented lower airway hyperresponsiveness were treated with intranasal beclomethasone dipropionate and placebo, each for 4 weeks. Outcomes measured included symptom scores, AM and PM PEFs, and response to methacholine challenge (a concentration of methacholine suffi-

cient to induce a 20% decrease in FEV<sub>1</sub> [PC<sub>20</sub>]). These were measured at baseline and at the end of each of the treatment periods. After 4 weeks of treatment, intranasal beclomethasone significantly ( $P = 0.05$ ) reduced global rhinitis symptom scores. Significant changes were not seen in global asthma scores or PEFs. Yet PC<sub>20</sub> methacholine measures improved significantly ( $P = 0.04$ ) after intranasal beclomethasone, but not after placebo, suggesting that treatment of inflammation in the upper airway can decrease bronchial hyperreactivity.<sup>27</sup>

In another study, 12 patients with cat allergies, 6 of whom had concurrent asthma, underwent 1 hour of cat exposure in an enclosed room at baseline and after 1 week of treatment with either intranasal triamcinolone or placebo. In this setting, patients underwent nasal as well as lung challenge to cat dander. After the intranasal corticosteroid treatment, lower respiratory and nasal symptoms were significantly reduced. Previous triamcinolone use also resulted in improvement in FEV<sub>1</sub>, ( $P < 0.05$ ) but only at one time-point (T+30 minutes).<sup>28</sup> This study suggests that treatment of the upper airway with nasal corticosteroids improves both upper and lower airway symptoms after allergen exposure and can possibly improve indices of airway obstruction.

The role of systemic therapy in the treatment of both rhinitis and asthma has also been investigated. A double-blind, randomized, parallel-group study explored the effects of cetirizine (10 mg daily) versus placebo in 186 patients with AR and mild-to-moderate bronchial asthma. The study was conducted during a well defined fall pollen season, a period during which the patients displayed symptoms of AR. During this 6-week study, symptoms were evaluated twice daily and spirometry was performed weekly. Although rhinitis symptoms worsened for patients treated with placebo, significant ( $P < 0.05$ ) improvements were noted after cetirizine treatment in both rhinitis and asthma symptoms. No differences were seen between groups in pulmonary function, which did not deterio-

rate with the onset of allergy season.<sup>29</sup> These results suggest that therapeutic antihistamine doses can improve both nasal and bronchial symptomatology, but that other mediators of inflammation involved must be targeted to produce improvements in pulmonary function.

The combination antihistamine/decongestant was evaluated in a 6-week, randomized, double-blind, placebo-controlled trial. The efficacy of loratadine (5 mg) plus pseudoephedrine (120 mg) twice daily was evaluated in 193 patients with seasonal AR and mild asthma. Compared with placebo, the concomitant administration of loratadine/pseudoephedrine produced significant reductions in total rhinitis and asthma symptom scores throughout the study and significant increases in PEFR at weeks 2 through 6. Improvements were also noted in quality of life measures in the loratadine/pseudoephedrine group.<sup>30</sup> This study is one of the few to show a significant improvement in pulmonary function indices with antihistamine therapy in patients with asthma symptoms.

The above studies demonstrate the efficacy of both antiinflammatory medications and those that target specific mediators involved in AR in alleviating both rhinitis and asthma symptoms in those with concomitant disease. A recent study compared the effects of combined mediator blockade using an antihistamine (cetirizine) and a leukotriene receptor antagonist (montelukast) to combined inhaled and intranasal use of corticosteroid (budesonide) on asthma in people with both asthma and AR.<sup>31</sup> Both combined mediator blockade and combined topical steroid use improved asthma symptom scores, PEFR measurements, and decreased the need for rescue inhaler use. Allergic rhinitis symptom scores were not reported. The combined mediator blockade resulted in decreased BHR compared with topical steroid use, but there was no diminution in exhaled nitric oxide. The decrease in this asthma inflammatory marker was only realized in the topical steroid group. This study shows that although both treatment strategies are effective ther-

apeutic options for asthma control in those who have AR and asthma, further understanding is needed on how these medications modulate immune responses to achieve efficacy. Further, this study further strengthens the pathophysiologic link between AR and asthma through common mediators and inflammatory properties.

Immunotherapy was also evaluated in the treatment of coexisting rhinitis and asthma. A double-blind, randomized, placebo-controlled, parallel group, 3-year study that included 44 patients with seasonal AR (36 with asthma symptoms and 28 with BHR) examined the effects of grass pollen immunotherapy on symptoms, BHR, and quality of life. After symptom monitoring for one summer, patients received injections of either grass-pollen vaccine or placebo for 4 weeks, followed by monthly injections for 2 years. Compared with placebo, significant reductions were observed in seasonal AR symptoms ( $P = 0.01$ ), need for asthma rescue medication ( $P = 0.007$ ), and seasonal chest symptoms ( $P < 0.05$ ) in the immunotherapy group. Further, during the pollen season, no changes were noted in airway methacholine PC<sub>20</sub> in the immunotherapy group versus a significant reduction in the amount needed (32 to 4.5 mg/mL) to induce bronchoconstriction in the placebo group ( $P = 0.04$ ). Additionally, impairment in quality of life during the pollen season was significantly ( $P = 0.02$ ) less in the immunotherapy group when compared with the placebo group.<sup>32</sup> Thus, grass pollen immunotherapy can be a useful tool in reducing seasonal asthma symptoms and BHR, as well as in improving quality of life in patients with seasonal AR and asthma.

The production of systemic immunoglobulin (Ig)E antibodies to culprit antigens is the sine qua non of AR. Elevations of these antigen-specific IgE antibodies can be induced by both seasonal allergen exposure and repeated nasal challenges.<sup>33</sup> Consequences of increased systemic circulation of specific IgE antibodies and repeated allergen exposure through in-

duction of downstream mediators from mast cells and basophils are realized in several end-organs of allergy including the skin and respiratory tract.<sup>34</sup> The recent introduction of an IgE monoclonal antibody (omalizumab) offers a new approach in treating both AR and asthma. Phase 3 clinical trials have established safety and efficacy for use in both conditions, and it would be very plausible that treatment of AR with this modality would lead to improvement of asthma in those with concomitant disease.<sup>35,36</sup>

## CONCLUSION

Recent evidence has shed more light on the link between upper respiratory disorders such as AR and rhinosinusitis and asthma, but it has not completely defined the relationship. A debate continues as to whether asthma and upper respiratory disorders are causally linked or whether they represent manifestations of the same underlying immunologic disorder. Clinical data show a temporal link between rhinitis and asthma. Studies suggest that rhinitis is a risk factor for the development of asthma. A direct relationship has also been shown between presence of and poor control of AR with asthma severity. Growing evidence suggests shared systemic inflammatory processes between rhinitis and asthma. Finally, there is a significant amount of literature showing that treatment of AR through various modalities with the capacity to modulate different aspects of the inflammatory cascade leads to improvement in concomitant asthma. Thus, it is reasonable to propose that these conditions are part of a larger systemic inflammatory syndrome encompassing the upper and the lower airways. The signs and symptoms of this syndrome may vary depending on whether it principally affects the nose, sinuses, or lower airways; nevertheless, the presence of inflammation remains a constant.

Several important questions remain to be answered before the nature of the relationship between lower and upper airway disorders is fully understood. First, does the allergen travel from the

nose to the lung? Second, are there qualitative and quantitative differences in the nature of the allergen or in the way that it is processed that induce a specific response in the nose and in the lung? Third, are there differences in the immunologic milieu in the nose and in the airways that allow them to respond differently to a specific allergen? Fourth, what is the role of priming and repeated viral infections in antigen processing and end-organ response in these conditions? Are there genetic trademarks that account for these differences?

Further, in those patients where rhinitis precedes asthma, future research will also need to explore how rhinitis may be a risk factor for asthma and whether timely rhinitis treatment can delay, or even prevent, asthma development. In the primary care setting, prompt recognition and diagnosis of AR may be the first step in the identification of a systemic inflammatory syndrome that can encompass both upper and lower respiratory disorders.

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