

# The united allergic airway: Connections between allergic rhinitis, asthma, and chronic sinusitis

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## ABSTRACT

**Background:** The united allergic airway is a theory that connects allergic rhinitis (AR), chronic rhinosinusitis, and asthma, in which seemingly disparate diseases, instead of being thought of separately, are instead viewed as arising from a common atopic entity.

**Objective:** This article describes patients with such diseases; explores ideas suggesting a unified pathogenesis; elucidates the various treatment modalities available, emphasizing nasal corticosteroids and antihistamines; and provides an update of the literature.

**Methods:** A literature review was conducted.

**Conclusion:** The aggregation of research suggests that AR, asthma, and chronic rhinosinusitis are linked by the united allergic airway, a notion that encompasses commonalities in pathophysiology, epidemiology, and treatment.

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Allergic rhinitis (AR) occurs when the nasal passages become inflamed; it is characterized by rhinorrhea, nasal congestion, postnasal drip, and itchiness of the nose. The inflammatory cascade in AR involves an immediate IgE-mediated mast cell response and a late-phase response of basophils, eosinophils, and T cells driven by the cytokines IL-4 and IL-5.<sup>1</sup> In adults, risk factors for AR include eczema and a family history of atopy.<sup>2</sup> In children, risk factors for AR include maternal cigarette smoking and higher blood IgE levels.<sup>3</sup> Since the onset of the Industrial Revolution, AR has become the most common atopic disorder in the United States, affecting 20–40 million people annually, including up to 30% of adults and 40% of children.<sup>4,5</sup> Asthma, on the other hand, involves inflammation of the bronchial tree and can cause wheezing, shortness of breath, coughing, and chest tightness. This condition, compared with AR, is far more prevalent at a younger age and affects 10% of children and 8% of adults.<sup>6</sup>

Although AR, on the spectrum of medical afflictions, is considered a relatively benign disease, patients with AR can have an impaired quality of life, with difficulty sleeping, exhaustion during the day, cognitive disturbances, and mood changes.<sup>7</sup> Having AR also causes socioeconomic consequences, because patients are forced to take time off from school and work.<sup>8,9</sup> Patients with asthma, by contrast, are more likely to have physical limitations, impacting both their activities of daily living, such as going up stairs and performing chores, and their ability to exercise. However, in patients with both asthma and AR, there are more physical limitations when compared with AR-only patients, but no further impairment in quality of life.<sup>7</sup>

## ALLERGIC RHINITIS AND ASTHMA

AR and asthma, rather than being considered two distinct diseases, can be unified by the concept of a “united airway,” where allergic symptoms of the upper and lower airways can be thought of as manifestations of a common atopic entity.<sup>10</sup> Epidemiological evidence suggests a strong relationship between AR and asthma. AR can occur in >75% of patients with asthma, whereas asthma can affect up to 40% of patients with AR.<sup>11</sup> Both diseases, which are IgE mediated, can be triggered by similar allergens, including mold, animal dander, and house-dust mites.<sup>12,13</sup> Temporally, AR often occurs before the onset of asthma. In a 10-year longitudinal study of children with AR, asthma was eventually found in 19% of cases, and in 25% of the sample size, asthma and AR developed simultaneously.<sup>12</sup>

Indeed, AR is a risk factor for asthma, and its presence is related to asthma severity. For example, in a 23-year follow-up study of almost 2000 college students, patients with AR, when compared with controls without AR, were about three times more likely to develop asthma.<sup>14</sup> This idea was confirmed by a 15-year prospective study of Finnish twins, which found that in patients with AR, male patients were four times and female patients were six times as likely to get asthma when compared with patients without AR.<sup>15</sup> Taking this notion one step further, Guerra *et al.*<sup>11</sup> found that, after adjusting for age, sex, atopic status, years of follow-up, smoking status, and the presence of chronic obstructive pulmonary disease, AR was still an independent risk factor for asthma. Of importance, AR and asthma were linked, autonomous of the fact that they shared atopy as a common causal agent.

In addition to the epidemiological evidence, several clinical reports point to a common pathophysiological relationship between AR and asthma. In the 1980s, allergists noted not only that AR patients hyperresponsive to methacholine had a greater risk of developing asthma, but also that the increase in bronchial reactivity was correlated with the pollen season.<sup>16,17</sup> These findings were confirmed in studies led by Ciprandi and colleagues, who showed that in a majority of patients with AR but no asthma, there is an increase in bronchial hyperreactivity (BHR) after methacholine challenge.<sup>17,18</sup> Moreover, in the subset of patients with BHR, there is impairment in spirometry, including forced vital capacity, forced expiratory volume in 1 second (FEV<sub>1</sub>), and forced expiratory flow at 25–75%.<sup>17,18</sup> More recently, Ciprandi *et al.*<sup>19</sup> showed that ~2/3 of patients with AR showed reversibility to bronchodilation testing (defined as an increase of >12% in

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basal FEV<sub>1</sub> values), despite having normal baseline FEV<sub>1</sub> measurements. In fact, a forced expiratory flow at 25–75% value of  $\leq 58.5\%$  predicts BHR and reversibility in patients with AR, and an FEV<sub>1</sub>  $< 83\%$  is a good marker for early bronchial impairment in children with AR.<sup>20,21</sup>

Four mechanisms have been postulated to account for the relationship between asthma and AR.<sup>22</sup> First, the nose, by virtue of its anatomic location, warms, filters, and humidifies inhaled air. In fact, exercise-induced bronchospasm is caused by cooling and drying in the airways, which occurs with obligate mouth breathing during vigorous activity. In addition, *via* the numerous submucosal glands located in the nasal passages, the nose is able to sterilize air through the release of antibacterial enzymes. With AR, nasal function may be partially or completely lost as the congestion forces the patient to become a mouth breather. Second, during an exacerbation of AR, the inflammatory products from the upper airways may be aspirated directly into the lower airways. Third, nasal inflammation may result in local cytokine release into the bloodstream, which eventually causes bronchoconstriction in the lower airways. Fourth, a nasal-bronchial reflex may exist, where histamine and bradykinin stimulate the afferent nasal sensory nerve. The neural signal then travels to the central nervous system and activates the efferent vagus nerve, resulting in bronchial smooth muscle hyperreactivity.

The etiology for the connection between asthma and AR is likely multifactorial. The data supporting a nasal-bronchial reflex is controversial. Although nasal blockage and aspiration of nasal contents have long been accepted as contributing factors, there is a growing body of evidence that suggests that a systemic response plays an important role in the AR-asthma relationship. For example, in patients with seasonal AR but no asthma, nasal allergen testing not only instigates bronchial airway responsiveness, but also increases eosinophil counts in the sputum samples of these patients.<sup>23</sup>

In another study, bronchial and nasal biopsy specimens were taken before and 24 hours after nasal allergen testing in patients with AR. At the 24-hour time point, there was an increase in eosinophils in both the nasal and the bronchial epithelium.<sup>24</sup> By the same token, segmental bronchial provocation in nonasthmatic AR patients resulted in inflammation in the nose, as well as an increase in peripheral blood eosinophilia.<sup>25</sup> Supporting the idea from a different angle, a study showed that eosinophil infiltration was present on nasal biopsy in asthmatic patients who did not have AR.<sup>26</sup> Ultimately, the eosinophilia, in both the upper and the lower airways results from an increase in inflammatory cytokines, especially IL-5.<sup>27,28</sup>

If AR and asthma are linked, then it should not be surprising that treating AR will also improve asthma symptoms. This was first noticed in 1984, when intranasally administered beclomethasone and flunisolide were, in asthmatic patients, found to markedly reduce self-reports of shortness of breath and wheezing.<sup>29</sup> Subsequent more quantitative studies supported this notion. For instance, 4 weeks of intranasal budesonide was found to reduce the severity of exercise-induced asthma in children, as measured by FEV<sub>1</sub>,<sup>30</sup> and 5 weeks of intranasal beclomethasone led to a decrease in bronchial responsiveness.<sup>31</sup>

Furthermore, in a separate crossover study, patients with AR but no asthma were found to have decreased bronchial hyperresponsiveness after 2 weeks of intranasal beclomethasone, but no change from baseline after 2 weeks of bronchial beclomethasone.<sup>32</sup> Although these studies, taken together, suggest that treating AR will help control asthma, it is important to note that their sample sizes were small, ranging from 11 to 26 patients. Indeed, a much larger study of 262 subjects randomized patients to either 6 weeks of intranasal fluticasone, inhaled fluticasone, their combination, or inhaled placebo, and found that only inhaled fluticasone—and not intranasal fluticasone—was effective in controlling bronchial reactivity.<sup>33</sup> Thus, whether nasal steroids are effective in treating asthma is still subject to debate. Although nasal corticosteroids are of questionable efficacy, antihistamines, the first-line treatment for AR, have been shown to be highly

effective in treating asthma. Antihistamines, when compared with nasal corticosteroids, are systemic, rather than local, medications that directly target the histamine receptors on mast cells and T cells, in the process stabilizing these cells and promoting anti-inflammatory activities. The presence of histamine receptors in both the nasal passages and the lungs, and the fact that AR and asthma are simultaneously improved with antihistamines, provides further support for the united airway hypothesis.

One of the first large studies indicating that an antihistamine treats AR as well as asthma randomized 186 patients with both conditions to receive placebo or cetirizine, a second-generation H<sub>1</sub>-antagonist, for 6 weeks.<sup>34</sup> Cetirizine-treated patients reported a significant improvement in chest tightness, wheezing, shortness of breath, cough, and nocturnal asthma when compared with controls. Similarly, a study published by Spector *et al.*<sup>35</sup> evaluated pulmonary function tests in 12 asthmatic patients who were given varying doses of oral cetirizine (5, 10, and 20 mg) as well as albuterol. All three cetirizine doses were found to significantly improve pulmonary function measures throughout the 8-hour testing period and provided a demonstrable bronchodilatory effect. At the same time, the administration of both albuterol and cetirizine appears to have an additive bronchodilatory effect. And finally, Ubier *et al.*<sup>36</sup> randomized asthmatic patients to either cetirizine at 10 mg daily or placebo for 2 weeks, after which there was a marked improvement in bronchial hyperresponsiveness, as measured by methacholine challenge.

The use of antihistamines in combination with other medications has also shown promise in asthma treatment. In a randomized trial conducted by Corren *et al.*,<sup>37</sup> 193 patients with a history of seasonal AR and asthma were administered a combination of loratadine and pseudoephedrine, or placebo, for 6 weeks. Both groups were evaluated daily for nasal symptoms, chest symptoms, albuterol use, and peak expiratory flow rates, as well as with weekly spirometry. By the end of the study, the total nasal symptom score, total asthma symptom score, peak expiratory flow rates, weekly FEV<sub>1</sub>, and asthma quality of life measures were all significantly improved when compared with placebo.

Ultimately, the treatment of AR not only reduces the physical symptoms of asthma, but also has beneficial socioeconomic consequences. One retrospective cohort study examined, over the course of a year, the rate of asthma-related emergency room (ER) visits and hospitalizations in patients with asthma and AR after they were treated with AR medications.<sup>38</sup> Of 4944 subjects, 3587 patients were treated for AR, and 1357 patients were untreated. Asthma-related hospitalizations fell from 2.3 to 0.9 (61% decrease), and the incidence of two or more asthma-related ER visits decreased from 1.3 to 0.6 per patient (54% reduction). These findings were corroborated in a case-control study, which showed that patients with both AR and asthma, who were treated with intranasal corticosteroids, had a significantly lower risk of both asthma-related ER visits and hospitalizations.<sup>39</sup> Moreover, treatment with both intranasal steroids and second-generation antihistamines was associated with an even lower risk of ER visits or hospitalization.

## ALLERGIC RHINITIS AND SINUSITIS

Patients afflicted with allergies have a predisposition for developing sinusitis. One study determined that both disorders exist in the same patient 25–70% of the time,<sup>40</sup> and another study found that 72 of 121 patients with chronic nasal symptoms and positive skin tests for allergies had positive sinus computed tomography scans showing sinusitis.<sup>41</sup> By the same token, asthma severity is associated with a more severe clinical presentation of rhinosinusitis.<sup>42</sup> Moreover, Berrettini *et al.*<sup>43</sup> found a statistically significant increase in sinusitis on computed tomography scans in patients with perennial AR when compared with a control group, and Baroody *et al.*<sup>44</sup> determined that nasal allergen challenge induced eosinophilic inflammation in the maxillary sinus. Finally, in a cohort of patients with chronic sinusitis

who were challenged with nasal allergen provocation tests, 41 positive nasal responses occurred in 29 patients. Of the 41 nasal responses, 31 were associated with radiographic changes on Water's view sinus radiographs, including increased mucosal edema and opacification of the sinuses, suggesting that nasal allergens trigger changes in the mucosal membranes of patients with sinusitis.<sup>45</sup>

The etiology of the link between AR and sinusitis is, akin to the etiology between AR and asthma, likely multifactorial. Anatomically, patients with AR have edematous nasal mucosa, damaged nasal cilia, and overproduction of secretions, which could lead to a blockage of ostial drainage from the sinuses. This blockage results in stagnant debris that then becomes infected. From an immunologic perspective, eosinophils, more prevalent during an AR flare, can cause chronic inflammation in the mucosa, even when bacteria are not present.<sup>43</sup> Notably, patients with both allergies and sinusitis, when compared with patients with nonallergic sinusitis, have a distinct cytokine profile, with nasal polyp tissue that shows an increase in granulocyte macrophage colony-stimulating factor, IL-3, IL-4, and IL-5, along with an increased density of CD3<sup>+</sup> T lymphocytes.<sup>46</sup>

Although chronic rhinosinusitis (CRS) can develop independently of allergic pathways, there is a group of patients, diagnosed with allergic fungal rhinosinusitis (AFRS), whose sinusitis and nasal polyposis are related to allergic inflammation. Hutcheson *et al.*<sup>47</sup> compared the antibody responses in 64 patients with AFRS to 35 patients with CRS and found no evidence of allergic disease. In the AFRS cohort, serum total IgE, mean IgG anti-*Alternaria*-specific antibodies, and the mean number of IgE antifungal antibody bands on immunoblotting, were all increased, showing that AFRS is a distinct entity from CRS, with a unique allergic etiology. Although the existence of AFRS does not necessarily support the notion of a united airway, the fact that sinusitis can arise directly from allergic inflammation indicates the close relationship between allergies and rhinosinusitis.

Of course, AFRS is not the only clinical entity associated with nasal polyposis—nasal polyps are found in a number of other diseases, including cystic fibrosis, aspirin-exacerbated respiratory disease, and Churg-Strauss syndrome.<sup>48</sup> Furthermore, a retrospective study revealed that of 4986 hospitalized patients, 6.7% of asthmatic patients, 5% of CRS patients, and 2.2% of rhinitis patients had nasal polyps.<sup>49</sup> Interestingly, IgE-mediated pathways are thought to play a role in the pathogenesis of nasal polyposis, providing further support for the connection between allergies and sinusitis. Specifically, Bernstein *et al.*<sup>50</sup> discovered increased serum levels of IgE antibodies to both *Staphylococcal* enterotoxin B and toxic shock syndrome toxin in CRS patients with nasal polyps, when compared with controls. Moreover, there were high levels of IgE against *Staphylococcal* enterotoxin A and B in the nares of these same patients. Thus, *Staphylococcus aureus* exotoxins may act as superantigens in the nasal mucosa of CRS patients. Subsequently, IgE antibodies directed against these exotoxins create a local allergic inflammatory reaction, resulting in the growth of nasal polyps. Indeed, the presence of *S. aureus* actively affects the clinical course of rhinosinusitis by augmenting the inflammatory response in nasal polyposis while also increasing local IgE production in the nares.

## CONCLUSION

The aggregation of research suggests that AR and asthma are, in fact, one syndrome in two parts of the respiratory tract—this notion is supported pathophysiologically, epidemiologically, and through numerous clinical studies. Being afflicted with AR is often the harbinger of asthma at a future date. By the same token, allergies are associated with an increased likelihood of having sinusitis, with a common pathophysiology, and possibly treatment, tying the two disorders together. Ultimately, we can posit that the united airway—where AR, asthma, and sinusitis are inextricably linked—truly exists. Thus, when entertaining a diagnosis of asthma, an evaluation of the upper airways should be considered.<sup>51</sup> In addition, when treating sinusitis,

attention should be given to the management of any concurrent AR as well.

The information we have, to date, although promising, leaves a number of questions that still require addressing. What is the exact inflammatory cascade that leads a patient with AR to independently have bronchial hyperactivity, and *vice versa*? Has the severity and epidemiology of the diseases changed with the onset of a new generation of medications? What is the optimal treatment of patients with both AR and asthma? And how can we better elucidate the relationship between sinusitis and asthma? We eagerly await the answers in future studies.

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