

Aeroallergen sensitization in asthma: Prevalence and correlation with severity

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ABSTRACT

Aeroallergen sensitization occurs in most patients with asthma and is noted in a high percentage of patients with mild and moderate asthma. The percentage of those that are atopic with severe asthma appears less, but still approximates the percent seen in patients with mild and moderate asthma. The objective of this study was to review the prevalence of positive skin tests and atopic disease in patients with asthma. A review was performed of the literature with searches to include "skin test and asthma," "allergic asthma," and "allergies and asthma" in both PubMed and Ovid and selected articles that were relative to our objective. Most studies highlight the significances that allergic disease plays in asthma. However, the prevalence of allergic disease in mild to moderate asthma ranges from 50 to 95% and recent data suggest that 95% may be very accurate. In severe asthma the percentage is less, but still recent data suggest it may be as high as 90%. Patients with high IgE, high exhaled nitric oxide (eNO), low provocative concentration of methacholine causing a 20% fall in forced expiratory ventilation in 1 second (PC₂₀) and minority ethnicity have a higher number of positive skin tests and presumably are hypersensitive to more aeroallergens. Patients with late-onset asthma are less likely to be allergic; nonetheless, the vast majority even >65 years of age have an allergic component to their disease. Female gender, late-onset asthma, nasal polyps, severe asthma, and, possibly, patients with a reaction to autologous serum injection increases the likelihood that asthma may be nonallergic, as defined by negative skin tests. The vast majority of patients with mild-to-moderate and even severe asthma have an allergic component to their disease. Avoidance, omalizumab, and allergen immunotherapy may be useful in all severities of asthma, even in the elderly, if indicated and not contraindicated. As many as 90–95% of patients with asthma have aeroallergen sensitization and the pattern varies with ethnicity, location of residence, and onset of asthma, but not age. Higher levels of IgE and eNO and lower values of PC₂₀ are noted in patients with asthma and aeroallergen sensitization.

(Allergy Asthma Proc 31:96–102, 2010; doi: 10.2500/aap.2010.31.3310)

Key words: Aeroallergens, allergies, asthma, autologous skin test, hypersensitivity, mild asthma, moderate asthma, severe asthma, skin testing

Asthma and other IgE-mediated diseases continue to increase in prevalence in the United States and throughout the world.¹ Allergens, both occupational and environmental, comprise one of the multiple triggers for asthma, along with others, including exposure to tobacco smoke, air pollution, viral infection, irritant exposure, exercise, cold dry air, and sinusitis. Skin testing and *in vitro*-specific IgE testing are both sensitive and specific and have been

used to objectively determine patient sensitization to allergens that may be a trigger for asthma and other allergic disorders.^{2–5} Allergic sensitization to aeroallergens has been shown to vary by economic status, location, ethnic identity, and other factors.^{6–11} More recently, correlations between aeroallergen sensitization and asthma characteristics in a large number of objectively diagnosed patients with mild-to-moderate asthma has been established.⁹ Another recent study using patient recall of skin test reactivity in those with severe asthma suggested that the vast majority of such asthmatic patients were allergic to aeroallergens.¹² Patients with asthma that are more likely to be free of hypersensitivity to aeroallergens include those with late-onset asthma, those with nasal polyps and aspirin sensitivity, and possibly those with skin test positivity to autologous serum.^{13–15} It was our objective to review the recent literature on aeroallergen hypersensitivity and asthma and to summarize these data in this article.

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Presented at the Eastern Allergy Conference, Palm Beach, Florida, May 3, 2009

T. Craig has nothing to disclose pertaining to this article

Supported from an educational grant from Genentech and Novartis

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Table 1 Review of five publications and percent positive to aeroallergens

	ACRN ⁹	Ogershok <i>et al.</i> ¹⁰	Knudsen <i>et al.</i> ¹⁵	Inner City ¹⁶	Huss <i>et al.</i> ²⁸
Subject no.	1338	687	1186	927	
Age	Adult	Children	Adults	Children	Elderly adults
Seasonal allergies only	2%				
Perennial allergies only	26%				
Both perennial and seasonal	67%				
Cockroaches	38%			69%	
Mites	56% DF, 61% DP			62%	
Mice				22%	
Molds		32%		50%	
Seasonal	95%	70%			
Perennial		70%			
Percent with positive to aeroallergen	95%		61%		75%

ACRN = Asthma Clinical Research Network.

METHODS

We reviewed the literature with searches to include "skin test and asthma," "allergic asthma," and "allergies and asthma" in both PubMed and Ovid and selected articles that were relative to our objective (Table 1). In addition, we summarized findings of a recent study that described characteristics of subjects with asthma who participated in the Asthma Clinical Research Network (ACRN) investigations and complemented these data with additional references.⁹

RESULTS

Allergic sensitization to aeroallergens has been shown to vary by economic status, location, ethnic identity, and other factors.⁶⁻¹² Recently, we assessed the data of 1338 subjects who participated in the ACRN⁹ investigations. Patients ranged in age from 12 to 65 years with 58% being female and 42% male patients. Ethnicity distribution included 65% white, 21% black, 8% Hispanic, and 6% others populations. Ninety-five percent of the ACRN subjects had at least one positive skin test and were considered to have aeroallergen sensitization. The average number of positive tests per subject was five and 81% had a positive reaction to three or more allergens. Most subjects had positive tests to both perennial and seasonal allergens (67%); however, 26% were positive only to perennial antigens and 2% were positive only to seasonal allergens. Further exploration of these data failed to suggest that age influenced the number of positive tests to which subjects were positive to or to the percentage that were positive to at least one allergen (Figs. 1 and 2⁹). In the 6th decade of life 89% had at least one positive skin test. These data help to confirm that allergic sensitization is not lost with increasing age in patients

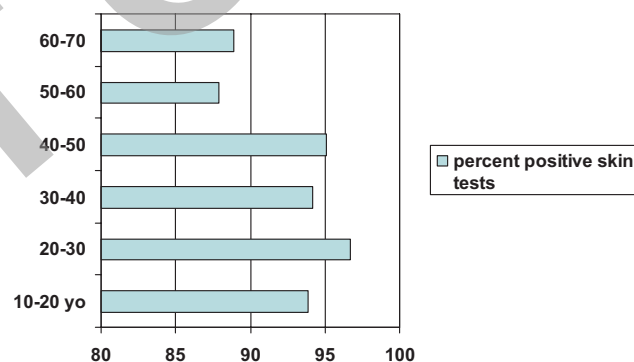


Figure 1. Percent positive skin tests per decade of life ($p = \text{NS}$). (Modified from Ref. 9.)

with asthma. Nonetheless, the decade of onset of asthma did influence the probability of having positive skin tests and subjects with onset of asthma before 30 years of age were more likely to be sensitive to aeroallergens (96%) than those whose onset of asthma was later (88%; $p = <0.001$).

Ogershok and colleagues¹⁰ recently published data suggesting that acquisition of pollen allergies starts at a younger age than anticipated. They evaluated 687 children with asthma with skin testing to pollen and perennial allergens over a 10-year period of time. Although sensitization to pollen allergens after the age of 12 years did not change according to the ACRN⁹ studies, during early childhood, as expected, pollen allergies changed.¹⁰ No child <12 months of age had positive tests, but by the age of 2 years, 27% of children with asthma were positive to pollens. By 3 years of age the rate of positivity to pollen approached the level of positivity for perennial allergens. The incidence of positive tests to pollen was 46% by the age of 4 years. The

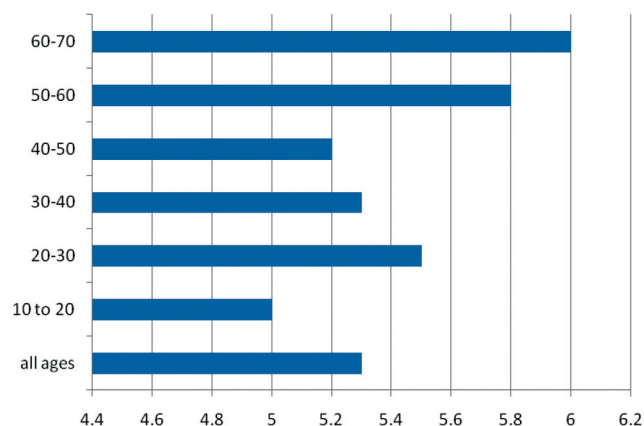


Figure 2. Number of skin tests per decade of life ($p = NS$). (Modified from Ref. 9.)

three pollen allergens that were most frequently positive were box elder, ragweed, and June grass. Other frequent allergens were elm and ash trees and English plantain. By the age of 10 years, 70% of patients were positive to perennial allergens (such as house-dust mite), 70% were positive to outdoor allergens, and 32% were positive to molds. These data are considerably different from the incidence of positive tests to pollen and perennial allergens than were found in the ACRN database. However, Ogershok's study was performed in West Virginia and, obviously, the data can not be applied to dissimilar floral areas of the United States, whereas the ACRN data were collected from multiple diverse areas in the United States. In addition, the ACRN data were patients who were >12 years of age, while Ogershok's cohort included patients who were <10 years of age. Guilbert *et al.* from the Children's Asthma Research and Education network also showed the high incidence of allergic sensitization to aeroallergens in children. Guilbert *et al.*'s study assessed characteristics of those that were likely to develop asthma and thus their data describe a different population than the other studies discussed. Doctor Guilbert's statements "The majority of the children (60.7%, $n = 148$) were sensitized to either food or aeroallergens. Male children were significantly more likely to be sensitized to aeroallergens ($p = 0.03$) and to have a blood eosinophil level of 4% or greater ($p = 0.03$) and a total serum IgE level of greater than 100 IU/mL ($p = 0.0004$). "Additionally, eosinophilia and total serum IgE level had the strongest correlation with aeroallergen sensitization. The high prevalence of aeroallergen sensitization in this high-risk cohort suggests that aeroallergens might have an important role in the early development of asthma," emphasizes the importance of aeroallergen sensitivity in asthma.¹¹

Similar to other investigators, the ACRN database showed that ethnicity influenced skin test positivity. Nonwhite populations had a higher frequency of positive

tests than white populations. Ninety-six percent of male subjects and 94% of female subjects were aeroallergen sensitive and gender did not significantly influence aeroallergen sensitization as they did in the Children's Asthma Research and Education network trials.⁹

We also assessed skin tests of subjects in the ACRN studies by geographic location in the United States, which was determined by the center that recruited the subject. As expected, there was a high prevalence of positive skin tests to cats and dust mites and a relatively uniform distribution of positive tests for these allergens across the United States. An expected exception to this uniform distribution was the low prevalence of dust mite and cockroach sensitization in Denver, secondary to the low humidity associated with the high elevation in Denver. Also as expected, because ragweed is rarely found west of the Rocky Mountains, the percent of positive tests to ragweed in San Francisco was low. Positive reactions to tree mix and dogs in San Francisco were also lower than other geographic areas, but with an uncertain explanation.⁹

Positive reactions to *Alternaria* were highest in Wisconsin and prior studies have confirmed the importance of this fungus in the agricultural areas of the Midwest of the United States. Sensitivity to *Aspergillus* and *Cladosporium* were lower than that noted to essentially all other allergens tested.⁹

Contrary to the ACRN data a recent study by Knudsen *et al.* assessing subjects for "allergic asthma and non-allergic asthma" found an incidence of "allergic asthma" in just 61% of the 1186 subjects between the age of 14 and 44 years.¹⁵ In Knudsen *et al.*'s¹⁵ cohort, patients with "non-allergic asthma" were more likely to be female subjects, have worse asthma, have cough as the predominant symptom, be without food allergies, and be less likely to have hyperresponsiveness of the airway or rhinitis. It is not apparent why these values should vary so considerably from other studies noted previously.¹⁵ Opposing the aforementioned data and contrary to previously thought, a recent article using patient recall of skin test reactivity in those with severe asthma suggested that the vast majority of even severe asthmatic patients (approaching 90%) were allergic to aeroallergens.¹²

Recently, The Inner City Asthma Study was able to not only assess incidence of aeroallergen sensitization in patients with asthma, but also to show morbidity associated with these allergens when exposed. Studying 927 children between the age of 5 and 11 years residing in inner cities they were able to show cockroach allergy in 69%, house-dust mite allergy in 62%, and mold allergy in 50%. Sites included in this network were Bronx, NY; Seattle, MA; Dallas, TX; and Chicago, IL, and location of residence effected the aeroallergen sensitization of the study population. In the inner city population it appeared that cockroach allergen had the

greatest effect on morbidity.¹⁶ Additional studies in this population have also defined rodents as a significant allergen. Twenty-two percent of children were positive to mouse allergen and sensitization and exposure to mouse allergen was an independent risk factor for asthma morbidity.¹⁷

DISCUSSION

As noted previously, the ACRN data suggested that as many as 95% of subjects with mild-to-moderate asthma may have an allergic component to their asthma. The percentage of patients in our studies with positive skin tests is higher than that noted in previously published studies. Previously published rates of aeroallergen sensitization in patients with asthma have ranged from 50 to 81.9% with other studies reporting results between these extremes.^{18–22}

The important issue is not as much the incidence of aeroallergen sensitivity in asthma, but how it affects the patient with asthma. The Inner City Asthma studies were able to establish an association between sensitization, exposure, and morbidity.^{16,17} To accomplish this, the home environment was assessed and patients were skin tested, questioned, and examined. This process is very expensive and time-consuming, but allows a true assessment of the association between sensitivity, exposure, and asthma stability. In addition, interventions, such as avoidance measures were instituted and were able to establish a reduction of allergen and improvement of sleep-related symptoms and activity disturbance.¹⁷

In the ACRN database we were unable to show an association between symptoms, sensitization, and exposure. Nonetheless, when measures used to characterize asthma were compared with aeroallergen sensitization, exhaled nitric oxide (eNO) and IgE increased significantly with an increased number of positive tests, whereas provocative concentration of methacholine causing a 20% fall in forced expiratory ventilation in 1 second (FEV₁ [PC₂₀]) decreased significantly as the number of positive skin tests increased.⁹ The change in eNO, IgE and PC₂₀ were greatest in those subjects with either positive skin test responses to perennial allergens alone or to both seasonal and perennial allergens. The same was not found for those that responded only to seasonal allergens. In the ACRN aeroallergen study there were no consistent correlations between sensitization to aeroallergens and percent predicted FEV₁, FEV₁/forced vital capacity ratio, sputum eosinophils, peripheral blood eosinophils, FEV₁, or peak flow values in the morning or evening.

Although the data by Knudsen *et al.* assessing subjects for “allergic asthma and nonallergic asthma” found an incidence of “allergic asthma” in just 61% of subjects and conflicted with the ACRN data, Knud-

son’s group did show changes in asthma parameters that agreed with the ACRN data. Their subjects with allergic asthma were more likely to have hyperresponsiveness of the airway than those with nonallergic asthma.¹⁵

A recent study of patients with severe and/or difficult to manage asthma, that used patient recall of unstandardized and unwitnessed allergy skin tests, reports that 93.5% of those that recalled skin tests remembered being informed of a positive result.¹² Because most of the ACRN studies have focused on the larger population of patients with mild-to-moderate asthma we are unable to comment directly on skin test reactivity in severe asthma. This is important because some cohorts of those with severe asthma might be expected to be nonallergic. For example, the phenotypes of asthma with nasal polyps, chronic sinusitis, chronic rhinitis, and aspirin sensitivity and those with late-onset asthma lacking sputum eosinophilia often manifest as severe nonallergic asthma. Thus, being sensitive to aeroallergens can not be used to include or exclude the diagnosis of asthma, but may be an additional factor important to understand the multiple phenotypes of this increasingly prevalent disorder.²³

An increased prevalence of allergen sensitization during the early decades of life followed by a decline later in life has been described previously.^{24–26} As stated by Jayaratnam *et al.*, “random samples of patients with asthma identified by validated questionnaires, increased age, female gender, chronic rhinosinusitis, and more severe impairment of lung function are associated with an elevated chance of the patient being non-atopic.”²⁷ Although, the ACRN study⁹ is not longitudinal, the data suggested that aeroallergen sensitivity may not wane with time. This is of importance in two ways: first, efforts to reduce the acquisition of allergic sensitization in childhood may have important benefits even later in life and, second, that age alone should not obviate the search for allergic triggers of asthma. Others have also shown a high prevalence of skin test reactivity in the elderly with 74.7% of participants with at least one positive test to an airborne allergen.²⁸

Allergen sensitivity to perennial allergens has been associated with asthma severity. The Inner City Asthma and Childhood Asthma Management Program studies of the National Heart, Lung, and Blood Institute have confirmed sensitization and exposure to house-dust mite, indoor molds, and animal dander as independent variables for poor outcomes associated with asthma.^{7,29} Other studies have also found statistically significant associations between exposure to indoor allergens and asthma stability.^{30–34} Still others have shown correlations between asthma severity and eNO and serum levels of total IgE, as well as specific IgE as determined by skin testing.^{8,35} Several studies

have also shown increased asthma symptoms and associated inflammation during specific seasonal allergen exposures.^{36–38} The inability to establish such a statistical correlation between asthma severity measures and skin test responses to seasonal allergens in the ACRN study⁹ may be a consequence of the fact that exposure to most seasonal allergens is limited to ≤ 2 month/year. In the ACRN studies, recruitment occurred throughout the year and only a small portion of the subjects with seasonal allergies would have had the appropriate evaluations performed at the time their seasonal allergy was active.

Differences in skin test reactivity between ethnic groups may reflect socioeconomic status, urban versus nonurban living, region of the country they reside in, country of origin, occupation, and other living conditions such as air conditioning, crowding, and pet ownership.^{7,34,39} The ACRN study suggested a correlation between minority ethnicity and sensitivity to multiple aeroallergens. Similarly, we confirmed that the most common allergen sensitizations across all sites were to dust mites and cats and that high altitude locations with low humidity, such as Denver, have a lower prevalence of positive skin tests to cockroach and dust mite. Additionally, areas west of the Rocky Mountains have a lower prevalence of ragweed and, hence, fewer positive reactions to ragweed allergen. These data are relevant, especially when avoidance is suggested as an asthma control measure without objective evidence of a patient's specific sensitivities. Empiric avoidance can be directed at expected exposures but is most relevant and effective when directed by knowledge of allergen sensitivity as defined by specific testing.^{34,39,40}

As noted previously, we were able to establish a correlation between an increased number of positive skin tests and eNO, IgE, and PC₂₀. The correlation with IgE is to be expected; however, the failure to show a similar correlation with spirometric values, peak flow, and sputum eosinophils was unexpected. Spirometric values and peak flows may not reflect the degree of inflammation in the airways; however, correlations between sputum eosinophilia and inflammation have been repetitively noted and would be expected to move in tandem with eNO and PC₂₀.^{3,41–46} I suspect that if we included all severities of asthma instead of the inclusion of only mild-to-moderate asthma that a correlation between skin testing and sputum eosinophils would have been positive. Nonetheless, the strong statistical correlations between eNO, PC₂₀, and IgE and positive skin tests suggest that allergy is an important factor in inflammation in mild-to-moderate asthma and that allergen avoidance or other allergy-directed measures may reduce inflammation.

As noted earlier, because the vast majority of our subjects had mild-to-moderate asthma these data do not permit the same generalization to be applied to those

with severe asthma. In some phenotypes of severe asthma, especially in those with late-onset disease, aeroallergen sensitivity may not correlate with severity. These same individuals may have low geometric mean total IgE serum levels when the IgE level is age and gender adjusted. In turn, others with severe late-onset asthma may be nonallergic and still have a nonspecific elevation in IgE. Finally, another subset of patients with severe nonallergic asthma has predominately neutrophils on sputum induction.^{23,47} Despite these observations the results of other studies support extension of the importance of allergen sensitization to patients with severe or difficult-to-treat asthma as well.¹²

Those with asthma that are more likely to be free of hypersensitivity to aeroallergens include those with late-onset asthma, those with nasal polyps and aspirin sensitivity, and, possibly, those with skin test positivity to autologous serum.^{13,14} These studies showing skin test positivity to autologous serum^{13,14} suggest that IgE may play a role in some patients with asthma who are not sensitized to aeroallergens. Similar findings have implemented autologous serum in patients with chronic urticaria.¹⁸ Unfortunately, these findings are not specific or sensitive for nonallergic asthma or chronic urticaria and can be found in patients that are otherwise healthy with neither disease state.¹⁸ However, it is apparent that avoidance and desensitization would not be indicated in this subset of patients, but omalizumab may be effective, although not approved for this indication.

In summary, aeroallergen hypersensitivity occurs in the vast majority of patients with asthma no matter what their asthma severity and the incidence of aeroallergen hypersensitivity appears to approach 90–95%. Data support that exposure to aeroallergens in those sensitized can affect asthma control. Airway hyperresponsiveness as defined by a low PC₂₀, high eNO, elevated IgE, increased sputum eosinophils, and eosinophilia have all correlated with having asthma and being positive to aeroallergens. Avoidance and immunotherapy have a role in asthma of all ages and should be used when indicated and not contraindicated to enhance asthma control.

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