

Skin test reactivity to indoor allergens as a marker of asthma severity in children with asthma

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Background: Specific IgE responses to common indoor aeroallergens in children with asthma have been found to be associated with acute asthma.

Objective: The purpose of this study was to examine the association between asthma severity and skin test reactivity to four common indoor allergens.

Methods: The charts of 139 asthmatic children, aged 5 to 18 years, seen in a pediatric allergy clinic were reviewed to obtain the results of skin tests to cat, dog, cockroach, and dust mite allergens, FEV₁, anti-asthma medication requirements and demographic characteristics. Logistic regression for ordinal data was used to examine the association between skin test reactivity and asthma severity (mild, moderate or severe) as determined from FEV₁ and medication usage.

Results: The rate of allergen sensitivities were dust mite 55%, cockroach 50%, cat 29% and dog 17%. Children with positive skin test to cat allergen were more likely to have a higher asthma severity rating than children with a negative cat allergen skin test [proportional odds ratio (OR) = 3.0, 95% confidence interval (CI) = 1.4 to 6.1, $P = .003$]. This association remained significant after we controlled for skin test reaction to the other three allergens and various sociodemographic factors (adjusted OR = 3.0, 95% CI = 1.3 to 7.2, $P = .013$). The ORs for sensitivity to dog, cockroach, and dust mite allergen did not differ significantly from one, but children who were sensitized to all four allergens had an OR of 4.8 (95% CI = 1.3 to 18, $P = .019$) relative to children who were not sensitized to any of the four allergens. This association also remained significant after controlling for sociodemographic variables ($P = .030$).

Conclusion: Children with combined sensitivity to cat, dog, dust mite, and cockroach allergens were at increased risk of having more severe asthma. Our data also suggest that sensitization to cat allergen per se is a risk factor for more severe disease in these asthmatic children.

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INTRODUCTION

It has become increasingly clear that the pathophysiologic picture of severe asthma includes recruitment of eosinophils and the presence of activated T cells on exposure to allergens.¹ Given that most people spend the greater part

of the day indoors, it is not surprising that increasing attention has focused on the role of foreign proteins that accumulate indoors.^{2–8} Recent advances in immunology have allowed extensive studies of these indoor allergens.

Allergens involved in causing asthma include those derived from house dust mites, cockroach, cat, and dog.^{2–6} In particular, it has been suggested that exposure to animal and cockroach allergens even in schools may provoke asthma symptoms in children sensitized to these allergens.^{7,8} Zimmerman et al and other investigators have demonstrated a direct rela-

tionship between the number of positive skin tests to a variety of allergens and the severity of asthma.^{9–12} None of these studies, however, focused primarily on the four most common indoor allergens.

This report addresses the hypothesis that sensitization to common indoor allergens in children with asthma is associated with more severe disease. We examined the association between sensitization to each of the four specific indoor allergens and asthma severity as well as the relationship between the number of positive skin tests and the degree of asthma severity.

METHODS

Study Design

This is a retrospective, chart review study of children with asthma referred to the outpatient clinic of the Department of Pediatric Allergy at the University of Chicago Children's Hospital over a 6½-year period. Demographic and clinical data were collected as well as the results of skin testing to common indoor inhalant allergens and pulmonary function tests.

Patients

The study group consisted of 139 children, aged 5 to 18 years, who were referred to the outpatient clinic between March 1990 and September 1996 and had spirometric evaluation of pulmonary function. Excluded were patients on immunotherapy and those with other specific respiratory diseases such as cystic fibrosis. We also excluded 20 patients who had incomplete data on asthma medication requirements because this information was needed to construct our severity index (see below). Otherwise, the sample consisted of consecutively evaluated

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patients. Most of the patients seen were self referrals; however, a significant proportion were referred from community urgent health care centers and most of these patients did not have a primary care physician. At the initial visit a diagnosis of asthma was made by a pediatric allergist/pulmonologist on the basis of clinical symptoms of the characteristic bronchospasm. Demographic and medical history data, including medication requirements, were also collected at the time of the pulmonary function test. The source of medical insurance and area of residence were documented. Suburban versus urban residence was determined by zipcode; if the home was in one of 55 zipcodes that lay within the Chicago city boundaries, residents were considered to be urban dwellers. Children were grouped as either on public aid/self pay or as having commercial insurance.

Skin Tests

Immediate wheal and flare skin tests were performed at the initial visit by the prick-puncture method with bifurcated needle and glycerinated full strength mixed (German and American) cockroach, dust mite (*farinae* and *pteronysinus*), and cat and dog extracts (Bayer, Spokane, WA). The wheal diameters observed at 15 minutes were compared with skin test reactions produced by a histamine (10 mg/mL) positive control and phenol-saline-human serum albumin negative control. Wheal diameters greater than or equal to the histamine control were considered positive. All the eligible patients denied use of oral and nasal medications containing antihistamine and had acceptable histamine response (≥ 5 mm above the negative control).

Pulmonary Function Tests

The results of the first pulmonary function test done after the initial visit and not during an acute pulmonary exacerbation were used. Subjects were tested at least six hours after the last dose of inhaled bronchodilator and 12 hours after the last dose of oral bronchodila-

tor. An acceptable spirometry met the American Thoracic Society guidelines¹³ (using a pneumotach spirometer 2200 Sensor Medics, Yorba Linda, CA): at least a 6-sec duration, or 4-sec if no change in the slope of the tracing; no cough in the slope of the tracing; no cough in the first second; no cough affecting the accurate measurement of the FVC; and back-extrapolated volume less than 10% of measured FVC. Measurements were corrected to body temperature and pressure saturated with water vapor (BTPS). The best FEV₁ value of three satisfactory efforts was recorded and compared with predicted norms. Reference values of Pulgar¹⁴ based on gender, age, and height were used. This reference was not race normed. FEV₁ data are expressed as percent predicted FEV₁ = (FEV₁/FEV₁ predicted) $\times$ 100%.

Construction of Asthma Severity Score

An asthma severity score was constructed based on asthma medication requirements (at the time the pulmonary function test was performed) and the percent predicted FEV₁. Use of a bronchodilator was assigned 1 point, use of inhaled anti-inflammatory drugs or xanthine preparation scored 2 points, and use of oral steroids scored 3 points. For patients on more than one medication, the points were added to give a summed medication score. The subjects were then classified according to their FEV₁ response (baseline): FEV₁ $>$ 80% was assigned a score of 1, 60% to 80% a score of 2, and $<$ 60% a score of 3. The medication and FEV₁ scores were then totaled to give a final asthma severity score ranging from 1 to 9. The 9-point range was then further categorized as mild (1–3), moderate (4–6), or severe (7–9).

Statistical Analysis

Analysis of the association between sensitization to specific (cat, dog, cockroach, and dust mite) and multiple (0, 1, 2, 3, 4) aeroallergens and asthma severity level was performed using logistic regression for ordinal responses.

Table 1. Demographic and Clinical Characteristics

Variable	Number (%)
Gender	
Male	90 (64.7)
Female	49 (35.3)
Race	
Black	101 (72.7)
White	25 (18.0)
Other	13 (9.4)
Age (mean $\pm$ SD*)	10.1 $\pm$ 2.9
Range (yr)	5–18
Residence	
Urban	111 (79.9)
Suburban	28 (20.1)
Insurance type	
Public aid/self pay	98 (70.5)
Commercial	41 (29.5)
Positive skin test	
Cockroach	69 (49.7)
Dog†	23 (16.8)
Cat	40 (29.0)
Dust mite	76 (54.7)
Anti-asthma medication use	
Bronchodilator	124 (89.2)
Anti-inflammatory/xanthine	84 (60.4)
Oral steroid	78 (56.1)
FEV ₁ (mean $\pm$ SD*)	83.0 $\pm$ 20.4
Range	42–145

* SD = standard deviation.

† Missing skin test data in two cases.

The logistic regression analysis employed a proportional odds model for the three categorized levels of response (mild, moderate, or severe asthma).¹⁵ This model assumes that, for a given risk factor, the ratio of the odds of having moderate or severe asthma, as opposed to mild asthma, for those with and without the risk factor is the same as the ratio of the odds of having severe asthma as opposed to mild or moderate asthma. Hence a single odds ratio is extracted corresponding to all of the possible “cutpoints” on the ordinal scale (two in our case). Tests of the proportional odds assumption did not indicate any significant lack of fit of the model. Multivariate analyses were performed to adjust for potential confounding variables (specifically, age, gender, race, residence, and type of medical insurance as a marker of disadvantaged children).

Table 2. Association Between Skin Test Results and Other Factors and- Asthma Severity

Variable	Univariate			Multivariate		
	OR	95% CI	P Value	OR	95% CI	P Value
Positive skin test						
Cockroach	1.53	(0.82, 2.85)	0.179	0.73	(0.31, 1.72)	0.471
Dog	2.26	(0.94, 5.44)	0.068	1.40	(0.51, 3.83)	0.508
Cat	2.96	(1.43, 6.12)	0.003	3.02	(1.26, 7.21)	0.013
Dust mite	1.45	(0.78, 2.70)	0.239	1.18	(0.54, 2.60)	0.676
Race						
White	1.0*	...		1.0*	...	
Black	2.64	(1.16, 6.01)	0.020	3.80	(1.43, 10.1)	0.008
Other	2.08	(0.60, 7.21)	0.249	2.05	(0.54, 7.80)	0.291
Insurance (Medicaid/self pay)	1.44	(0.73, 2.83)	0.290	1.56	(0.69, 3.54)	0.283
Gender (male)	1.45	(0.76, 2.76)	0.263	1.18	(0.59, 2.35)	0.633
Residence (urban)	0.92	(0.42, 1.98)	0.824	0.41	(0.15, 1.09)	0.075
Age (per year)	0.93	(0.84, 1.04)	0.206	0.91	(0.81, 1.02)	0.101

* Reference category.

RESULTS

Patients

Descriptive statistics for the 139 study subjects are shown in Table 1. There were 90 boys (65%) and 49 girls (35%). The majority of patients were

black (73%), resided in urban areas (80%), and were on Medicaid/self pay (70%). The mean age and SD was 10.1 ± 2.9 years, with a range from 5 to 18 years. Approximately 55% of the children were sensitive to dust mite

allergen, 50% to cockroach allergen, 29% to cat allergen, and 17% to dog allergen. Skin test results were associated with one another; specifically, dust mite sensitization was associated with cockroach sensitivity ($\chi^2 = 37$,

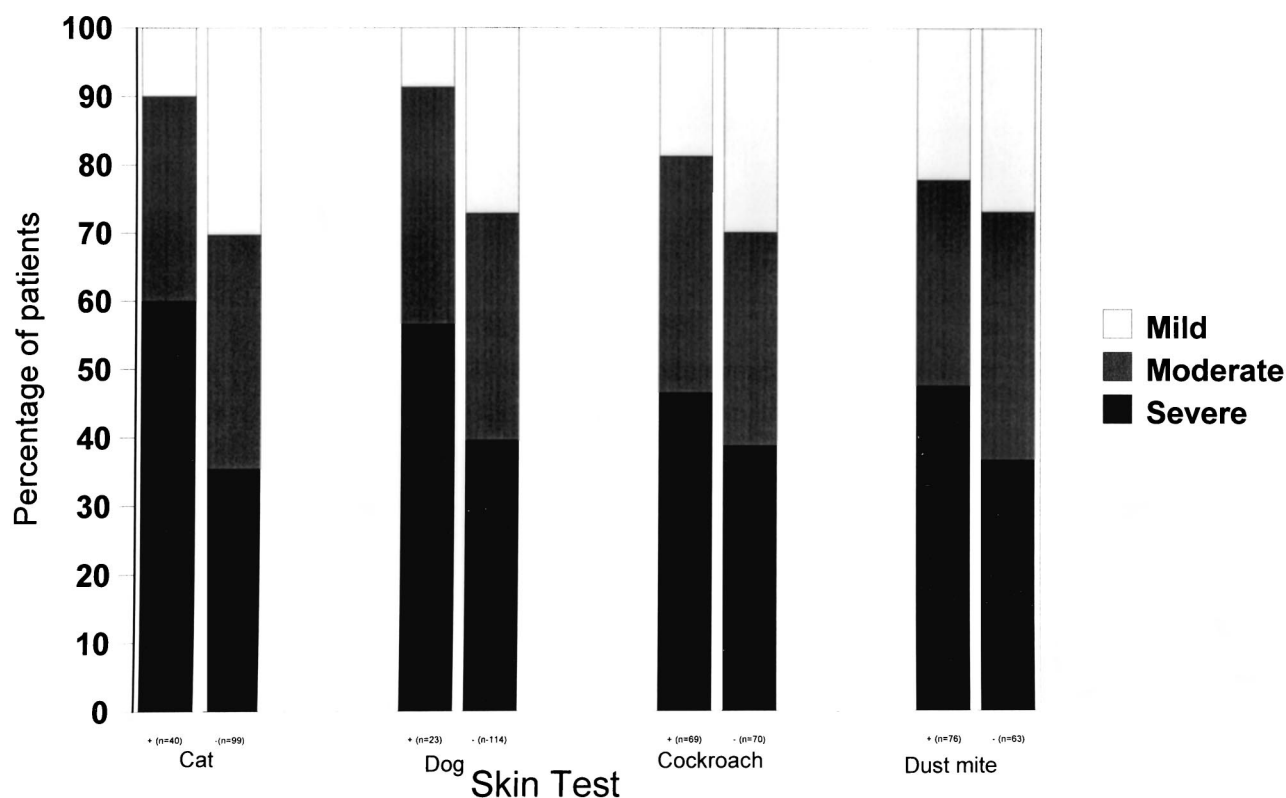


Figure 1. Percentage of patients with mild, moderate, or severe asthma who were positive or negative to cat, dog, cockroach, and dust mite allergen.

Table 3. Association Between Number of Positive Skin Tests and Asthma Severity

Variable	Univariate			Multivariate		
	OR	95% CI	P Value	OR	95% CI	P Value
No. of positive skin test(s)						
0	1.0*	...		1.0*	...	
1	1.22	(0.50, 2.99)	0.659	1.21	(0.48, 3.08)	0.689
2	1.09	(0.48, 2.46)	0.831	1.03	(0.44, 2.38)	0.950
3	2.32	(0.81, 6.62)	0.116	2.32	(0.77, 6.93)	0.134
4	4.84	(1.30, 18.1)	0.019	4.52	(1.16, 17.6)	0.030
Race						
White				1.0*	...	
Black				3.24	(1.23, 8.54)	0.018
Other				2.05	(0.54, 7.84)	0.294
Insurance (Medicaid/self pay)		See Table 2		1.28	(0.58, 2.84)	0.545
Gender (male)				1.22	(0.62, 2.44)	0.563
Residence (urban)				0.45	(0.17, 1.21)	0.115
Age (per year)				0.92	(0.82, 1.02)	0.122

* Reference category.

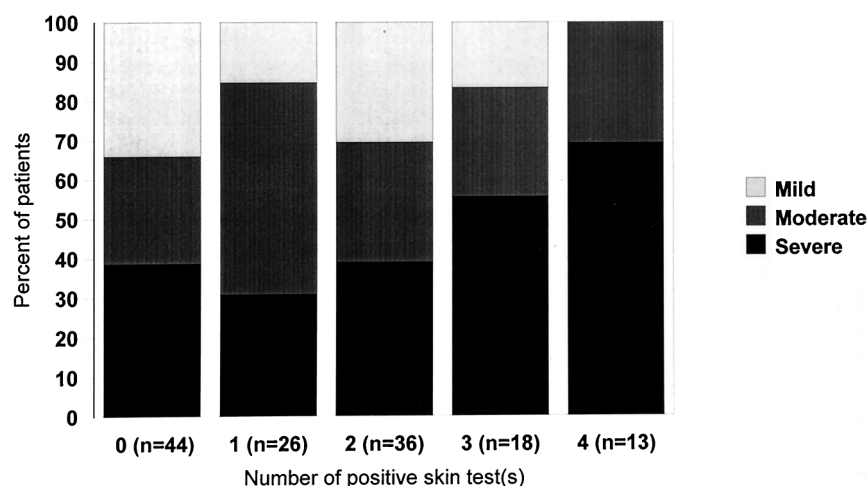


Figure 2. Percentage of patients with mild, moderate, or severe asthma by number of positive skin tests.

$P < .001$), cat sensitivity ($\chi^2 = 13$, $P < .001$), and dog sensitivity ($\chi^2 = 7.8$, $P = .005$). Cockroach sensitivity was associated with cat sensitivity ($\chi^2 = 19$, $P < .001$) but only marginally with dog sensitivity ($\chi^2 = 3.5$, $P = .062$). Cat sensitivity was associated with dog sensitivity ($\chi^2 = 21$, $P < .001$). Most of the children used bronchodilator (89%), 60% were on inhaled anti-inflammatory drugs or xanthine, and 56% reported use of oral steroids at the time the pulmonary function test was completed. The mean

FEV₁ (percent of predicted) was 83.0%, and ranged from 42% to 145%.

Factors Related to Asthma Severity

The patients were classified as having mild, moderate, or severe asthma using a disease severity score derived from the FEV₁ values and medication usage at the time of the pulmonary function test as described under "Methods." Overall, 34/139 (24.5%) of the patients were classified as having mild asthma using this index, 46/139 (33.1%) as having moderate

asthma, and 58/139 (42.4%) as having severe disease.

The results of univariate analyses examining the association between disease severity and each of the skin test results and various demographic factors are shown in Table 2. Statistically significant associations were detected between asthma severity and sensitization to cat allergen and race. Specifically, the odds of having more severe disease were nearly three times greater for children sensitized to cat allergen (95% CI: 1.4 to 6.1). The proportional odds ratio for sensitization to dog allergen was approximately 2.3 but did not reach statistical significance ($P = .068$). Figure 1 shows the proportion of patients with mild, moderate, and severe asthma for those with and without sensitization to each of the four allergens. A greater percentage of children who were sensitized to cat and dog allergen had severe disease and a correspondingly smaller percentage had only mild disease. The same was true for sensitization to cockroach and dust mite allergen, but the differences were fairly small in each case.

The right hand side of Table 2 displays the results of multivariate analyses incorporating the four skin test results and demographic variables. Sensitivity to cat allergen and black race remained as significant indepen-

dent risk factors, with estimated proportional odds ratios of 3.0 (95% CI: 1.3 to 7.2) and 3.8 (95% CI: 1.4 to 10.1), respectively.

The asthma patients were also categorized according to the number of positive skin tests (0, 1, 2, 3 or 4) to evaluate the effects of multiple allergen sensitivity on asthma severity. The results are shown in Table 3 and Figure 2. Sixty-nine percent of children with four positive skin test results had severe disease, 31% had moderate disease, and none had mild disease, whereas the majority of children with zero, one, or two positive skin tests had mild or moderate disease. From the logistic regression analyses, children with positive results on all four skin tests were estimated to have a 4-fold to 5-fold increase in the odds of having more severe disease compared with children with negative results on all four skin tests (adjusted $P = .030$). The estimated proportional odds ratio for children with three positive skin test results was 2.3, but this figure did not differ significantly from one. Among the demographic variables, race was again the only significant risk factor (adjusted $P = .018$ for blacks compared to whites).

DISCUSSION

There are many factors that can contribute to severe asthma in children with atopic asthma. The present study was designed to investigate the role that sensitization to specific indoor allergens plays in severe asthma. Other risk factors were not addressed, eg, air pollution, allergen exposure, fungal and outdoor allergen sensitivities, dietary factors and the role of acute viral infections. Previous studies have suggested that sensitization to indoor allergens (cockroach, cat, and dust mite) is associated with increased health care utilization, but the complex interrelationship between sensitization to these allergens, race, poverty, urban residence, and severe asthma has been difficult to unravel.² It is important to understand to what degree each of these factors is related to asthma severity because each has a different impli-

cation for corrective public health policy.

Severity of asthma is difficult to define objectively.¹⁶ We scored the severity of the asthma on the basis of a combined index of bronchial obstruction, as measured by forced expiratory volume in one second (FEV₁), and the type of medication recommended for the patients at that time. Although there is likely to be some overlap in the actual level of disease severity between the various scores, there should be a very distinct difference between mild scores (1–3) and severe scores (7–9), and better discrimination than with indices based primarily on medication usage^{9,16} or FEV₁ alone.

Our data share certain similarities with the patient populations studied by McNicol and Williams,¹¹ Gregg¹⁰ and Zimmerman et al.⁹ As previously reported by these authors there is both high prevalence of atopy in children with asthma and increasing skin test positivity with increasing severity of asthma. They did not, however, relate this specifically to the role that indoor allergen sensitivity, including sensitivity to cockroach, plays in severe asthma.

It is important to emphasize that we do not mean to imply from our data that asthma severity in children is simply a result of allergy to certain inhaled allergens. Indeed, it is possible that the immunologic changes associated with viral infections induce a general tendency to form IgE.¹⁷ It is also plausible that the tendency to develop atopic asthma is itself an inherited trait which becomes manifest when provocative factors such as infectious agents, irritants, or allergy to inhalants supervene.¹⁸ Although skin tests are only an indirect method for detecting allergens relevant to airway inflammation, we interpret our data to mean that the child with severe asthma is more easily sensitized, and therefore is more likely to have allergen-induced inflammation in the airways, including an active immunologic response to perennial allergens.^{1,19}

Our data do suggest that the development of IgE response to multiple

indoor allergens and cat allergen in particular is an important factor in the persistence of bronchial obstruction in children with asthma. The patient with severe asthma has been reported to present at less than 3 years of age with frequent episodes of asthma.⁹ Clearly, if the course of severe asthma is to be modified, such children must be recognized early. Evidence is accumulating that in homes and schools where there are no pets like dogs or cats, there are reportedly significant levels of allergens brought in from outside that can induce and maintain bronchial hyperresponsiveness in sensitized individuals.⁷ Black and disadvantaged children are also at increased risk to be sensitized and exposed to cockroach allergen both in school and at home.^{4,8}

Much research is needed to define regimens effective for reducing exposure to cockroach allergen and animal danders as has been done with dust mite allergen.^{20,21} While avoidance measures are currently difficult, if not impossible, this should not deter further research in this area. Advice will have to be tailored to suit the sociodemographic background of the patient and controlled trials of allergen avoidance measures in this population should be carried out. Effective aeroallergen avoidance may not only reduce the severity of established asthma, but may also have the potential to prevent the development of the disease in the first place.

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