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MEDICINE

Allergy Evaluation During Hospitalized Asthma Improves Disease Management Outcomes

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Abstract

Hospitalization for asthma exacerbation is significantly related to overall poor asthma control. The study aimed to contrast post-hospitalization outcomes of those asthmatics who underwent serologic specific IgE (sIgE) testing for regional environmental allergens to an untested cohort. Of 8061 asthma encounters, 273 subjects who met the criteria were included in this retrospective cohort study. Those asthmatics identified with persistent disease were hospitalized at Miller Children's Hospital during the period June 2008–October 2015. A total of 207 patients underwent sIgE testing during initial hospitalization for asthma and 66 were not tested. The Cox regression analysis assessed time from discharge to first emergency room (ER) visit, required systemic steroids, and next hospitalization in sIgE vs. non-tested groups, stratified by severity (mild or moderate-severe) and adjusted for age (≥ 12 or < 12), gender, and race. Serum allergy evaluation by sIgE testing reduced the hazard of an ER visit and systemic corticosteroids requirement by half in mild asthmatics ($p < 0.05$). The average time to next ER visit was almost 1 year in the allergy-tested group compared to < 6 months in the no-test group. Blood-based allergy evaluation as part of inpatient asthma treatment was shown to improve disease management specifically in time to next ER and/or exacerbation and systemic corticosteroids requirement in patients with mild disease. In more severe adolescent asthmatics, sIgE testing appeared protective against future hospitalization. Inpatient serologic testing may be beneficial in raising alertness in the asthma population, deploying early comprehensive care and lowering the rate of hospitalization.

Keywords Asthma · Allergens · Hospitalization · Immunoglobulin E · Status asthmaticus

Introduction

Nearly 25 million Americans suffer from asthma encompassing 8% of adults and 9% of children. Asthma prevalence continues to increase in all age, gender, and racial groups [1]. Asthma is the most common chronic condition among children [2] and remains the third-ranking cause of hospitalization in children [3]. The average length of stay (LOS) for asthma hospitalizations is 3.4 days [4]. Despite socioeconomic factors, asthma hospitalization is strongly correlated with poor asthma control [5].

Adherence to the 2007 NIH asthma guidelines remains difficult in the outpatient setting [6, 7]. The frequency of asthma exacerbations requiring hospitalization has decreased in the past decade limited to geographic improvement in ambient environmental air quality [8]. However, the asthmatic population reduction in rescue systemic steroid use has not been achieved despite specialist care post-hospital follow-up [9].

Failed outpatient asthma management results in hospitalization of "at risk" moderate-severe asthmatics. These asthmatics maintain the highest risk of morbidity and mortality [10]. The primary end points of initial asthma management paradigms involve a reduction in systemic steroid use, determination of atopic predisposition, and improvement of forced

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expiratory volume in 1 s percent predicted (FEV_1%). To date, no study has analyzed the efficacy of such objective parameters to determine post-hospitalization asthma treatment. Our study analyzed post-hospitalization outcomes of hospitalized asthmatics who underwent objective allergy and lung function testing to a cohort which did not.

Methods

Study Population

We performed a single-center, large population, retrospective cohort study. The project was approved by our institutional review board. Charts were obtained via electronic medical record from June 2008 to October 2015 for children and young adults, aged 4 to 21 years of age, treated at the Miller Children's Hospital (MCH) of Long Beach, CA, for asthma exacerbation. Charts were selected with diagnosis (ICD-9 and ICD-10 code) for status asthmaticus, asthma exacerbation, acute bronchospasm, or wheezing with hypoxia. Selected charts then underwent further evaluation utilizing inclusion and exclusion criteria. Retrospective post-hospitalization data abstraction restricted to patients with persistent disease who had a subsequent asthma exacerbation that required an ER visit or hospitalization during the study period. Clinician report of asthma severity as either mild, moderate, or severe persistent was based upon the clinician electronic medical record report and consistent with acceptable standard classification. Exclusion criteria included prior or known allergy testing (Radioallergosorbent test (RAST), serum sIgE or skin prick), immunodeficiency, congenital lung disease, genetic lung diseases, musculoskeletal disease, daily systemic steroid use, omalizumab therapy, and FEV_1% < 40% predicted at baseline.

Data Collection

Data was collected from MemorialCare Health Services (MHS) patient medical records. Initial electronic medical records captured using ICD-9 and ICD-10 diagnostic codes for primary diagnoses of asthma yielded 8061 patient encounters during the study time period for the identified age range. After restriction of exclusion criteria, a total of 41 patients were excluded from study enrollment. (See Fig. 1 for further delineation of the data collection process.)

Demographic characteristics abstracted from charts included age, gender, and race. Initial hospitalization data included LOS, medications, FEV_1% (if available), and albuterol frequency. Post-hospitalization follow-up data included medication use, emergency room (ER)/urgent care visits, systemic steroid requirement, and outpatient (baseline) FEV_1%. Asthma severity was defined as mild, moderate, and severe

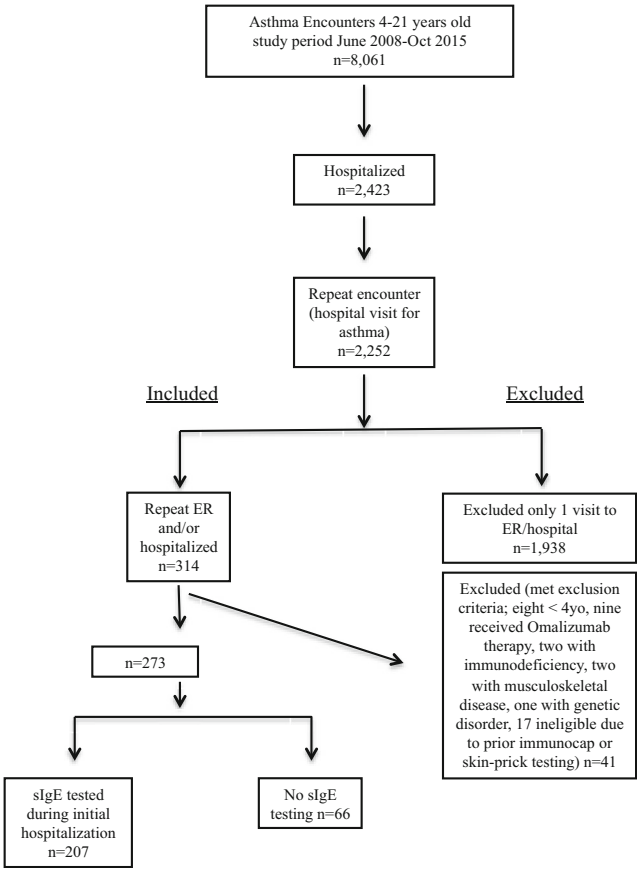


Fig. 1 Flow diagram showing selection criteria for study population

disease per the 2007 NIH asthma guidelines. Data was de-identified prior to analyses.

Statistical Analysis

Power analysis was performed for determination of identified cohorts. The study included 207 patients in the "allergy-tested" arm, while comparison "untested" cohort totaled 66 patients. Statistical analysis was completed using IBM Statistical Package for the Social Sciences (SPSS) software (IBM Corp, Armonk, NY). Cox regression analysis assessed time from discharge of initial hospitalization to first ER visit, required systemic steroids, and next hospitalization in serologic sIgE tested vs. non-tested groups, stratified by baseline severity (mild or moderate-severe) and adjusted for age (≥ 12 vs. < 12), gender, and race (African-American vs. other).

Results

Of 8061 asthma encounters, 273 subjects met inclusion criteria. Those asthmatics identified with persistent disease were hospitalized at MCH of Long Beach, CA, from June 2008–October 2015. At initial hospitalization, the average age of patients was 9.6 years, 62% were male, and the

Table 1 Characteristics of patient population

Column %, mean (SD) or median (IQR)	Overall, $N = 273$	Serologic sIgE-tested group, $N = 207$	Non-tested group, $N = 66$	p value [a]
Age, years mean (SD)	9.6 (3.4)	9.4 (3.1)	10.1 (4.2)	$p = 0.219$
Adolescents (≥ 12 years; %)	20.9%	19.3%	25.8%	$p = 0.263$
Male (%)	61.9%	61.8%	62.1%	$p = 0.967$
African-American (%)	46.2%	46.4%	45.5%	$p = 0.896$
Hispanic (%)	41.4%	42.5%	37.9%	$p = 0.506$
Moderate-severe baseline severity (%)	61.9%	65.7%	50.0%	$p = 0.022$*
FEV_1% predicted, mean (SD)[b]	63.6 (19.1)	64.1 (18.2)	60.8 (24.0)	$p = 0.431$
LOS, baseline hospitalization, mean (SD)	3.8 days (2.3)	4.2 days (2.4)	2.6 (1.3)	$p < 0.001$*
Systemic steroid days during baseline hospitalization, mean (SD)	6.1 days (2.9)	6.5 days (3.1)	5.1 (2.1)	$p = 0.001$*
Eosinophils (cells/μL), median (IQR)	0.0 (0.0–0.2)	0.0 (0.0–0.2)	0.0 [0.0–0.3]	$p = 0.387$
IgE, median (IQR)		573 (253–1046)		
IgE elevated (≥ 300; %)		69.3%		

[a] p value assessing significance of between group difference was based on chi-square test for categorical factors and independent t test for continuous factors normally distributed (equal variances not assumed when Levene's test significant, $p < 0.05$) and the Mann-Whitney U test when non-normality is apparent

*$p < 0.05$, significant between group difference

[b] Tested in 154 patients in serologic sIgE-tested group and 25 patients in non-sIgE-tested group

majority were African-American (46.2%) or Hispanic (41.4%) (Table 1). Demographic composition of patients allergy tested was similar to the untested group; however, a greater percentage of patients in the tested group had moderate-severe disease (65.7% vs. 50.0%), longer average LOS (mean = 4.2 vs. 2.6 days), and greater average number of systemic steroid days (mean 6.5 vs. 5.1 days) during initial hospitalization ($p < 0.05$). Among patients allergy tested, 69% were found to have significantly elevated total serum immunoglobulin E (IgE) level of greater than 300 IU/mL.

The more severe compared to mild asthma subtype represented a greater percentage of African-American patients (53.8% vs. 33.7%), with lower average FEV_1% (mean = 57.2% vs. 80.2%) and more days on systemic steroids during baseline hospitalization (mean = 6.4 vs. 5.6 days, $p < 0.05$; Table 2). Median eosinophil level, average age, and gender distribution were similar in the two severity stratums ($p > 0.05$).

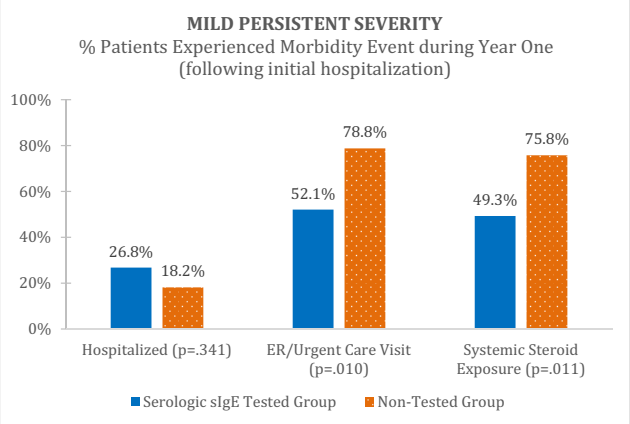
Figure 2 displays the percentage of patients who experienced a morbidity event during the year that followed initial

Table 2 Characteristics of patient population described by baseline asthma severity

Column %, mean (SD) or median (IQR)	Mild persistent, $N = 104$	Moderate-severe, $N = 169$	p value [a]
Age, mean years (SD)	10.0 (3.8)	9.3 (3.2)	$p = 0.117$
Adolescents (age ≥ 12 years; %)	21.2%	20.7%	$p = 0.930$
Male, %	62.5%	61.5%	$p = 0.874$
African-American, %	33.7%	53.8%	$p = 0.001$*
Hispanic, %	47.1%	37.9%	$p = 0.132$
FEV_1% predicted, mean (SD)	80.2 (16.7), *N= 50*	57.2 (15.9), *N= 129*	$p < 0.001$*
LOS, baseline hospitalization, mean (SD)	3.5 (2.1)	4.0 (2.4)	$p = 0.060$
Systemic steroid days during baseline hospitalization, mean (SD)	5.6 (2.7)	6.4 (3.0)	$p = 0.020$*
Eosinophils (cells/μL), median [IQR]	0.0 [0.0–0.3]	0.0 [0.0–0.2]	$p = 0.428$
Serologic sIgE-tested group only	$N = 71$	$N = 134$	
IgE elevated (≥ 300, %)	63.4%	72.4%	$p = 0.184$

[a] p value assessing significance of between severity group difference was based on chi-square test for categorical factors and independent t test for continuous factors normally distributed (equal variances not assumed when Levene's test significant, $p < 0.05$) and the Mann-Whitney U test when non-normality apparent

*$p < 0.05$, significant between severity group difference



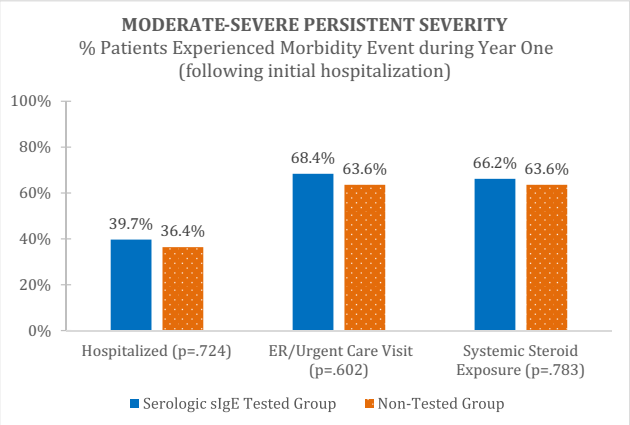


Fig. 2 Percentage of patients who experienced a morbidity event (hospitalization, ER/urgent care visit, or systemic steroid exposure) during the year following their initial hospitalization. *p* value based on chi-square test statistic

hospitalization in the allergy tested compared to the untested group, after stratification by disease severity. In patients with mild persistent asthma, those who underwent serum allergy testing were less likely to require an ER visit (52.1% vs. 78.8%) or systemic steroid (49.3% vs. 75.8%) during the follow-up year compared to the untested group ($p < 0.05$). In asthmatics with moderate-severe persistent disease, serum sIgE-tested group differentials in morbidity event occurrence during year 1 follow-up were not significant. Two deaths due to acute respiratory failure from an asthma attack occurred during the study time period (data not shown).

Serum allergy evaluation by sIgE reduced the hazard of an ER visit and systemic corticosteroids requirement by half in mild persistent asthmatics ($p < 0.05$) (Table 3). Average time to next ER visit was almost a year in the serologic sIgE-tested group compared to less than 6 months in the untested group. In more severe (moderate-severe persistent) asthmatics, the hazard of an ER visit and systemic corticosteroid requirement during year 1 follow-up did not show significant differentials by sIgE groups. However, the hazard of a subsequent hospitalization was reduced by more than half in adolescent patients with moderate-severe asthma who underwent serologic sIgE testing compared to those who did not (HR = 0.32, $p = 0.10$). Cumulative probability of hospitalization, ER visit, and systemic steroid use is displayed in Figs. 2, 3, and 4.

Table 3 Adjusted hazard of event (hospitalization, ER/urgent care visit, systemic steroid exposure) during year 1 follow-up, adjusted analyses[a]

	Hazard rate (95% CI) Serologic sIgE-tested group vs. non-tested group	*p* value
Mild persistent		
Hospitalization	1.30 (0.51–3.32)	$p = 0.585$
ER/urgent care visit	0.50 (0.29–0.86)	$p = 0.012$ *
Systemic steroid exposure	0.51 (0.29–0.88)	$p = 0.015$ *
Moderate-severe		
Hospitalization[b]		
Children 4–11	1.32 (0.65–2.68)	$p = 0.450$
Adolescents ≥ 12	0.32 (0.08–1.26)	$p = 0.103$~
ER/urgent care visit	1.05 (0.66–1.70)	$p = 0.832$
Systemic steroid exposure	0.99 (0.61–1.59)	$p = 0.953$

[a] Adjusted for gender (M vs. F), age (adolescents vs. children), and race (African-American vs. other). Hazard ratios and *p* values determined using the Cox proportional hazards regression

[b] In patients with moderate-severe baseline severity, indication that hazard of hospitalization in serologic sIgE-tested group vs. non-tested groups depended on age of child (interaction effect borderline significant, $p = 0.073$)

Discussion

Our study represents the first inpatient analysis of pediatric status asthmaticus long-term outcomes focused on allergic evaluation at the time of exacerbation. Allergy testing is recommended in any state of persistent asthmatic disease. Given sIgE testing is available during acute hospitalization, as opposed to skin prick testing, the opportunity to analyze sIgE data on acute and long-term asthma outcomes reflects an opportunity to maximize long-term management of chronic disease during an acute event.

This study found inpatient knowledge of atopic predisposition via sIgE testing in asthmatics who required hospitalization correlated with improved outpatient disease management with respect to time to next ER visit and systemic corticosteroid requirement. While this study evaluated for post-hospitalization outcomes between known asthmatics who underwent sIgE testing and those that did not, prescribed outpatient asthma controller/rescue therapy or subsequent outpatient allergy/immunologic therapies were not included in this data analysis. Statistically significant prolongation of the time to ER and systemic corticosteroid requirement, and reduction in subsequent hospitalization for asthma exacerbation, was demonstrated particularly in patients aged 4 to 21 years with

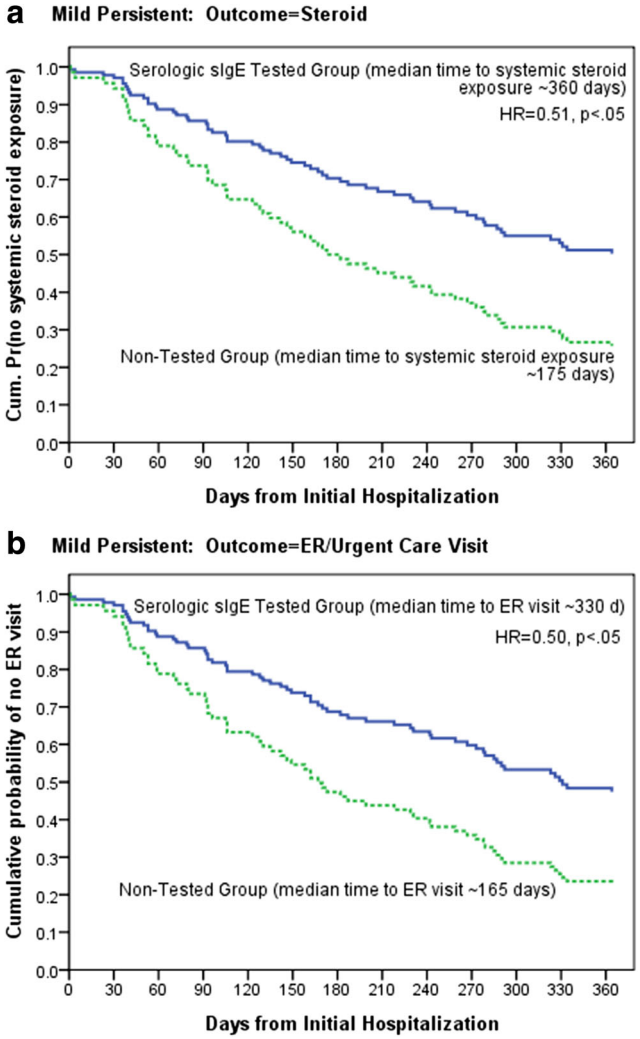


Fig. 3 In mild persistent patients, time to first ER/urgent care visit and systemic steroid exposure during year following initial hospitalization was significantly extended in serologic sIgE-tested compared to non-tested patients ($p < 0.05$). Estimated in adjusted model at distribution of factors in population (21.2% adolescent, 62.5% male, and 47.1% African-American). Blue solid line = serologic sIgE-tested group; green dash line = non-tested group

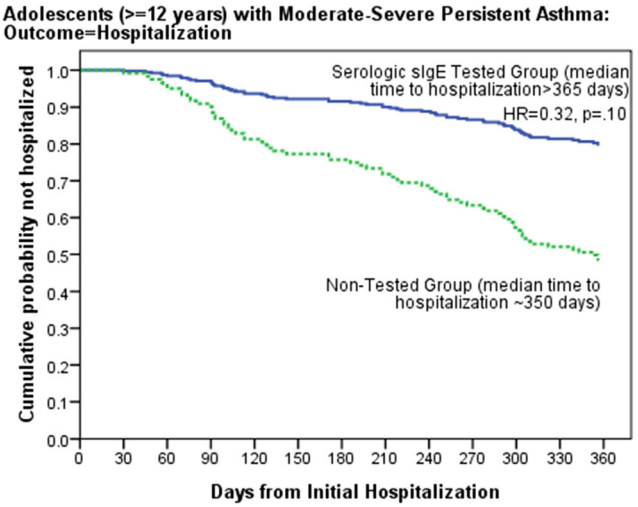


Fig. 4 In moderate-severe patients, time to subsequent hospitalization requirement during year following initial hospitalization was extended in the serologic sIgE-tested compared to non-tested group ($p = 0.103$). Estimated in adjusted model at distribution of factors in population (61.5 male and 37.9% African-American). Blue solid line = serologic sIgE-tested group; green dash line = non-tested group

mild persistent asthma classification. While these outcome data were not found to be statistically significant in asthmatics with moderate-severe subtypes, the average time to subsequent hospitalization during the year following initial hospitalization was extended in adolescent asthmatics who underwent serologic sIgE testing at initial hospitalization compared to those who did not.

Blood-based allergy evaluation as part of inpatient asthma treatment helps inform education efforts aimed to trigger avoidance strategies and the therapeutic approach to achieve and maintain well-controlled disease. Given the difficulties in controlling asthma including medication noncompliance, barriers to care, lack of follow-up, psychosocial stressors, and environmental exposures in our large intervention cohort, our results are particularly meaningful. Serologic sIgE testing in patients hospitalized for an asthma exacerbation corresponded to the reduced hazard of a future ER visit and systemic steroid exposure in asthmatics with mild persistent disease. In more severe adolescent asthmatics, serologic sIgE testing appeared protective ($p = 0.10$) against future hospitalization due to asthma exacerbation.

Our study has several limitations. Generalizability of study findings are limited to patients deemed high risk due to asthma-related hospitalization. Potential for selection bias due to patients with more severe asthma being more likely to undergo serologic sIgE testing was mitigated by applying asthma severity stratification in the analyses. Asthma exacerbation severity at baseline hospitalization did confer a higher tendency for serologic sIgE testing at our center as deemed "protective" against future ER visits, hospitalizations, or deployment of systemic steroids. Other limitations include the inclusion of only one hospital site and medical record review shortcomings. There was insufficient data to compare improvement in outpatient lung function based on $FEV_1\%$.

Conclusions

Serum allergy evaluation by sIgE during hospitalization for acute asthma exacerbation reduced the hazard of an ER visit and systemic corticosteroids requirement by half in mild persistent patients ($p < 0.05$). Atopic diagnosis by serologic sIgE in asthmatics requiring hospitalization was shown to improve outpatient disease management specifically in time to next ER visit and next exacerbation (systemic corticosteroid

requirement). In the current cost-contained environment of incentives to lower the LOS of hospitalized asthmatics, it is prudent to balance such perceived incentives against major future benefits of longer hospital stay which incorporates justified important allergy testing. The cost utilization of this testing approach will be evaluated in further prospective studies.

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Contributions Dr. Brock and Dr. Randhawa donated substantial contributions to the conception and design of the work, in addition to all other aspects of authorship as below. Other listed authors contributed to the acquisition, analysis, or interpretation of data for the work, drafting the work, and revising it critically for important intellectual content, final approval of the version to be published and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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At a Glance Commentary: To date, no study has analyzed the efficacy of blood-based allergy evaluation (serologic sIgE testing) as part of inpatient asthma management to determine post-hospitalization asthma treatment and clinical outcomes. The goal of this study is to compare post-hospitalization outcomes of asthmatics who underwent objective allergy and lung function testing during initial hospitalization to a cohort which did not.