Original Article

# Fungal Sensitization Is Associated with Increased Risk of Life-Threatening Asthma

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***What is already known about this topic?*** Fungal sensitization in patients with asthma has been associated with severe asthma and worse asthma outcomes.

***What does this article add to our knowledge?*** Fungal sensitization is common in patients with asthma referred to an urban pulmonary subspecialty clinic and is associated with sensitization to more nonfungal allergens and increased risk of life-threatening asthma compared with patients with nonfungal sensitization or no sensitization.

***How does this study impact current management guidelines?*** The results of this study suggest that patients with persistent asthma should be tested for fungal sensitization, and those patients with asthma found to have fungal sensitization should have close follow-up and optimization of treatment to reduce their risk of life-threatening asthma episodes.

**BACKGROUND: Fungal sensitization in patients with asthma has been associated with severe asthma and worse asthma outcomes.**
**OBJECTIVE: The purpose of this study was to determine the relationship between fungal and nonfungal sensitization, asthma severity, and clinical outcomes.**
**METHODS: A retrospective review of patients with asthma evaluated in an urban pulmonary subspecialty clinic in the United States was performed. Patients with fungal and nonfungal allergen sensitization were identified based on serum-specific immunoglobulin E (sIgE) testing. Demographic, clinical, laboratory, and spirometric data were obtained. The relationship between fungal sensitization and asthma outcomes was examined.**
**RESULTS: Of 390 patients with asthma identified, 307 had sIgE testing, of whom 53 (17.3%) had fungal sensitization, 117 (38.1%) had nonfungal sensitization, and 137 (44.6%) had no sensitization. Patients with fungal sensitization were more likely to be sensitized to ≥5 allergens than patients with nonfungal sensitization (66% for fungal vs 29% for nonfungal, $P < .001$). Serum IgE concentrations were highest in patients with fungal sensitization compared with patients with no sensitization or nonfungal sensitization (median, 825, 42, and 203 IU/mL, respectively, $P < .001$). Fungal sensitized patients were more likely to require intensive care unit (ICU) admission and mechanical ventilation than those with no sensitization or nonfungal sensitization (13.2%, 3.7%, and 3.4%, respectively, for ICU admission, $P = .02$; 11.3%, 1.5%, and 0.9%, respectively, for ventilation, $P < .001$).**
**CONCLUSIONS: Fungal sensitization is common in patients with asthma in an urban setting and is associated with greater sensitization to nonfungal allergens and increased risk of life-threatening asthma.** © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

***Key words:*** *Allergens; Atopy; Serum-specific immunoglobulin E; Severe asthma*

Asthma is a common respiratory disease that affects approximately 7.7% of the population of the United States.[1] Up to 10% of patients with asthma suffer from severe disease,[2] which is defined as asthma requiring treatment with high doses of inhaled corticosteroids (ICS) plus a second controller medicine and/or systemic corticosteroids.[3] Severe asthma is associated with increased morbidity, mortality, and health care cost.[4] However, asthma is a heterogeneous syndrome with variable clinical presentations and outcomes[5] that can be classified into different phenotypes. One proposed phenotype includes patients who show evidence of sensitization to fungal allergens.[6]

Sensitization to allergens, particularly inhaled ones, has been linked to the development of asthma[7] as well as asthma severity.[8,9] Fungal sensitization in patients with asthma has been associated with increased asthma severity[10-12] as well as worse clinical outcomes, including worse asthma control,[12] decreased lung function,[13] increased hospital and intensive care unit (ICU) admissions,[14,15] respiratory arrest,[16] and asthma-related deaths.[17] The relationship between sensitization to nonfungal allergens and asthma severity and

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*Abbreviations used*
*EMR- Electronic medical record*
*$FEV_1$- Forced expiratory volume in 1 second*
*FVC- Forced vital capacity*
*GINA- Global Initiative for Asthma*
*ICD- International Classification of Diseases*
*ICS- Inhaled corticosteroid*
*ICU- Intensive care unit*
*LABA- Long-acting β-agonist*
*NHANES- National Health and Nutrition Examination Survey*
*SAFS- Severe asthma with fungal sensitization*
*sIgE- Serum-specific immunoglobulin E*
*SPT- Skin prick test*

outcomes is less clear, with some studies finding an association[15,18] and others finding no association.[11,14] The mechanisms underlying the link between fungal sensitization and asthma severity are not completely elucidated. Some proposed mechanisms include fungal-derived proteins acting as allergens or directly leading to airway damage and allergic response, chronic colonization of atopic patients by fungi, and mold exposure in the environment.[6] Because of the link between severe asthma and fungal sensitization, Denning et al[6] proposed the term "severe asthma with fungal sensitization" (SAFS) to describe patients with severe asthma who demonstrate evidence of fungal sensitization. Clinical trials investigating the use of antifungal agents in patients with SAFS have had conflicting results.

A wide range of prevalence of fungal sensitization in asthma has previously been reported.[11,14,16,19] Factors contributing to the differences in prevalence include variation in the specific fungal allergens tested as well as the method of diagnosis. Although the diagnosis can be made by the skin prick test (SPT) or measurement of serum-specific immunoglobulin E (sIgE), there may be poor concordance between SPTs and sIgE in severe asthma.[19] In addition, many studies examining the prevalence of fungal sensitization were performed in highly select and small groups of patients, including patients with severe asthma,[19] patients admitted to the ICU,[14] and patients with a history of respiratory arrest.[16] Two large studies based on the European Community Respiratory Health Survey found that the prevalence of fungal sensitization in patients with asthma increased with asthma severity.[11] More information is needed about the rates of fungal and nonfungal sensitization and its impact on asthma severity in outpatients with asthma. The aim of this study was to determine the relationship between fungal and nonfungal sensitization, asthma severity, and clinical outcomes in an urban subspecialty clinic in the United States. We hypothesized that fungal sensitization increases with asthma severity and is associated with worse clinical outcomes.

## METHODS

This research was approved by the Institutional Review Board of Baylor College of Medicine and Affiliated Hospitals. A waiver of written consent was obtained.

### Participants

Patients with asthma were identified by search of the electronic medical record (EMR) of Ben Taub General Hospital in Houston, Texas. The hospital primarily serves the uninsured population of Harris County. Patients who had outpatient visits to the hospital or its associated outpatient clinic between January 1, 2010, and December 31, 2015, and carried an International Classification of Diseases (ICD)-9 or ICD-10 code for asthma were identified. Patients not seen in the pulmonary subspecialty clinic were then excluded. For the remaining patients, the EMR was then reviewed to confirm a clinical diagnosis of asthma and to determine if patients had undergone sIgE testing. Patients were excluded if they did not have a clinical diagnosis of asthma (if an alternate diagnosis was made to explain the patient's symptoms/presentation or if the treating physician did not agree with a clinical diagnosis of asthma) or if there was a greater than 2-year time difference between the time of sIgE testing and the pulmonary clinic visit.

### Clinical data

Data including sex, height, weight, asthma history, and existence of concomitant pulmonary diseases were obtained from a chart review. For patients with sIgE testing, the pulmonary clinic appointment closest to the date of testing was identified. For patients without sIgE testing, the most recent pulmonary clinic appointment was identified. Clinical data were extracted from this visit. Asthma medications and health care utilization in the year preceding the identified clinic appointments were recorded. Asthma control was assessed using the Global Initiative for Asthma (GINA) 2015 guidelines.[20] Laboratory data including sIgE testing results, serum IgE concentration, and blood eosinophil counts were collected. Spirometric parameters, based on the worst recorded forced expiratory volume in 1 second ($FEV_1$) when the patient was not in an exacerbation, were recorded.

### Allergy testing

Decision to order sIgE testing was made by the treating physician. The testing was performed by LabCorp (Houston, Tex) and included the quantitative measurement of sIgE for 29 common regional allergens (zone 6) via the ImmunoCAP method. Fungal allergens in this panel include *Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Mucor racemosus*, *Stemphylium herbarum*, and *Alternaria alternata*. The full panel of tested allergens can be found in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). An sIgE $\geq$0.35 kU/L was considered positive. Patients were considered to have fungal sensitization if they had a positive sIgE to one or more of the fungal allergens. Patients were considered to have nonfungal sensitization if they did not have a positive sIgE to any fungal allergens but had a positive sIgE to one or more nonfungal allergens.

### Data analysis

Summary statistics are presented for continuous variables as mean $\pm$ standard deviation if they were parametric and median (interquartile range) if they were nonparametric. Two-way comparisons were performed using the unpaired *t*-test for parametric variables and the Wilcoxon rank-sum test for nonparametric variables. Categorical variables were compared using the $\chi^2$ test or Fisher's exact test. Three-way comparisons were performed using ANOVA with post hoc Tukey's test for parametric variables and the Kruskal-Wallis test with post hoc Dunn's test for nonparametric variables. Poisson regression was performed for the number of episodes of clinical outcomes in patients with asthma and fungal sensitization compared with patients with asthma and no fungal sensitization (patients with no sensitization and nonfungal sensitization) in a model adjusted for race. All analyses were performed using Stata 11.0 software (StataCorp, College Station, Tex). All $P$ values are 2-sided with $P < .05$ considered statistically significant.

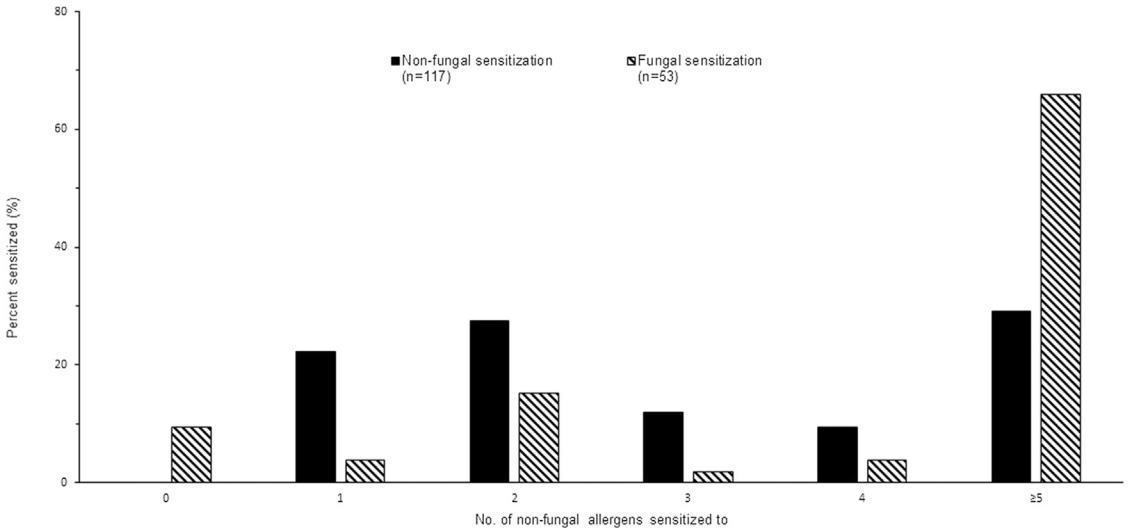


**FIGURE 1.** Sensitization to nonfungal allergens in patients with nonfungal sensitization (n = 117) compared with fungal sensitization (n = 53), $P < .01$, by $\chi^2$ analysis.

**TABLE I.** Baseline characteristics of patients with asthma with allergen testing

| | No sensitization (n = 137) | Nonfungal sensitization (n = 117) | Fungal sensitization (n = 53) | *P* value |
|---|---|---|---|---|
| Age, y | 50.8 ± 13.0 | 48.1 ± 13.8 | 47.8 ± 13.5 | .21 |
| Male, n (%) | 29 (21.2) | 23 (20.0) | 22 (41.5) | .005 |
| Hispanic, n (%) | 47 (34.3) | 52 (44.4) | 13 (24.5) | 03 |
| Race, n (%) | | | | |
| Non-black | 82 (59.9) | 75 (64.1) | 23 (43.4) | .04 |
| Black | 55 (40.1) | 42 (35.9) | 30 (56.6) | |
| BMI, kg/m$^2$ | 32.1 ± 7.6 | 32.7 ± 7.5 | 32.9 ± 8.0 | .77 |
| Current smoker, n (%) | 14 (10.2) | 6 (5.1) | 8 (15.1) | .09 |
| Never smoker, n (%) | 90 (65.7) | 79 (67.5) | 28 (52.8) | .16 |

*BMI*, Body mass index.
Values expressed as mean ± SD.

## RESULTS

A total of 894 patients with asthma were identified. Of these, 504 were not seen in the pulmonary subspecialty clinic or did not have a clinical diagnosis of asthma. Therefore, 390 patients were included in the analysis. Of these patients, 83 did not have prior sIgE testing and 307 did. Of the 307 patients who underwent sIgE testing, 137 (44.6%) had negative sIgE panels. Of the remaining 170 patients, 53 (17.3%) had fungal sensitization and 117 (38.1%) had nonfungal sensitization (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The majority of patients (85.7%) had allergen testing within 30 days of the index clinic visit. Results for individual allergen testing are provided in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). As shown in Figure 1, patients with fungal sensitization were less likely to have positive sIgE to less than 5 nonfungal allergens and more likely to have positive sIgE testing to 5 or more nonfungal allergens than patients with nonfungal sensitization.

Baseline characteristics of all patients with asthma are shown in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). Compared with patients without sIgE testing, patients with sIgE testing were more likely to be female, be prescribed ICS, long-acting β-agonists (LABA), and/or leukotriene receptor antagonists, have uncontrolled asthma, or be at a higher step of GINA treatment. Baseline characteristics of patients with asthma who underwent sIgE testing are presented in Table I. Compared with patients who had no sensitization or had nonfungal sensitization, patients with fungal sensitization were more likely to be male ($P < .005$) and black ($P = .04$) and less likely to be Hispanic ($P = .03$). As shown in Table II, there were no significant differences in asthma control, asthma medications, or GINA steps of therapy between patients with no sensitization, nonfungal sensitization, and fungal sensitization. Compared with patients with no sensitization, patients with fungal sensitization had a higher absolute but not predicted forced vital capacity (FVC) and lower $FEV_1$/FVC ratio (see Table III). Patients with fungal sensitization had a higher serum IgE level compared with patients with no sensitization and patients with nonfungal sensitization ($P = .0001$).

Patients with fungal sensitization were more likely to require ICU admission ($P = .02$), intubation and mechanical ventilation ($P < .001$), and noninvasive ventilation ($P = .03$) in the year before their index clinic visits compared with patients with no sensitization or nonfungal sensitization (see Table IV). They

**TABLE II.** Asthma control and medication usage in patients with asthma and allergen testing

| | No sensitization (n = 137) | Nonfungal sensitization (n = 117) | Fungal sensitization (n = 53) | *P* value |
|---|---|---|---|---|
| Control, n (%) | | | | .85 |
| Well controlled | 21 (15.3) | 15 (12.8) | 6 (11.3) | |
| Partially controlled | 37 (27.0) | 32 (27.4) | 12 (22.6) | |
| Uncontrolled | 79 (57.7) | 70 (59.8) | 35 (66.0) | |
| ICS, n (%) | | | | .76 |
| Low dose | 22 (16.1) | 23 (20.0) | 8 (15.4) | |
| Medium dose | 81 (59.1) | 60 (51.3) | 25 (48.1) | |
| High dose | 25 (18.3) | 19 (16.2) | 11 (21.2) | |
| LABA, n (%) | 112 (81.8) | 96 (82.1) | 43 (82.7) | .99 |
| LTRA, n (%) | 63 (46.0) | 45 (38.5) | 23 (44.2) | .47 |
| LAMA, n (%) | 14 (10.2) | 8 (6.8) | 5 (9.6) | .62 |
| Oral steroids, n (%) | 2 (1.5) | 2 (1.7) | 2 (3.9) | .56 |
| GINA step, n (%) | | | | .20 |
| 1 | 10 (7.2) | 19 (16.2) | 6 (11.5) | |
| 2 | 7 (5.1) | 3 (2.6) | 2 (3.9) | |
| 3 | 21 (15.3) | 23 (20.0) | 11 (21.2) | |
| 4 | 79 (57.7) | 63 (53.9) | 24 (46.2) | |
| 5 | 20 (14.6) | 9 (7.7) | 9 (17.3) | |

*GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *LAMA*, long-acting antimuscarinic agent; *LTRA*, leukotriene receptor antagonist.

**TABLE III.** Spirometric and laboratory values in patients with asthma and allergen testing

| | No sensitization (n = 137) | Nonfungal sensitization (n = 117) | Fungal sensitization (n = 53) | *P* value |
|---|---|---|---|---|
| $FEV_1$, L | 1.86 ± 0.65 | 1.99 ± 0.63 | 1.96 ± 0.74 | .25 |
| $FEV_1$, % | 70.4 ± 17.9 | 71.6 ± 17.3 | 65.8 ± 20.6 | .16 |
| FVC, L | 2.61 ± 0.83 | 2.71 ± 0.80 | 2.98 ± 1.10* | .03 |
| FVC, % | 78.7 ± 16.1 | 79.5 ± 14.7 | 83.1 ± 17.6 | .23 |
| $FEV_1$/FVC | 71.8 ± 11.3 | 73.1 ± 14.2 | 66.5 ± 13.3*,† | .008 |
| IgE, IU/mL | 42 (21, 132) | 203 (69, 453)* | 825 (330, 1810)*,† | .0001 |
| Eosinophils, K/μL | 1.06 ± 2.78 | 0.63 ± 0.60 | 1.36 ± 5.2 | .27 |

*$FEV_1$*, Forced expiratory volume in 1 second; *FVC*, forced vital capacity.
Values expressed as mean ± SD for parametric variables and median (interquartile range) for nonparametric variables.
*$P < .05$ compared with no sensitization group by post hoc testing.
†$P < .05$ compared with nonfungal sensitization group by post hoc testing.

were also more likely to have a lifetime history of intubation with mechanical ventilation ($P < .001$) and ICU admission ($P = .004$). However, there were no significant differences in the number of exacerbations, emergency department visits, or overall hospitalizations between the groups. Poisson regression demonstrated a significant increase in the rate of ICU admissions, intubations and mechanical ventilation, noninvasive ventilation, and lifetime ICU admissions and intubations in patients with asthma and fungal sensitization compared with patients with asthma and no fungal sensitization after adjustment for race (see Table V).

## DISCUSSION

The aim of this study was to determine the relationship of fungal sensitization with asthma severity and outcomes in outpatients with asthma in an urban setting. We found that patients who were tested for allergen sensitization had more severe asthma than patients who were not tested. Patients who had fungal sensitization were predominantly black and were more likely to be male than patients with no sensitization or nonfungal sensitization. Although asthma severity as defined by medication usage was not different between patients with and without fungal sensitization, patients with fungal sensitization were more likely to have life-threatening asthma than patients with no sensitization or nonfungal sensitization.

We compared patients with asthma who did and did not receive sIgE testing to identify any selection bias in patients who were tested. In this cohort of patients, sIgE testing was more frequently performed if patients were female or had uncontrolled asthma requiring higher steps of therapy. This finding aligns with current recommendations for allergen testing in patients with asthma. The National Asthma Education and Prevention Program recommends the use of skin testing or *in vitro* testing to assess sensitivity to allergens in patients who have persistent asthma, because exposure to inhaled allergens to which patients are sensitized can increase asthma symptoms or precipitate exacerbation.[21] GINA guidelines state that allergen testing

**TABLE IV.** Asthma history in all patients with asthma and allergen testing

| | No sensitization (n = 137) | Nonfungal sensitization (n = 117) | Fungal sensitization (n = 53) | *P* value |
|---|---|---|---|---|
| Exacerbations*, n | 1 (0, 3) | 1 (0, 3) | 1 (0, 2) | .84 |
| ED visits*, n | 0 (0, 1) | 0 (0, 1) | 0 (0, 1) | .93 |
| Hospitalizations*, n | 0 (0, 1) | 0 (0, 0) | 0 (0, 1) | .34 |
| ≥1 ICU admission*, n (%) | 5 (3.7) | 4 (3.4) | 7 (13.2) | .02 |
| ≥1 intubation*, n (%) | 2 (1.5) | 1 (0.9) | 6 (11.3) | <.001 |
| ≥1 episode noninvasive ventilation*, n (%) | 5 (3.7) | 3 (2.6) | 6 (11.3) | .03 |
| Lifetime history of Intubation, n (%) | 10 (7.3) | 7 (6.0) | 13 (24.5) | <.001 |
| Lifetime history of ICU, n (%) | 15 (11.0) | 13 (11.1) | 15 (28.3) | .004 |

*ED*, Emergency department; *ICU*, intensive care unit.
Data reported as median (interquartile range).
*In the last 1 y.

**TABLE V.** Poisson regression of clinical outcomes in a model adjusted for black race in patients with fungal sensitization compared with patients with no fungal sensitization

| Outcome | Incidence rate ratio | *P* value |
|---|---|---|
| Hospitalization(s)* | 0.86 (0.52, 1.42) | .55 |
| ICU admission(s)* | 3.29 (1.21, 8.98) | .02 |
| Intubation(s)* | 7.08 (1.75, 28.57) | .006 |
| Noninvasive ventilation* | 2.97 (1.02, 8.68) | .047 |
| Lifetime history of intubation | 3.30 (1.58, 6.87) | .001 |
| Lifetime history of ICU | 2.40 (1.27, 4.54) | .007 |

*ICU*, Intensive care unit.
Data expressed as incidence rate ratio (95% confidence interval).
Incidence rate ratio defined by patients with asthma and fungal sensitization compared with patients with asthma and no fungal sensitization. Outcomes are numbers of episodes per patient.
*In the year prior.

should be performed in patients with persistent symptoms and/or exacerbations despite treatment with ICS.[20] However, because the untested patients included some patients with more severe asthma, it is possible that patients with fungal sensitization were not identified because of lack of testing.

Sensitization to all tested allergens other than cat hair/dander, *Dermatophagoides pteronyssinus*, and *D. farinae* was more common in patients with fungal sensitization than in those with nonfungal sensitization. In addition, more than twice as many patients with fungal sensitization as compared with nonfungal sensitization were sensitized to 5 or more nonfungal allergens. In the general population, sensitization to multiple allergens is more common than sensitization to a single allergen. Two studies using data from the National Health and Nutrition Examination Surveys (NHANES) found that less than 30% of patients with sensitization were sensitized to a single allergen.[22,23] However, the percentage of the population sensitized decreased as the number of positive test responses increased.[22] In patients with asthma, sensitization to multiple allergens is common, and sensitization to molds alone has been found to be extremely rare.[11] In a study of patients with severe asthma, half had sensitization to both fungal and nonfungal allergens.[19] The finding of greater sensitization in patients with asthma and fungal sensitization suggests that fungal sensitization may be a marker of an allergic phenotype. Allergic asthma is defined by the presence of allergic sensitization and a correlation between allergen exposure and asthma symptoms.[24] One biomarker of allergic asthma is total serum IgE level, which is more commonly elevated in allergic compared with nonallergic asthma,[25] is inversely associated with lung function in asthmatics,[26] and is associated with the prevalence of asthma.[27] In the present study, patients with fungal sensitization had a higher total serum IgE concentration than patients with no sensitization or nonfungal sensitization. Although there is considerable overlap in IgE between atopic and nonatopic populations,[28] the finding of a higher serum IgE concentration in patients with fungal sensitization compared with patients with no sensitization or nonfungal sensitization suggests that fungal sensitization may be a marker of allergic asthma. In support of the link between T2 inflammation and fungal-associated asthma, omalizumab, a monoclonal antibody against IgE, has been reported to have efficacy in the treatment of allergic bronchopulmonary aspergillosis. To date, there have been no clinical trials of omalizumab or other biologic therapy targeted at T2 inflammation in the subset of patients with fungal sensitization.[29]

Compared with patients with no sensitization or nonfungal sensitization, patients with asthma and fungal sensitization were more likely to be black and male. In the United States, emergency department visits, hospitalizations, and fatalities related to asthma occur more frequently in blacks.[30,31] Although socioeconomic differences such as income, education, and access to health care likely play a role in the increased health care utilization and mortality from asthma in blacks, racial differences in allergic sensitization may also contribute to disparities in asthma outcomes. Prior studies also support the finding of a higher rate of allergen sensitization in blacks compared with whites. In one NHANES study,[22] males were more likely than females to have more than one positive skin test, and non-Hispanic blacks had an odds ratio of 1.6 compared with non-Hispanic whites of having a positive skin test. In another NHANES study, non-Hispanic blacks had the highest rate of sensitization to all tested allergens, including *Aspergillus* and *Alternaria*.[32] Another study of allergen-specific IgE in pregnant women in Boston found that more black women had sensitization to individual allergens than white women, and that black women were 2.5 times more likely than white women to have sensitization to 3 or more allergens, even after adjustment for socioeconomic factors.[33] Because fungal sensitization in this study was associated with greater overall sensitization, the finding that more patients with fungal sensitization were black is consistent with these other studies.

We demonstrated an association between fungal sensitization and severe manifestations of asthma. However, other assessments of asthma severity, such as medication usage, were not different between patients with and without fungal sensitization. Although there was a higher FVC and a lower $FEV_1$/FVC ratio in patients with fungal sensitization compared with those with no sensitization, these results may be inaccurate due to inconsistent schedule of testing in this group of patients, leading to inability to identify the worst lung function in some patients. Prior studies demonstrating an association between fungal sensitization and asthma severity had asthma severity classified as mild, moderate, and severe based on a model described by Ronchetti et al[34] that includes a number of elements.[10,11] Therefore, it is not possible to know which specific elements of the model were different between patients with and without fungal sensitization. A previous study did find that patients admitted to the ICU were more likely to have fungal sensitization than non-ICU hospitalized patients with asthma or outpatients with asthma.[14] In the present study, we showed that multiple outcomes that are consistent with life-threatening asthma, including ICU admission and need for invasive and noninvasive mechanical ventilation, both by history and in the year before evaluation, differed between patients with and without fungal sensitization, thus providing strong evidence for a link between life-threatening asthma and fungal sensitization. The exact reason why fungal sensitization leads to greater risk of life-threatening asthma is unclear and needs further exploration. The finding that medication usage is not different in patients with and without fungal sensitization suggests that fungal sensitization may impact only acute exacerbations in patients with asthma. It is possible that acute exposure to fungal allergens in patients who are sensitized leads to severe exacerbations. In support of this hypothesis, increased exposure to fungal allergens has been shown to be associated with an increase in asthma attacks.[35] Because black patients with asthma have more hospitalizations and fatalities than non-black patients, we cannot exclude that black race was a confounder in the increased life-threatening events seen in patients with fungal sensitization. However, an analysis adjusted for black race demonstrated a statistically significant increase in the rate ratio of life-threatening events with fungal sensitization compared with no fungal sensitization.

Our study has several limitations. Patients were initially identified using ICD coding, which may have missed patients if ICD coding was incorrect. This was a retrospective study, and although correlations between fungal sensitization and asthma outcomes were found, we cannot say that any of these associations were causative in nature. Decision to order sIgE testing was based on the treating physician's clinical assessment, and sIgE testing may not have been performed on some patients with fungal sensitization. Finally, this is a select population of patients who required pulmonary subspecialty evaluation for asthma, which represents a population with more severe and symptomatic asthma and may not be generalizable to all patients with asthma.

## CONCLUSIONS

Fungal sensitization is common in patients with asthma referred to an urban pulmonary subspecialty clinic. Patients with asthma and fungal sensitization are more likely to have a higher serum IgE concentration and sensitization to more nonfungal allergens than patients with nonfungal sensitization, suggesting that fungal sensitization may be a marker of an allergic phenotype. Having fungal sensitization was associated with worse outcomes, as evidenced by higher rates of ICU admission and need for invasive and noninvasive ventilation. Identification of patients with fungal sensitization may lead to further study of targeted interventions that may improve outcomes in these patients.

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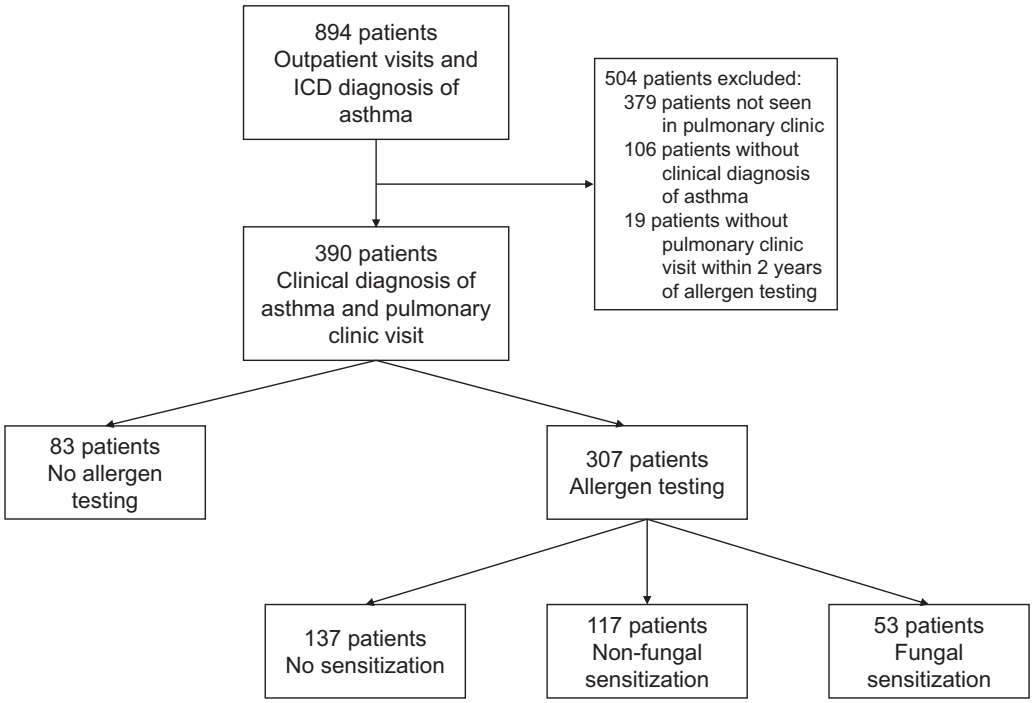


**FIGURE E1.** Flow of patients through the study. *ICD*, International Classification of Diseases.

**TABLE E1.** Number of patients sensitized to individual allergens in all patients with asthma and allergen testing

| | Nonfungal sensitization (n = 117) | Fungal sensitization (n = 53) | *P* value |
|---|---|---|---|
| *Dermatophagoides pteronyssinus* | 67 (67.3) | 31 (58.5) | .88 |
| *Dermatophagoides farinae* mite | 74 (63.3) | 36 (67.9) | .55 |
| Cat hair/dander | 47 (40.2) | 20 (37.7) | .76 |
| Bermuda grass | 32 (27.4) | 30 (57.7) | <.001 |
| Timothy | 33 (28.2) | 32 (61.5) | <.001 |
| Johnson grass | 25 (21.4) | 26 (50.0) | <.001 |
| Bahia grass | 27 (23.1) | 27 (51.9) | <.001 |
| *Penicillium chrysogenum* | | 26 (50.0) | |
| *Cladosporium herbarum* | | 18 (34.0) | |
| *Aspergillus fumigatus* | | 22 (41.5) | |
| *Mucor racemosus* | | 12 (22.6) | |
| *Stemphylium herbarum* | | 29 (55.8) | |
| Oak, white | 19 (16.2) | 21 (40.4) | .001 |
| Elm, American, white | 13 (11.1) | 19 (36.5) | <.001 |
| Dog epithelia | 27 (23.1) | 21 (39.6) | .03 |
| Cockroach, American | 23 (20.0) | 19 (35.9) | .02 |
| *Alternaria tenuis* | | 32 (60.4) | |
| Hickory, white | 14 (12.0) | 17 (32.7) | .001 |
| Sycamore, American | 14 (12.0) | 17 (32.7) | .001 |
| Mulberry, red | 7 (6.0) | 15 (28.9) | <.001 |
| Sweet gum | 9 (7.7) | 11 (21.2) | .012 |
| Cedar, mountain | 21 (18.0) | 26 (50.0) | <.001 |
| Ragweed, short/common | 25 (21.4) | 27 (51.9) | <.001 |
| Mugwort | 18 (15.4) | 15 (28.9) | .04 |
| Plantain, English | 14 (12.0) | 16 (30.8) | .003 |
| Pigweed, rough | 12 (10.3) | 23 (44.2) | <.001 |
| Sheep sorrel | 16 (13.7) | 17 (32.7) | .004 |
| Nettle | 12 (10.3) | 16 (30.8) | .001 |
| Maple/Box elder | 14 (12.0) | 18 (34.6) | .001 |

All data reported as n (%).

**TABLE E2.** Characteristics of all patients with asthma

| | No allergen testing (n = 83) | Allergen testing (n = 307) | *P* value |
|---|---|---|---|
| Age, y | 52 ± 14 | 49 ± 13 | .15 |
| Male, n (%) | 29 (34.9) | 74 (24.1) | .047 |
| Hispanic, n (%) | 19 (22.9) | 112 (36.5) | .02 |
| Race, n (%) | | | .10 |
| Caucasian | 34 (41.0) | 156 (50.8) | |
| Black | 36 (43.4) | 127 (41.4) | |
| Asian | 13 (15.7) | 23 (7.5) | |
| Other | 0 (0.0) | 1 (0.33) | |
| BMI, kg/m$^2$ | 31.2 ± 8.8 | 32.5 ± 7.6 | .19 |
| Current smoker, n (%) | 11 (13.3) | 28 (9.1) | .27 |
| Never smoker, n (%) | 47 (56.6) | 197 (64.2) | .21 |
| Asthma control, n (%) | | | <.001 |
| Well controlled | 44 (53.0) | 42 (13.7) | |
| Partially controlled | 14 (16.8) | 81 (26.4) | |
| Uncontrolled | 25 (30.1) | 184 (60.0) | |
| Treatment, n (%) | | | |
| ICS | 63 (75.9) | 276 (90.0) | .001 |
| LABA | 55 (66.3) | 251 (82.0) | .002 |
| LTRA | 16 (19.3) | 131 (42.8) | <.001 |
| LAMA | 8 (9.6) | 27 (8.8) | .82 |
| Oral steroids | 2 (2.4) | 6 (2.0) | .80 |
| GINA step, n (%) | | | <.001 |
| 1 | 22 (26.5) | 35 (11.4) | |
| 2 | 6 (7.2) | 12 (3.9) | |
| 3 | 10 (12.1) | 55 (18.0) | |
| 4 | 44 (53.0) | 166 (54.3) | |
| 5 | 1 (1.2) | 38 (12.4) | <.001 |
| $FEV_1$, % predicted | 67 ± 22 | 70 ± 18 | .29 |
| $FEV_1$/FVC | 71 ± 15 | 71 ± 13 | .93 |

*$FEV_1$*, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *LAMA*, long-acting antimuscarinic agent; *LTRA*, leukotriene receptor antagonist.
Values expressed as mean ± SD.