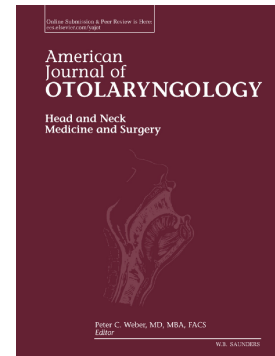


Accepted Manuscript

Inhalant allergen sensitization is an independent risk factor for the development of angioedema

Jacob E. Kuperstock, Nicholas Pritchard, Michal Horný, Christopher C. Xiao, Christopher Brook, Michael P. Platt



PII: S0196-0709(17)30844-X

DOI: <https://doi.org/10.1016/j.amjoto.2017.12.013>

Reference: YAJOT 1951

To appear in:

Received date: 24 October 2017

Please cite this article as: Jacob E. Kuperstock, Nicholas Pritchard, Michal Horný, Christopher C. Xiao, Christopher Brook, Michael P. Platt, Inhalant allergen sensitization is an independent risk factor for the development of angioedema. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Yajot(2017), <https://doi.org/10.1016/j.amjoto.2017.12.013>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title: Inhalant Allergen Sensitization is an Independent Risk Factor for the Development of Angioedema

Jacob E. Kuperstock, MD¹, Nicholas Pritchard, MD^{2,3}, Michal Horný, Ph.D, MSc^{4,5}, Christopher C. Xiao, MD^{2,6}, Christopher Brook, MD¹, and Michael P. Platt, MD, MSc¹

1. Department of Otolaryngology – Head and Neck Surgery, Boston University School of Medicine, Boston, MA 02118
2. Boston University School of Medicine, Boston, MA 02118
3. Department of Otolaryngology – Head and Neck Surgery, University of South Florida, Tampa, FL 33612
4. Emory University School of Medicine, Department of Radiology and Imaging Sciences, Atlanta, GA 30322
5. Emory University Rollins School of Public Health, Department of Health Policy and Management, Atlanta, GA 30322
6. Department of Otolaryngology – Head and Neck Surgery, Kaiser Permanente Northern California, Oakland CA 94612

Keywords: Angioedema, Hypersensitivity, Atopy, Allergy, Immunoglobulin E, sensitization, allergic rhinitis, Type I hypersensitivity, aeroallergen, inhalant allergen

Conflicts of Interest/Financial Disclosure: Jacob Kuperstock, MD and Michal Horný, Ph.D, have equity interest in Doc Odds, LLC. All other authors do not have any conflicts to disclose. The research presented is not related to the disclosed interests above.

Corresponding author:

Michael P. Platt, MD, MS

820 Harrison Avenue, FGH Building, 4th Floor

Boston, MA 02118

Ph: 617-638-8124

Fax: 617-638-7965

Michael.platt@bmc.org

ACCEPTED MANUSCRIPT

Title: Inhalant Allergen Sensitization is an Independent Risk Factor for the Development of Angioedema

Jacob E. Kuperstock, MD¹, Nicholas Pritchard, MD^{2,3}, Michal Horný, Ph.D, MSc^{4,5}, Christopher C. Xiao, MD^{2,6}, Christopher Brook, MD¹, and Michael P. Platt, MD, MSc¹

ABSTRACT

Background/Objective: The etiology and risk factors for angioedema remain poorly understood with causative triggers often going undiagnosed despite repeated reactions. The purpose of this study was to determine the relationship between inhalant allergen sensitization and angioedema.

Methods: A retrospective review of patients who had in vitro inhalant allergy testing from 2006 to 2010 was performed. Patients with a diagnosis of angioedema who underwent inhalant allergy testing were identified. Analyses for co-morbidities, class of sensitization, seasonal timing of angioedema, and concurrent use of known hypertensive medications that can cause angioedema were performed.

Results: There were 1,000 patients who underwent inhalant allergy testing and qualified for the study. 37/1000 had at least one episode of angioedema and of these patients, 34 had positive inhalant sensitization testing results. Multivariate regression models showed overall sensitization status, seasonal allergen and epidermal/mite sensitization as independent risk factors ($p<0.001$, $p=0.005$, $p=0.025$ respectively) when controlling for ACE inhibitor use and other covariates. Tree, and epidermal/mite sensitizations were independent risk factors for angioedema in mono-sensitized subject analysis ($p=0.028$, $p=0.029$, respectively).

Conclusion: Both seasonal and perennial allergen sensitizations are independent risk factors for the development of angioedema. In patients with angioedema and an unknown trigger, inhalant allergen sensitization should be considered as a potential contributing factor to the development of angioedema.

Keywords: Angioedema, Hypersensitivity, Atopy, Allergy, Immunoglobulin E, sensitization

LEVEL OF EVIDENCE: 4, Retrospective case series

INTRODUCTION

Angioedema is a serious reaction characterized by an acute onset of localized edema of the subcutaneous and submucosal tissue from an increase in vascular permeability mediated by vasoactive agents.^[1] Angioedema often requires immediate evaluation by multiple healthcare providers and at times critical airway intervention on the part of otolaryngologists, allergists, emergency medicine physicians and anesthesiologists. It is a rare cause of death with an incidence of 0.1-2.2%, yet it is commonly treated in the emergency setting and often requires significant resources for hospitalization.^[2-4] Although numerous studies have reported on angioedema, the causes are poorly understood.^[5,6]

Angioedema has been classified into two major groups, acquired and hereditary.^[2] Hereditary is often recurrent and related to a C1-esterase inhibitor deficiency.^[7] The other classifications include angiotensin converting enzyme inhibitor (ACE-I) related, idiopathic histaminergic and idiopathic non-histaminergic.^[1,7] A recent retrospective analysis of 1,058 patients with angioedema found that ACE-I related angioedema made up 17% of the cohort while idiopathic histaminergic and non-histaminergic comprised a combined 42%.^[3] These groups, however, are often related and there can be continued recurrent angioedema events of unknown etiology despite discontinuation of ACE-I use.^[8] Since angioedema is related to type I hypersensitivity reactions, this study was completed to better determine the relationship between common inhalant allergen sensitizations and angioedema.

MATERIAL AND METHODS

IRB approval, study number H-33251, was obtained at Boston University Medical Center.

Patients were identified for inclusion in the study if they had undergone in vitro sensitivity testing at a single tertiary academic medical center between 2006 and 2010. Allergy testing was performed by ELISA (ImmunoCap, Phadia, Sweden) for 29 inhalant allergens. Several patients had repeated visits for testing of which their sensitization data were combined. The final study sample comprised of 1,046 encounters of which 1,000 individual patients qualified.

Retrospective chart review was then completed identifying demographics including age, sex, ethnicity, and hypertension status determined by patients' use of hypertensive medications including ACE-I, beta-blockers, thiazides and calcium channel blockers (CCB). Initial use or duration of hypertensive medications was not included due to chart review restrictions. Allergen sensitizations were recorded for individual inhalant allergens and also organized by class (trees, grasses, weeds, molds, epidermal/mites). Epidermal allergens were defined as cat and dog sensitizations. Mites were defined as *dermatophagoides farinae* and *dermatophagoides pteronyssinus* sensitizations. Class of allergen sensitization was assigned to a season; i.e., trees = spring (March, April, May), grasses = summer (June, July, August), weeds = fall (September, October, November). Mold, epidermal and mite sensitizations were designated as perennial and therefore not associated with any specific season. Finally, the season of each angioedema event was determined based on the date of diagnosis. The type of angioedema and location of edema were not included in the study since not all patients were examined at the single institution during their angioedema episode and due to variation in clinical documentation.

A set of multivariate logistic regression models was used to assess whether allergen sensitization was a risk factor for angioedema. The first model used an indicator of any allergen sensitization as the main independent predictor of angioedema (Model 1). The second model disentangled the main predictor into sensitization to seasonal allergens and sensitization to perennial allergens (Model 2). The third model further separated the predictor into five major allergen classes as the main predictors of angioedema (Model 3). Because the estimates in Model 2 and Model 3 could suffer from multi-collinearity due to an association among the main predictors (poly-sensitization), a sensitivity analysis was performed by restricting the sample to individuals who were sensitized only to the particular group or class of allergens of interest or not sensitized at all. All multivariate models were adjusted for age, gender, ethnicity, and the use of ACE inhibitors. Models were also adjusted for the diagnosis of asthma, nasal polyposis and the use of other hypertensive medication besides ACE inhibitors when possible (restrictions were due to sample size and the consequent lack of degrees of freedom). The same set of three multivariate analyses were stratified by hypertension status in order to understand if hypertensive patients had similar risk factors compared to non-hypertensive patients.

To determine the effect of seasonal occurrence on angioedema, it was hypothesized that angioedema is equally likely to occur in each of the four seasons among those with no allergen sensitization and those with only perennial allergen sensitization, whereas angioedema is more likely to occur during the appropriate allergy season (“in-season”) rather than during the other seasons (“off-season”) among those with seasonal allergens sensitization. To test these hypotheses, a unit of analysis, one “person-season”, allowed for control of the different length of exposure for mono-sensitized and poly-sensitized patients. This analysis describes the number of

seasonal opportunities a patient has during the study period to have an angioedema event during the season of their associated allergen sensitization. The sample comprised of 20,000 person-seasons (1,000 individuals followed for 20 seasons). For each person-season, it was noted whether the individual was sensitized to allergens associated with the particular season. Chi-squared tests (or Fisher's exact tests when appropriate) were performed to assess the association between season and angioedema events among those with no allergen sensitization and among those with perennial but no seasonal allergens sensitization. Finally, a multivariate logistic regression model was completed with angioedema as the outcome and an indicator of the appropriate allergy season as the main predictor using the subsample of individuals with seasonal allergen sensitization. This model also controlled for season, perennial allergens sensitization, age, gender, ethnicity, diagnosis of asthma and the use of various hypertensive medications. Because perennial allergen sensitization might have confounded the estimates, the authors fitted the same model also to a subsample restricted to individuals with seasonal but no perennial allergen sensitization.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina). A level of statistical significance was set as $\alpha = 0.05$.

RESULTS

A total of 1,000 patients, predominantly comprised of African American (29.5%), Caucasian (29.0%) and Hispanic (22.5%) patients were included in the study (Table 1). The majority of subjects were females (59.8%). Over the five-year study period, the observed average annual rate of angioedema was 7.4 per 1,000 individuals, which is in line with the generally reported incidence rate.^[2,4,9] More than 60% patients tested positive to at least one allergen. Being sensitized to an allergen from a major allergen class was significantly associated with being sensitized to an allergen from another major allergen class (Figure 1). Analogously, sensitization to seasonal allergens was significantly associated with sensitization to perennial allergens (OR = 7.47, $p < 0.001$, Supplemental Table A1).

Table 2 summarizes the results of multivariate logistic regression models for angioedema risk factors when looking at all patients. All three models confirmed the existing knowledge that older patients, African Americans and ACE inhibitor users are at increased risk of angioedema. Model 1 showed that individuals with at least one allergen sensitization had significantly increased odds of angioedema (OR = 9.32, $p < 0.001$). When stratifying the sample by hypertensive status (Supplemental Tables A2), the odds of angioedema among those with hypertension were increased 14.2 times ($p = .012$) for those with sensitization to at least one allergen compared to those with no allergen sensitization even after adjusting for the specific hypertensive medication use and other covariates. Sensitization to at least one allergen was associated with the increased odds of angioedema among non-hypertensive patients as well (OR = 6.73, $p = .012$).

Model 2 separated the effect of seasonal and perennial allergen sensitization. When controlling for perennial allergen sensitization and other covariates, sensitization to seasonal allergens was associated with the increased odds of angioedema (OR = 3.79, $p = .003$). The association between angioedema and perennial allergen sensitization after adjusting for other covariates in all patients was not significant (OR = 2.30, $p = .073$). When patients with perennial allergen sensitization were removed as part of the sensitivity analysis, sensitization to seasonal allergens was associated with a significantly increased risk of angioedema (OR = 8.49, $p = .005$, Supplemental Table A4). Similarly, after removing patients with seasonal allergen sensitization, sensitization to perennial allergens was also significantly associated with an increased risk of angioedema (OR = 5.40, $p = .025$). Among those with hypertension, the odds of angioedema adjusted for perennial allergen sensitization, hypertensive medication use and other covariates were increased 6.91 times ($p = .008$) for those with seasonal allergen sensitization compared to those with no seasonal allergen sensitization (Supplemental Table A3).

Model 3 further separates allergens into the major allergen classes. No specific allergen class showed a statistically significant increased risk of angioedema. However, the estimates of Model 3 could suffer from multi-collinearity due to the significant poly-sensitization between the major allergen classes. Thus, for each major allergen class, the authors compared mono-sensitized and non-sensitized individuals, a better representation of the effect of individual allergen sensitization (Supplemental Table A5). The authors were not able to estimate the effect of sensitization to grasses, or weeds due to the small number of mono-sensitized individuals in these classes. The odds of angioedema were increased 8.59 times ($p = .028$) for those sensitized

to trees, 11.85 times ($p = .053$) for those sensitized to molds, and 5.35 times ($p = .029$) for those sensitized to epidermal allergens or mites.

To address the question of “in-season” occurrence, the authors examined the number of person-seasons with angioedema in exposed versus non-exposed patients. For exposed or “in-season” person seasons, 17 out of 4,055 (0.42%) resulted in an angioedema event, and 11 out of 4,125 non-exposed or “off-season” person-seasons (0.27%) resulted in an angioedema event (Table 4). After adjusting for sensitization to perennial allergens, demographic characteristics and the use of hypertensive medication, the odds of angioedema in the appropriate allergy season were 2.16 times higher ($p = 0.18$) compared to “off-season” for those with seasonal allergens sensitization (supplemental Table A6). When the sample was restricted only to individuals not sensitized to perennial allergens, the odds of “in-season” angioedema were increased 3.85 times ($p = 0.27$) compared to “off-season”.

DISCUSSION

Multiple independent risk factors were confirmed and new factors were discovered with the modeled multivariate regression analyses. Age, ACE inhibitor use and African American ethnicity were each confirmed as risk factors, consistent with prior literature.^[2,10,11] New risk factors included overall allergen sensitization, seasonal allergen sensitization, and perennial allergen sensitization. Perennial allergen sensitization trended towards an independent risk factor when looking at all patients but was not statistically significant until those patients with seasonal sensitization were removed from the regression during the sensitivity analysis. In isolating mono-sensitized patients during multivariate regression, tree ($p = 0.028$) and epidermal/mite (p

= 0.029) sensitization were statistically significant. Molds were also statistically significant but with a mono-sensitized sample size of only 12, generalization is limited. It is important to recognize that poly-sensitization is common and remains to be a confounder during the analysis. The low frequency of mono-sensitization as demonstrated in this study limits ideal comparisons for angioedema and its risk factors.

When looking at hypertensive patients only, sensitization to seasonal allergens was the only statistically significant inhalant allergen variable ($p = 0.008$) even when controlling for ACE-I use. Interestingly however, seasonal and perennial allergen sensitizations were not found to be independent risk factors in the non-hypertensive population. The difference of inhalant allergen risk between these patient populations may indicate that angioedema is triggered by slight alterations in hypersensitivity mechanisms depending on a patient's hypertensive and sensitization status.

There remains varying data on the impact of pollen counts and seasonality on the risk of angioedema.^[12-14] The results of this study did not demonstrate a statistically significant “in season” occurrence of angioedema for sensitized patients. However, angioedema is a rare condition, and therefore reaching the conventional statistical significance is difficult to achieve with a small sample size of angioedema patients. It is suspected that with a larger cohort that “in-season” occurrence would become statistically significant.

In this series, 60% of patients were sensitized, compared to sensitization rates of 45-50% in the general United States population and in patients with atopic diseases.^[14-16] Those patients with

angioedema also had a much higher rate of sensitization. This data set also suggested that being sensitized to one allergen class made it more likely to be sensitized to others. This correlative data has been studied previously and is consistent with the data presented here.^[17] Of the three patients with angioedema but without allergen sensitization, two were suspected of a food allergy and the other was on an ACE-I.

There are many important clinical implications from the findings in this study. Patients with allergic rhinitis and a history of angioedema should be educated and counseled on the risks of allergen sensitization and allergen overload both seasonal or with high local environmental exposure. Secondly, for patients without a readily identifiable cause of angioedema, further testing of sensitizations in patients with clinical symptoms of inhalant allergy, may identify environmental exposures which could have contributed to the onset of angioedema and could be avoided to prevent future reactions. Perennial allergen sensitization was also discovered to be an independent risk factor when eliminating those patients with seasonal sensitization. Considering that a significant portion of the perennial allergen sensitizations were to epidermal allergens, avoidance of cats and dogs by patients with a history of idiopathic or recurrent angioedema when there is sensitization present should be considered to avoid severe reactions. Finally, selection of hypertensive medications in patients with inhalant allergy sensitizations should include a consideration of the risk of ACE-I use, especially in patients with multiple risk factors.

There are several limitations to this study. While the population examined in this study is similar and comparable to previous publications, it does show some demographical differences and likely a selection bias as only patients undergoing allergy testing were examined.^[2,5,6,8,18–20] In

addition, in vitro allergy testing was used which may have a lower testing sensitivity, although the quantitative results allowed for robust statistical analyses. In vitro testing is also limiting since it does not indicate clinical relevance or symptomatology. All patients with the diagnosis of angioedema were not tested for angioedema in a prospective fashion, and therefore an additional selection bias exists. There were also very few patients with mono-sensitization. Furthermore, some patients were not tested for all allergens, which could theoretically underestimate the relationship of allergen sensitization and angioedema. In addition, while there were many indications for testing, it is expected that this population would be skewed toward having higher rates of sensitization given that there was clinical suspicion for allergen sensitization that prompted the initial testing.

CONCLUSIONS

In vitro sensitization status, seasonal and perennial sensitization status, including tree, and epidermal/mite sensitization are independent risk factors for the development of angioedema. Patients with angioedema and an unknown trigger should be evaluated for an inhalant allergen sensitization as a potential contributor and risk factor to the development of angioedema.

ACKNOWLEDGEMENTS

ACCEPTED MANUSCRIPT

REFERENCES

- [1] Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy* 2014;69:602–16. doi:10.1111/all.12380.
- [2] Mahoney EJ, Devaiah AK. Angioedema and angiotensin-converting enzyme inhibitors: Are demographics a risk? *Otolaryngol -- Head Neck Surg* 2008;139:105–8. doi:10.1016/j.otohns.2008.03.029.
- [3] Mansi M, Zanichelli A, Coerezza A, Suffritti C, Wu MA, Vacchini R, et al. Presentation, diagnosis and treatment of angioedema without wheals: a retrospective analysis of a cohort of 1058 patients. *J Intern Med* 2015;277:585–93. doi:10.1111/joim.12304.
- [4] Kostis JB, Kim HJ, Rusnak J, Casale T, Kaplan A, Corren J, et al. Incidence and characteristics of angioedema associated with enalapril. *Arch Intern Med* 2005;165:1637–42.
- [5] Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: Outcome after switching to a different treatment. *Arch Intern Med* 2004;164:910–3. doi:10.1001/archinte.164.8.910.
- [6] Malde B, Regalado J, Greenberger PA. Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Ann Allergy Asthma Immunol* 2007;98:57–63. doi:10.1016/S1081-1206(10)60860-5.
- [7] Zingale LC, Beltrami L, Zanichelli A, Maggioni L, Pappalardo E, Cicardi B, et al. Angioedema without urticaria: a large clinical survey. *CMAJ Can Med Assoc J J Assoc Medicale Can* 2006;175:1065–70. doi:10.1503/cmaj.060535.
- [8] Roberts DS, Mahoney EJ, Hutchinson CT, Aliphas A, Grundfast KM. Analysis of Recurrent Angiotensin Converting Enzyme Inhibitor-Induced Angioedema. *The Laryngoscope* 2008;118:2115–20. doi:10.1097/MLG.0b013e318182f805.
- [9] Banerji A, Clark S, Blanda M, LoVecchio F, Snyder B, Camargo Jr CA. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department. *Ann Allergy Asthma Immunol* 2008;100:327–32. doi:10.1016/S1081-1206(10)60594-7.
- [10] Baram M, Kommuri A, Sellers SA, Cohn JR. ACE inhibitor-induced angioedema. *J Allergy Clin Immunol Pract* 2013;1:442–5. doi:10.1016/j.jaip.2013.07.005.
- [11] Felder S, Curtis RM, Ball I, Borici-Mazi R. Prognostic factors in outcome of angioedema in the emergency department. *Allergy Asthma Proc Off J Reg State Allergy Soc* 2014;35:362–70. doi:10.2500/aap.2014.35.3787.
- [12] Wilson M, Frohna W, Trent G, Sauter D. Evaluating for seasonal variation in angiotensin-converting enzyme inhibitor- and angiotensin receptor blocker-induced angioedema. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol* 2014;112:178–9. doi:10.1016/j.anai.2013.11.016.
- [13] Straka B, Nian H, Sloan C, Byrd JB, Woodard-Grice A, Yu C, et al. Pollen count and presentation of angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol Pract* 2013;1:468–73.e1–4. doi:10.1016/j.jaip.2013.05.003.
- [14] Krouse JH. Allergy and Chronic Rhinosinusitis. *Otolaryngol Clin North Am* 2005;38:1257–66. doi:10.1016/j.otc.2005.07.002.

- [15] Salo PM, Arbes SJ, Jaramillo R, Calatroni A, Weir CH, Sever ML, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. *J Allergy Clin Immunol* 2014;134:350–9. doi:10.1016/j.jaci.2013.12.1071.
- [16] Warm K, Hedman L, Lindberg A, Lötval J, Lundbäck B, Rönmark E. Allergic sensitization is age-dependently associated with rhinitis, but less so with asthma. *J Allergy Clin Immunol* n.d. doi:10.1016/j.jaci.2015.06.015.
- [17] Platt M, Howell S, Sachdeva R, Dumont C. Allergen cross-reactivity in allergic rhinitis and oral-allergy syndrome: a bioinformatic protein sequence analysis. *Int Forum Allergy Rhinol* 2014;4:559–64. doi:10.1002/alr.21340.
- [18] Kieu MCQ, Bangiyev JN, Thottam PJ, Levy PD. Predictors of Airway Intervention in Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema. *Otolaryngol -- Head Neck Surg* 2015;0194599815588909. doi:10.1177/0194599815588909.
- [19] Ishoo E, Shah UK, Grillone GA, Stram JR, Fuleihan NS. Predicting airway risk in angioedema: Staging system based on presentation. *Otolaryngol -- Head Neck Surg* 1999;121:263–8. doi:10.1016/S0194-5998(99)70182-8.
- [20] Rai MR, Amen F, Idrees F. Angiotensin-converting enzyme inhibitor related angioedema and the anaesthetist. *Anaesthesia* 2004;59:283–9.

Figure Captions and Legends Only:

Figure 1: “Heat” map of sensitizations demonstrating poly-sensitization overlap between major allergen classes.

ACCEPTED MANUSCRIPT

Probability of sensitization to (%)	Conditional on sensitization to				
	Trees	Grasses	Weeds	Mold	Epidermal allergens or mites
Trees	100.0%	82.5%	79.6%	72.7%	51.1%
Grasses	56.5%	100.0%	64.4%	62.8%	39.1%
Weeds	59.8%	70.6%	100.0%	59.5%	42.4%
Mold	26.4%	33.3%	28.8%	100.0%	19.8%
Epidermal allergens or mites	75.4%	84.2%	83.2%	80.2%	100.0%

Legend				
0%-19%	20%-39%	40%-59%	60%-79%	80%-100%

Note: All associations were statistically significant with $p < 0.001$.

TABLES

Table 1: Demographics

	Mean	SD
Age	37.1	15.9
	n	%
	(N = 1,000)	
Male	402	40.2%
Ethnicity		

African American	295	29.5%
Asian	70	7.0%
Hispanic	225	22.5%
White	290	29.0%
Other	70	7.0%
<i>n/a</i>	50	5.0%
Asthma	241	24.1%
Hypertensive medication use ¹	231	23.1%
ACE inhibitor	82	8.2%
Beta blockers	100	10.0%
Calcium channel blockers	61	6.1%
Nasal Polyps	109	10.9%
Positive inhalant in vitro	604	60.4%
Sensitization to at least one allergen ²	603	60.3%
Sensitization to at least one seasonal allergen ³	409	40.9%
Sensitization to trees (spring)	333	33.3%
Sensitization to grasses (summer)	228	22.8%
Sensitization to weeds (fall)	250	25.0%
Sensitization to at least one perennial allergen ⁴	515	51.5%
Sensitization to mold	121	12.1%
Sensitization to epidermal allergens/mites	491	49.1%
Total number of angioedema cases (over 5 years)	37	

¹) Some patients were using more than one hypertension medication

²) Sensitization to at least one allergen from the following list: trees, grasses, weeds, mold, epidermal allergens, mites

³) Seasonal allergens: trees, grasses, weeds

⁴) Perennial allergens: mold, epidermal allergens, mites

Table 2: Multivariate logistic regression analysis of angioedema risk factors

	OR	Model 1 95% CI	<i>p</i>	OR	Model 2 95% CI	<i>p</i>	OR	Model 3 95% CI	<i>p</i>
Sensitization to at least one allergen ¹⁾	9.32	(2.78, 31.3)	<.001	-	-	-	-	-	-
Sensitization to seasonal allergens ²⁾	-	-	-	3.79	(1.60, 8.98)	.003	-	-	-
Trees (spring)	-	-	-	-	-	-	2.40	(0.932, 6.180)	.070
Grasses (summer)	-	-	-	-	-	-	1.47	(0.580, 3.727)	.42
Weeds (fall)	-	-	-	-	-	-	0.955	(0.384, 2.376)	.92
Sensitization to perennial allergens ³⁾	-	-	-	2.30	(0.924, 5.72)	.073	-	-	-
Mold	-	-	-	-	-	-	1.64	(0.688, 3.89)	.27
Epidermal/mite	-	-	-	-	-	-	2.30	(0.946, 5.58)	.066
Age	1.03	(1.01, 1.06)	.012	1.03	(1.00, 1.05)	.025	1.03	(1.01, 1.06)	.016
Male vs. female	0.961	(0.467, 1.98)	.91	0.827	(0.398, 1.72)	.61	0.755	(0.355, 1.61)	.47
African American vs. all other ethnicities	2.30	(1.48, 6.08)	.002	2.89	(1.42, 5.86)	.003	2.63	(1.28, 5.38)	.008
Asthma	1.47	(0.707, 3.08)	.30	1.39	(0.662, 2.90)	.39	1.24	(0.584, 2.61)	.58
Hypertensive medication use									
ACE inhibitor	3.16	(1.33, 7.51)	.009	3.29	(1.38, 7.83)	.007	2.96	(1.23, 7.11)	.015
Beta blockers	0.713	(0.243, 2.10)	.54	0.792	(0.270, 2.32)	.67	0.831	(0.277, 2.49)	.74
CCB	1.28	(0.422, 3.89)	.66	1.40	(0.455, 4.27)	.56	1.44	(0.455, 4.53)	.54

Dependent variable: Angioedema = Yes

¹⁾ Sensitization to at least one allergen from the following list: trees, grasses, weeds, mold, epidermal allergens, mites²⁾ Seasonal allergens: trees, grasses, weeds³⁾ Perennial allergens: mold, epidermal allergens, mites

Table 3: Association between the appropriate allergy season and angioedema among those with seasonal allergen sensitization (crude unadjusted estimate)

		Angioedema		
		<i>Yes</i>	<i>No</i>	TOTAL
Appropriate allergy season	<i>Yes</i>	17 0.42%	4,038 99.58%	4,055
	<i>No</i>	11 0.27%	4,114 99.73%	4,125
	TOTAL	28	8,152	8,180
OR = 1.58 (0.737, 3.37) RR = 1.57 (0.737, 3.35) p-value = .24				

Note: The percentages represent the risk over a season (3 months)