

Correlation between the number of allergen sensitizations and immunoglobulin E: monosensitization vs polysensitization

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Background: The purpose of this study was to determine if total serum immunoglobulin E (IgE) could predict monosensitization compared to polysensitization in patients with allergic rhinitis (AR).

Methods: This was a retrospective study of a cohort of 1073 patients who underwent allergy testing. Differences in total IgE level between unsensitized, monosensitized, and polysensitized subjects were calculated. Pearson correlation coefficient was calculated to determine whether there was a relationship between total IgE level and the number of positive allergen sensitizations. In addition, allergen sensitization class was calculated for each allergen sensitization and totaled for each patient. Pearson correlation coefficient was calculated to determine the relationship between total IgE level and weighted allergen sensitization by class.

Results: There were 159 patients who were monosensitized compared to 492 patients who were polysensitized. Of the monosensitized patients, almost 50% (74) were sensitized to one or both dust mites. Total IgE was higher in

polysensitized patients compared to monosensitized compared to controls ($p < 0.001$). Pearson correlation coefficient between total IgE and number of positive allergen sensitizations was 0.465 ($p \leq 0.001$). Pearson correlation coefficient between total IgE and allergen class-weighted sensitizations was 0.529 ($p \leq 0.001$).

Conclusion: IgE level can be used to predict monosensitization vs polysensitization. There is a moderate correlation between total IgE sensitization and the number of positive allergen sensitizations, as well as allergen class-weighted sensitizations. © 2016 ARS-AAOA, LLC.

Key Words:

hypersensitivity; atopy; allergy; immunoglobulin E; sensitization; allergic rhinitis

How to Cite this Article:

Kuperstock JE, Brook C, Ryan MW, Platt MP. Correlation between the number of allergen sensitizations and immunoglobulin E: monosensitization vs polysensitization. *Int Forum Allergy Rhinol*. 2017;7:385–388.

Allergic rhinitis (AR) and inhalant aeroallergen-related disease processes are some of the most prevalent pathologies with more than an estimated 300 million individuals from industrialized countries suffering from these diseases.¹ Patients can be sensitized to 1 or more allergens, resulting in a varying degree of disease severity based on environmental exposures and seasonal geographic factors.

It is unknown whether AR begins with a single sensitization or multiple allergen sensitizations. In addition, total serum immunoglobulin E (IgE) has been demonstrated to have predictive value in the in vitro diagnosis of AR.² However, it is unknown if IgE can predict the number of specific allergen sensitizations.

The treatment of AR, including immunotherapy, is dependent on accurate identification of sensitizations. Testing for allergen sensitization incorporates both in vitro and/or in vivo testing to identify targets for desensitization.^{3–8} In vitro testing utilizes serum IgE detection and quantitative level to assess the allergen. Once specific allergen sensitizations are confirmed, treatment of monosensitized and polysensitized individuals can occur via monoimmunotherapy or polyimmunotherapy, yet the treatment regimen varies between clinicians.^{9–12}

The degree to which treatment with a single-antigen immunotherapy can improve symptoms in monosensitized compared to polysensitized patients has been debated.¹³ The choice of immunotherapy can also be debated for

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Potential conflict of interest: None provided.

Presented at the 2016 AAOA Annual Scientific Meeting on September 16–18, 2016, in San Diego, CA.

Received: 31 August 2016; Revised: 23 October 2016; Accepted: 25 October 2016

DOI: 10.1002/alar.21890

View this article online at wileyonlinelibrary.com.

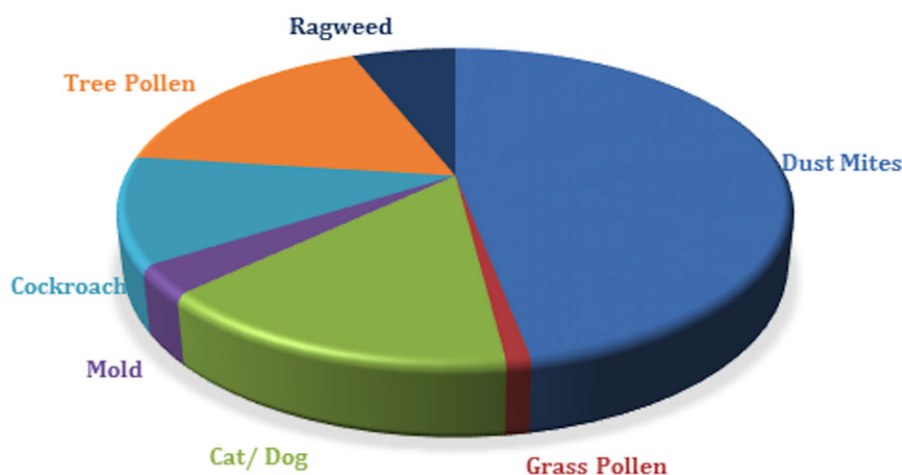


FIGURE 1. Allergens responsible for monosensitization.

polysensitized patients. Depending on timing of symptoms, season, exposures, and cross-reactivity of inhalant allergens, it may not be clear on how many antigens in which classes should be included for optimal reduction of symptoms. Total IgE serum concentrations have been associated with symptom severity in several allergic diseases, but it is unknown how different inhalant allergens quantitatively contribute to a patient's total serum IgE.^{14–17} It would be valuable to know the relative contributions of inhalant allergen sensitizations to total IgE to allow improved immunotherapy target selection with the end outcome of improved symptoms.

The purpose of this study was to determine if total serum IgE could predict monosensitization compared to polysensitization in patients with AR. Understanding the effect of allergen-specific IgE on total IgE level could have a significant impact on investigators' understanding of the disease process and treatment options of monoimmunotherapy or polyimmunotherapy.

Patients and methods

The study was approved by the Institutional Review Board at Boston University Medical Center, study number H-32860. Patients were retrospectively identified for inclusion in the study if they had presented with allergy-related symptoms and underwent in vitro hypersensitivity testing between 2006 and 2010. Indications for allergy testing included symptoms of allergic disease in the head and neck, including rhinitis, sinusitis, otitis, and laryngitis, and a clinical suspicion of atopic disease as determined by the treating provider. In vitro testing results were used due to an institutional physician practice pattern and desire for quantitative results.

Allergy testing was performed by enzyme-linked immunosorbent assay (ELISA) (ImmunoCap; Phadia AB, Uppsala, Sweden) for between 12 and 29 inhalant allergens. Statistical analysis was completed using R statistical

software, version 3.2.5 (R Project for Statistical Computing, R Foundation, Vienna, Austria; <https://www.r-project.org/>). Monosensitization was defined as positive testing for a single antigen or multiple cross-reactive antigens without other positive tests. Patients who were sensitized to either both dust mites, both cat and dog, or more than 1 grass, tree, or weed, respectively, were considered monosensitized due to principles of cross-reactivity.^{18–20} Analysis of variance (ANOVA) was used to compare IgE levels between unsensitized, monosensitized, and polysensitized patients. The total number of allergen-specific sensitizations were calculated for each patient followed by a weighted calculation of IgE sensitization that included identification of each class (1 to 6) of allergen-specific sensitization. The weighted classes were then added for all allergen-specific sensitizations per patient and correlated with total serum IgE. Pearson's product-moment correlation coefficient was used as the main statistical outcome measure.

Results

A total of 1073 patients were included in the study; 159 patients were monosensitized whereas 492 patients were polysensitized. Of the monosensitized patients, 47% (74) were sensitized to dust mite(s); 15% to cat (10), dog (1), or both cat and dog (13); 11% (17) to cockroach; 17% to a tree (17) or related trees (10); 3% (4) to a mold; 6% to ragweed (7) or ragweed and related weeds (3); 1 to grasses; and 1 to goose feather (Fig. 1).

The total IgE level did not differ between classes of allergen sensitization. Total serum IgE levels ranged from 0 to 8026, with a mean of 239. Unsensitized patients had a mean total IgE of 61.5, monosensitized had a mean total IgE of 153.7, and polysensitized had a mean total IgE of 418.2 ($p = 0.001$). The number of positive allergen-specific sensitizations ranged from 0 to 26, with a mean of 4.13 sensitizations per patient (Fig. 2). Weighted allergen class totals ranged from 0 to 130 with a mean of 13.5 (Fig. 3).

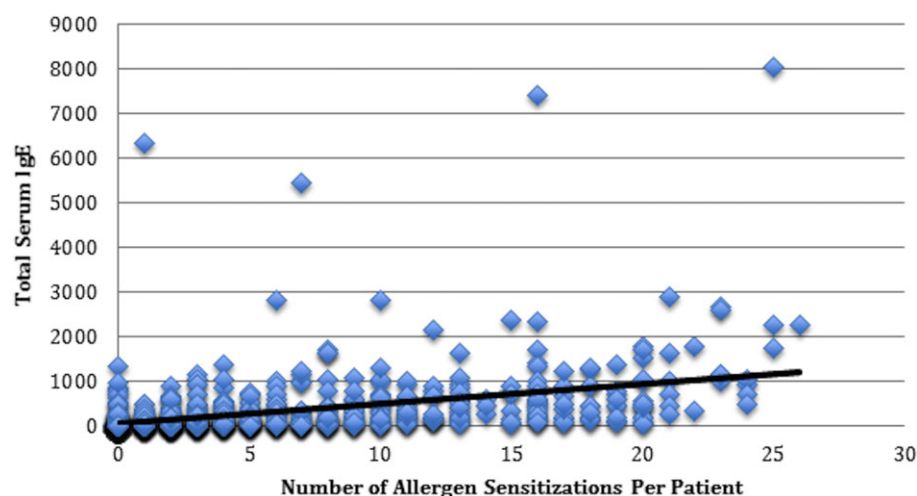


FIGURE 2. Number of allergen sensitizations per patient compared to total serum IgE. IgE = immunoglobulin E.

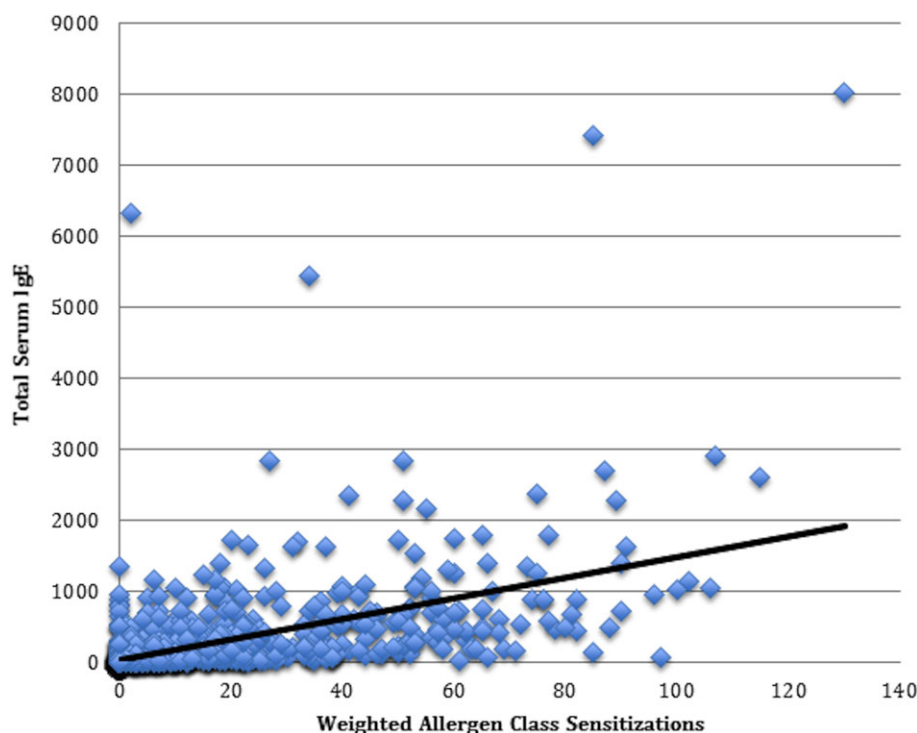


FIGURE 3. Weighted allergen class sensitization per patient compared to total serum IgE. IgE = immunoglobulin E.

Pearson correlation coefficient for total serum IgE compared with number of positive allergen-specific sensitizations was 0.465 (95% confidence interval [CI], 0.417 to 0.511), $p < 0.001$, while weighted allergen class comparison showed a coefficient of 0.529 (95% CI, 0.485 to 0.571) ($p < 0.001$).

Discussion

The results of this study demonstrate a moderate and statistically significant correlation between total IgE levels and the number of allergen-specific sensitizations. The total IgE

level was able to predict monosensitized compared to polysensitized patients. There remains controversy over the degree to which monosensitization represents a separate disease entity compared to polysensitization. Polysensitized patients have been associated with asthma and to have worsened clinical symptoms compared to monosensitized patients.^{5,21,22}

Dust mite sensitization was the most common allergen responsible for monosensitization, which is consistent with a prior report.⁵ There remains controversy on how to treat polysensitized patients with immunotherapy. The decision for monoallergen vs polyallergen immunotherapy differs

by provider and practice region.^{9,10,23} Several prospective, randomized trials have demonstrated efficacy of both monoallergen and polyallergen immunotherapy^{24–27} for the treatment of polyallergy patients. With the increase in availability of U.S. Food and Drug Administration (FDA)-approved sublingual immunotherapies, the decision for allergen selection in the setting of polysensitization is controversial. The use of IgE level as demonstrated in this study and quantitative allergy testing may aid in the decision process to identify the most relevant sensitizations in conjunction with clinical information regarding symptom and exposures.

Total IgE is partially dependent on the weighted contribution of each allergen sensitization class but it has been shown to be a predictor of AR and now to be a more specific identifier of monosensitized vs polysensitization. This may aid providers by allowing selection of the most clinically relevant and highest allergen-specific IgE level class to

decrease clinical symptoms. A limitation to this process, however, is the evidence that a significant portion of the patient population is observed to have measurable IgE allergen sensitization but remains clinically asymptomatic.^{4–7,28,29} Immunotherapy treatment must be guided by clinical relevance and exposure history in addition to any evidence of allergen-specific sensitization.

Conclusion

IgE levels correlate with monosensitization, polysensitization, and the strength of allergen sensitizations. In this cohort, dust mite sensitization was the most common allergen responsible for monosensitization. Quantitative testing may provide useful adjunctive information for selection of antigens for immunotherapy in polysensitized patients who undergo treatment with less than a full complement of sensitized antigens. ③

References

- Steinsvaag SK. Allergic rhinitis: an updated overview. *Curr Allergy Asthma Rep*. 2012;12:99–103.
- Chung D, Park KT, Yarlalagadda B, Davis EM, Platt M. The significance of serum total immunoglobulin E for in vitro diagnosis of allergic rhinitis. *Int Forum Allergy Rhinol*. 2014;4:56–60.
- Tay TR, Bosco J, Aumann H, O'Hehir R, Hew M. Elevated total serum immunoglobulin E (>1000 IU/mL): implications? *Intern Med J*. 2016;46:846–849.
- Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol*. 2005;116:377–383.
- Baatenburg de Jong A, Dikkeschei LD, Brand PLP. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized, and polysensitized children. *Pediatr Allergy Immunol*. 2011;22:166–171.
- Manise M, Bakayoko B, Schleich F, Corhay J-L, Louis R. IgE mediated sensitisation to aeroallergens in an asthmatic cohort: relationship with inflammatory phenotypes and disease severity. *Int J Clin Pract*. 2016;70:596–605.
- Bousquet P-J, Castelli C, Daires J-P, et al. Assessment of allergen sensitization in a general population-based survey (European Community Respiratory Health Survey I). *Ann Epidemiol*. 2010;20:797–803.
- Nepper-Christensen S, Backer V, DuBuske LM, Nolte H. In vitro diagnostic evaluation of patients with inhalant allergies: summary of probability outcomes comparing results of CLA- and CAP-specific immunoglobulin E test systems. *Allergy Asthma Proc*. 2003;24:253–258.
- Calderón MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. *J Allergy Clin Immunol*. 2012;129:929–934.
- Bahceciler NN, Galip N, Cobanoglu N. Multiallergen-specific immunotherapy in polysensitized patients: where are we? *Immunotherapy*. 2013;5:183–190.
- Kim KW, Kim EA, Kwon BC, et al. Comparison of allergic indices in monosensitized and polysensitized patients with childhood asthma. *J Korean Med Sci*. 2006;21:1012–1016.
- Soni A. *Allergic Rhinitis: Trends in Use and Expenditures, 2000 and 2005*. Medical Expenditure Panel Survey. Statistical Brief #204. Rockville, MD: Agency for Healthcare Research and Quality; 2008. https://meps.ahrq.gov/data_files/publications/st204/stat204.pdf. Accessed November 10, 2016.
- Cox L. The role of allergen immunotherapy in the management of allergic rhinitis. *Am J Rhinol Allergy*. 2016;30:48–53.
- Winther L, Reimert C, Skov P, Kærgaard Poulsen L, Moseholm L. Basophil histamine release, IgE, eosinophil counts, ECP, and EPX are related to the severity of symptoms in seasonal allergic rhinitis. *Allergy*. 1999;54:436–445.
- Laske N, Niggemann B. Does the severity of atopic dermatitis correlate with serum IgE levels? *Pediatr Allergy Immunol*. 2004;15:86–88.
- Lichtenstein LM, Ishizaka K, Norman PS, Sobotka AK, Hill BM. IgE antibody measurements in ragweed hay fever relationship to clinical severity and the results of immunotherapy. *J Clin Invest*. 1973;52:472–482.
- Borish L, Chipps B, Deniz Y, Gujrathi S, Zheng B, Dolan CM. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol*. 2005;95:247–253.
- Nilsson OB, Binnmyr J, Zoltowska A, Saarne T, Van Hage M, Grönlund H. Characterization of the dog lipocalin allergen Can f 6: the role in cross-reactivity with cat and horse. *Allergy*. 2012;67:751–757.
- Hilger C, Swiontek K, Arumugam K, Lehnert C, Hentges F. Identification of a new major dog allergen highly cross-reactive with Fel d 4 in a population of cat- and dog-sensitized patients. *J Allergy Clin Immunol*. 2012;129:1149–1151.e2.
- Spitzauer S, Pandjaitan B, Mühl S, et al. Major cat and dog allergens share IgE epitopes. *J Allergy Clin Immunol*. 1997;99:100–106.
- Toppila-Salmi S, Huhtala H, Karjalainen J, et al. Sensitization pattern affects the asthma risk in Finnish adult population. *Allergy*. 2015;70:1112–1120.
- Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943–948.
- Baena-Cagnani CE, Canonica GW, Zaky Helal M, et al. The International Survey on the Management of Allergic Rhinitis by Physicians and Patients (ISMAR). *World Allergy Organ J*. 2015;8:10.
- Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single-or double-blind, placebo-controlled studies. *Clin Ther*. 2000;22:342–350.
- Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2010;126:558–566.
- Penagos M, Passalacqua G, Compalati E, et al. Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest*. 2008;133:599–609.
- Shah-Hosseini K, Mioc K, Hadler M, Karagiannis E, Mösges R. Optimum treatment strategies for polyallergic patients - analysis of a large observational trial. *Curr Med Res Opin*. 2015;31:2249–2259.
- Ballardini N, Bergström A, Wahlgren C-F, et al. IgE antibodies in relation to prevalence and multimorbidity of eczema, asthma, and rhinitis from birth to adolescence. *Allergy*. 2016;71:342–349.
- Guo X, Meng G, Liu F, et al. Serum levels of immunoglobulins in an adult population and their relationship with type 2 diabetes. *Diabetes Res Clin Pract*. 2016;115:76–82.