

EDITORIAL

Clinical & Experimental Allergy

Provocation tests with objective measures remain more diagnostic than surrogate immunoglobulin E antibody measures of sensitization

This editorial discusses the findings of the paper in this issue by Huss-Marp et al. [3] pp. 1116–1124.

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Since the identification of reagin as IgE in 1967 [1], the allergy community has desired a readily measurable biomarker that could predict the presence of symptomatic allergic disease following allergen exposure. Unfortunately, due to multiple variables associated with the environment (e.g. allergen heterogeneity and exposure levels) and the host (immune response heterogeneity), IgE antibody by itself is known to be necessary but not sufficient for manifestation of allergic symptoms. Christensen et al. [2] confirmed in 2008, with chimeric IgE antibodies and recombinant allergens, that four humoral immune response parameters work in concert to alter mast cell and basophil mediator release in an allergic patient. These four humoral immune response parameters include IgE antibody concentration, affinity, clonality (e.g. heterogeneity in epitope specificity) and the IgE-specific activity (specific to total IgE ratio). Thus, it would be naïve of us to think that IgE antibody concentration in blood by itself, would allow us to predict symptomatic allergic disease, without factoring in these other three humoral immune response parameters as well as the many other host and environmental factors.

Huss-Marp et al. [3] are to be commended for their systematic attempt to show a relationship between the concentration of IgE antibody to one aeroallergen (Timothy grass) in the blood (and skin) and provocation verification measures for rhinoconjunctivitis. They point out in their discussion that their premise that IgE antibody levels in the blood may predict upper airway allergic symptoms was based on previous studies involving ingested food allergens and inhaled indoor aeroallergens

[4–7]. The authors also point out that IgE anti-peanut, egg and milk can have some predictive value for identifying children who will fail a food challenge [4–6]. Moreover, the sum of IgE antibody to dust mite, cat and dog can provide useful prediction of possible exacerbations of severe asthma in children [7]. Moreover, in their discussion, they provide a carefully reasoned listing of possible reasons why their study did not identify a correlation between quantitative blood levels of IgE anti-Timothy grass and Timothy grass-based provocation test results. Among these were differences in the provocation tests used (oral food challenge vs. nasal and ocular provocation), composition and heterogeneity of the allergens involved (peanut vs. Timothy grass), differences in end-organ reactivity (gut vs. nose and eyes), the potentially limited relevance of probability curves generated with defined patient groups to the general Timothy grass population that they studied and polysensitization of subjects in their study to aeroallergens in contrast to more a restricted food allergen sensitization.

One of the unique strengths of the Huss-Marp study is their examination of patients' provocation end-point measures in relation to the patient's own IgE-specific activity (e.g. Timothy grass-specific IgE antibody to total IgE ratio). In a seminal study by Johansson et al. [8], an IgE-specific activity of > 4% was shown to place allergic individuals undergoing anti-IgE (Omalizumab) therapy at a disadvantage for poor resolution of their allergy symptoms. Applying this conceptually to the Huss-Marp study, with a specific IgE to total IgE ratio > 4%, there would be sufficient Timothy grass-specific IgE antibodies in close enough proximity to each other on the surface of mast cells and basophils to produce the required number of IgE cross-links to activate these effector cells when the subject was exposed to Timothy grass allergen. However, importantly, an American population survey [9] has shown that only 15% of 384 randomly selected Timothy grass allergic individuals had an IgE-specific activity > 4%. This contrasts with 54% of 123 venom-sensitized patients and 33% of peanut 1289

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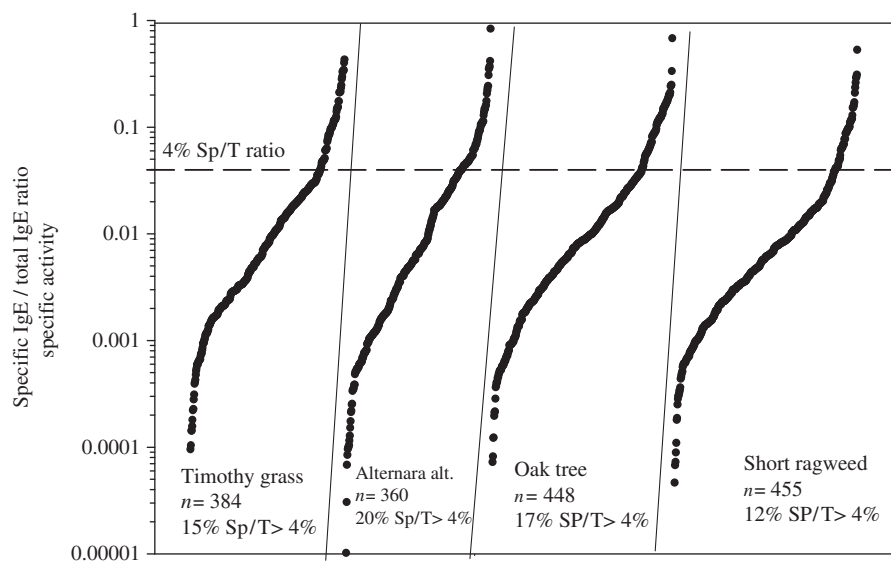


Fig. 1. Distribution of IgE-specific activities for four common outdoor aeroallergens: Timothy grass, Alternaria, Oak tree and short ragweed. IgE-specific activities for these six aeroallergen specificities spanned four log concentrations (0.01–82%). The percentage of these subjects who displayed IgE-specific activities greater than an arbitrary target threshold of 4% ranged from 12% with short ragweed to 20% for Alternaria.

sensitized patients who had IgE-specific activities > 4% [9]. Hymenoptera venom and peanut are among those few allergen sensitizations that can lead to severe allergic reactions and death following exposure. In contrast, aeroallergen-based allergic disease is most commonly associated with morbidity. Figure 1 provides a glimpse of the IgE-specific activity profiles for an American population to four common aeroallergens. All these display much lower percentages of subjects who have IgE-specific activities > 4% than that has been established for peanut or milk. Granted as noted above, IgE-specific activity is only one of the many variables that influence the translation of an allergen exposure into a clinically evident allergic symptom. But it is often the most overlooked parameter by the

practicing allergist and the Huss-Marp study should be commended for considering it in their analyses.

Ultimately, the age-old truth returns to us, as it has been recently re-emphasized in the NIAID and NICE guidelines [10, 11]. These documents remind us that serological (or skin test measures) of allergen-specific IgE antibody alone are not diagnostic of allergic disease. A controlled provocation test, despite its risk, required time commitment and cost, with objective measures of symptoms will most likely always remain a more powerful indicator of symptomatic sensitization in the diagnostic algorithm for human allergic disease. But ultimately, all of these diagnostic measures are limited by the fact that they must be interpreted back to the patient within the context of the patient's clinical history.

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