

Correspondence

Reply

To the Editor:

In a survey of 651 Italian children with moderate-to-severe seasonal allergic rhinoconjunctivitis, we found that a significant proportion of positive skin reactions to pollen extracts were not confirmed by the detection of serum IgE specific for major genuine allergen molecules. This inconsistency was partially explained in many cases by IgE sensitization to profilin, polcalcin, or both (ie, highly cross-reacting molecules that are shared by many different pollen sources).¹ The study also demonstrated that the use of molecular diagnosis profoundly affected the decision about allergen immunotherapy prescription based on international guidelines or a doctor's opinion.¹ Scala and Miceli Sopo² propose an alternative explanation and attribute the discrepancy between skin prick test (SPT) responses and IgE assay results to the cutoff level for IgE positivity (0.7 kU/L) we have adopted and propose to examine whether a lower cutoff point would have modified our results.

The present new analysis (Table I) shows that the frequency of class 1 serum levels (ie, between 0.35 and 0.7 kU/L) of IgE to major allergenic proteins of pollens was quite low, ranging from 0.4% (Par j 2) to 10.8% (Ole e 1, Table I). Accordingly, the discordance rate between a positive (≥ 3 mm) SPT response to a pollen extract and a positive IgE test result to its selected major allergenic protein or proteins, when defined by a cutoff of 0.35 kU/L, as suggested by Scala and Miceli Sopo,² did not significantly change for all pollens but olive (Table I).

In addition, we offer some answers to Scala and Miceli Sopo's comments and questions. First, patients with specific IgE levels of a minimum of class 2 (≥ 0.7 kU/L) are commonly enrolled in studies assessing the clinical efficacy of specific immunotherapy (SIT).³ Second, to the best of our knowledge, there is no published evidence that SIT might be of benefit in patients with specific IgE levels as low as between 0.1 and 0.35 kU/L. Third, in our pilot study of the same population, we adopted not only, as stated by Scala and Miceli Sopo,² a cutoff point of 0.35 kU/L but also a cutoff of 0.7 and 3.5 kU/L.⁴ In that study our results and conclusions (ie, the high heterogeneity of the molecular profiles of IgE sensitization to *Phleum pratense*) were also independent of the cutoff level.⁴

This confirmation of our previous result does not surprise us. Receiver operating characteristic analysis and "cutoff" or "decision" points, were first proposed in the field of allergy by de Blay et al⁵ and by one of us⁶ in this *Journal* more than 20 years ago. At that time, we wrote that allergy is not a yes/no phenomenon and

alerted that cutoff points cannot be extrapolated but are a variable function of the study's population and targets.⁶ A few years later, Sampson and Ho⁷ applied the same statistical approach to food allergies, and they tried to fix IgE cut-off levels to predict positive outcomes of food challenge tests. Later studies, as summarized by Miceli Sopo and others, demonstrated again that IgE cutoff points are population and food specific and cannot be extrapolated to other populations and settings.⁸

Similarly, the results of our study¹ led us to determine that SPTs with extracts, using a 3-mm wheal reaction as cut-off, cannot serve in all circumstances as a gold standard of specific sensitization, as proposed by Scala and Miceli Sopo.² Most SPT reactions to a pollen extract because of IgE corecognition of profilins, but not those to major allergenic proteins, produced weak wheal reactions of approximately 3 to 4 mm.⁹ Hence in our population and setting, a wheal reaction of 5 mm was more specific for genuine IgE reactivity and therefore a better cutoff point for SIT prescription.¹

When are IgE levels positive? Is this the right question? Beyond levels, many other factors (eg, IgE affinity, diversity, and specific activity¹⁰ and competition by IgG antibodies¹¹) affect IgE biological and clinical relevance. Having said that, we strongly believe now, as well as 20 years ago,⁶ that clinicians should not be rigidly fixed to one or another cutoff point but should rather interpret IgE levels with a probabilistic but not dichotomist approach in the context of other diagnostic information.

Finally, the core message of our article remains that before prescribing a long and expensive treatment, such as allergen immunotherapy, against one pollen source, it might be wise to be sure that the individual patient's IgE is not merely recognizing profilins or polcalcins in that pollen extract but that he or she is truly reacting against the major allergenic molecules.

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TABLE I. Discordance rate between SPT responses to pollen extracts and serum IgE levels to their major allergenic molecules

	SPT, >3 mm, no.	SPT, positive clinically relevant fraction, no.	Relevant SPT response positivity not confirmed by IgE to major allergenic proteins, no. (%)			P value*
			<0.70 kU/L	<0.35 kU/L	>0.35 and <0.70 kU/L	
Grass	592	568	56 (9.5)	38 (6.4)	18 (3.2)	.053
Olive	405	390	111 (27.4)	69 (17.0)	42 (10.8)	$<.001$
Pellitory	259	257	78 (30.1)	77 (29.7)	1 (0.4)	.924
Cypress	287	184	28 (9.8)	22 (7.7)	6 (3.3)	.374
Betulaceae	309	252	146 (47.2)	135 (43.7)	11 (4.4)	.374
Mugwort	163	65	45 (27.6)	42 (25.8)	3 (4.6)	.707

*The χ^2 test was used to compare frequencies (<0.70 vs <0.35 kU/L).

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REFERENCES

- Stringari G, Tripodi S, Caffarelli C, Dondi A, Asero R, Di Rienzo Businco A, et al. The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever. *J Allergy Clin Immunol* 2014;134:75-81.
- Scala G, Miceli Sopo S. When are specific serum IgE positive? *J Allergy Clin Immunol* 2015;135: XXX-XXX.
- Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71.
- Tripodi S, Frediani T, Lucarelli S, Macrì F, Pingitore G, Di Rienzo Businco A, et al. Molecular profiles of IgE to *Phleum pratense* in children with grass pollen allergy: implications for specific immunotherapy. *J Allergy Clin Immunol* 2012; 129:834-9.e8.
- de Blay F, Zana H, Offner M, Verot A, Velten M, Pauli G. Receiver operating characteristic analysis: a useful method for a comparison of the clinical relevance of two in vitro IgE tests. *J Allergy Clin Immunol* 1993;92:255-63.
- Matricardi PM, Nisini R, Biselli R, D'Amelio R. Evaluation of the overall degree of sensitization to airborne allergens by a single serological test: implications for epidemiological studies of allergy. *J Allergy Clin Immunol* 1994;192: 68-79.
- Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
- Miceli-Sopo S, Radzik D, Calvani M. The predictive value of specific immunoglobulin E levels for the first diagnosis of cow's milk allergy. A critical analysis of pediatric literature. *Pediatr Allergy Immunol* 2007;18:575-82.
- Asero R, Jimeno L, Barber D. Preliminary results of a skin prick test-based study of the prevalence and clinical impact of hypersensitivity to pollen panallergens (polcalcin and profilin). *J Invest Allergol Clin Immunol* 2010;20:35-8.
- Hamilton RG, MacGlashan DW Jr, Saini SS. IgE antibody-specific activity in human allergic disease. *Immunol Res* 2010;47:273-84.
- Custovic A, Soderstrom L, Ahlstedt S, Sly PD, Simpson A, Holt PG. Allergen-specific IgG antibody levels modify the relationship between allergen-specific IgE and wheezing in childhood. *J Allergy Clin Immunol* 2011;127:1480-5.

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