

Letter to the editor

The clinical use of specific IgE antibody testing – a further word of caution

In a recent paper, Söderström et al. suggested that a quantitative level of serum-specific immunoglobulin E (sIgE) could give the probability of an *in vivo* allergic reaction in any individual (1). Starting from the results of a study by Paganelli (2) and using a logistic model already published (3, 4), they calculated curves of probability of allergy vs Pharmacia UniCAP® (Pharmacia Biotech, Uppsala, Sweden) sIgE results for some allergenic products.

This paper deserves many critics. First, a bias entails the 'doctors' allergen-specific diagnosis': the authors argue that the doctor was not aware of the Pharmacia UniCAP® result but, being based on 'routine/locally established procedures', the doctor's diagnosis most probably included some serum sIgE assays. For example, a Pharmacia CAP® assay was used in clinic 3. Thus the diagnosis was not purely clinical.

Secondly, the original work by Paganelli (2) included six cohorts of patients but Söderström kept only four of them although the laboratory method used in the two discarded clinics were claimed by Paganelli to be strictly equivalent to the UniCAP®. In addition, these two clinics were included in the curves published by Ahlstedt (4). Thus the reason why some results were excluded in Söderström's paper is not clear.

Other differences are more puzzling:

- Söderström stated that 681 patients were included in the computation of their curves, but out of the 681 patients reported by Paganelli for clinics 1–4, 44 patients could not be classified as atopic or nonatopic: their clinical diagnostic was 'incertain'. Why and how the diagnostic of these 44 incertain patients was changed?
- Why prevalence data listed in Söderström's Table 3 did not match those found by Paganelli? There is a striking

Table 1. Serum-specific IgE levels (kU/l) giving a 90% 'probability of clinical allergy diagnosis' according to Söderström's Figure 2

	Clinic 1	Clinic 2	Clinic 3	Clinic 4
<i>Dermatophagoides pteronyssinus</i>	2.3	8	11	1.4
<i>Dermatophagoides farinae</i>	9.4	11	0.35	–
Cat dander	21	2.1	–	0.8
Dog dander	–	6.4	–	9.8
Ryegrass pollen	5	2.9	–	–
Timothy grass pollen	3.3	–	1.2	–
Birch pollen	–	–	1	2.1
Olive tree pollen	14	3.8	–	–
Mugwort pollen	–	–	4.5	6.0
<i>Alternaria alternata</i>	5.0	10.5	–	5.7

difference for dust mites (*Dermatophagoides pteronyssinus* = D1, *D. farinae* = D2) in clinic 3: 35% instead of 20% for D1 and 75% instead of 17% for D2! What justifies the exclusion of some patients (all nonatopic) from original data in this clinic for D1 and D2?

- As a matter of fact, one must suspect the results claimed for D2 in clinic 3 (100% sensitivity and 100% specificity).

Regarding the probability curves obtained by Söderström, one can discuss some points too:

- Why these authors criticized classes as an outdated means for reporting sIgE results but kept on using them for the abscissa of their probability curves?
- The authors stated that for allergens other than *D. pteronyssinus* and cat dander 'no statistically significant differences between the clinics could be found'. What statistical method was used for comparing the curves? If a statistical analysis was done, why 95% confidence limits are not shown along with the curves? From the Figure 2 of Söderström's paper one can estimate the sIgE levels giving a 90% 'probab-

ility of clinical allergy diagnosis' for each clinic (see Table 1). Strong differences between clinics are evident for all allergenic products and not only for *D. pteronyssinus* and cat dander as stated by Söderström.

What can be concluded from this work? Söderström and co-authors acknowledged that these risk curves cannot be transferred from one clinical setting to another one. This is at odds with previous hopes (5) and casts doubt on any usefulness of such curves in daily practice. Contrary to the opinion of some authors (1, 4) and to the advertisements of the UniCAP® manufacturer, crude quantitative sIgE results should not be used by general practitioners: specific IgE data must be confronted to specialized pieces of information, like skin test results. Even with good clinical data at hand, it is sometimes difficult for an allergist to differentiate a true sensitization from a cross-reaction, and cross-reactions are far more frequent *in vitro* than *in vivo*....

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References

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Reply

We appreciate the comments raised by Dr Malandain concerning our article (1). The questions and objections raised give us an opportunity to further emphasize the importance of quantification, rather than the dichotomization, of immunoglobulin (IgE) antibody results. The issues raised regarding both the re-evaluation of a previous study by Pagannelli et al. (2), and the concept of risk and probability for a quantitative-specific IgE antibody test result rather than the dichotomous 'yes' or 'no' answer. As the questions and objections raised in many cases are rather philosophical, we would like to address them in a similar way.

The re-evaluation of the original work (2) used only the prospective studies performed in 1995, leaving out the retrospective studies from the original article. All definitions were the same as in the original study; we, however, focused on the allergen-specific diagnosis for each patient, which implies that the number of patients differed. We also estimated the prevalence for each allergen based on the number of patients tested for that allergen.

Dr Malandain also expresses concern about our use of clinical diagnosis as reference. One must remember that there is, however, nothing like a 'clear diagnosis' because there is no gold standard in allergy or allergy diagnosis. A purely clinical diagnosis, i.e. a diagnosis consisting only of case history and physical examination, may often be subjective and susceptible to bias, which make comparisons to test results even more difficult, as recently exemplified by Williams et al. (3).

In our study (1), we used a logistic regression model for evaluating the relationship between the quantitative IgE antibody level and doctors' allergen-specific diagnosis, expressing the estimated model as a curve. As the slope in the logistic regression model is the logarithm of the odds ratio, these curves can also be regarded as risk curves. The indication of the well-known classes in the graphs is deliberately chosen not only to avoid confusion but also to illustrate the big difference in probability that can occur within a single class.

The different curves illustrated that there were differences between clinics as well as allergens, however, as expected, not all

differences were significant. Unfortunately, an inclusion of confidence bands would have made the graphs unreadable. Tests and confidence limits (Fig. 1) are both based on the method by Wald (4).

Relations between allergen and possible cross-reactions need to be considered and evaluated in the quantitative assessment as well as in the dichotomous evaluation. The estimated risk curves calculated in our study illustrate well that there is a relationship between the level of specific-IgE antibodies and a doctor's diagnosis. The model used not only showed this link, but it also provided a more meaningful way to interpret the results. However, different populations resulted in different point estimates

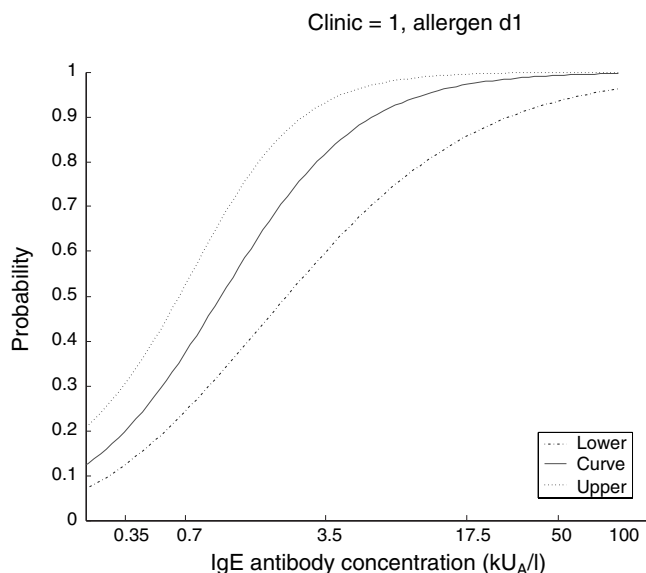


Figure 1. Example of probability curve with 95% confidence bands.

of traditional performance characteristics as well as in different shapes of the curves. This implies that probability curves need to be cautiously interpreted if used in daily practice. However, over the measuring range they do continuously show that there

is an increasing probability for a positive diagnosis with an increased IgE antibody level.

Our study emphasized our hypothesis that the extension from a qualitative statement of whether IgE is present or not, to a

risk assessment using the quantitative levels, increases the amount of useful clinical information from measurements of IgE antibodies.

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