

Reference Values of Total Serum IgE and Their Significance in the Diagnosis of Allergy in Young European Adults

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Key Words

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Abstract

Allergic sensitization mediated by immunoglobulin E (IgE) is the basis of allergic diseases, and elevated total IgE, in spite of some well-known limitations, is frequently included as a diagnostic criterion for allergic diseases. The reference value of total IgE (IgE-t) in the literature (1.5–144 kU/l) was established almost 2 decades ago. The aim of this study was to establish IgE-t reference values, establishing an updated cutoff value able to identify atopic subjects, defined as a positive CAP-radioallergosorbent test to at least one of a panel of common allergens, among young European adults. The study included 6,670 subjects from 10 Western European countries within the framework of the European Community Respiratory Health Survey II. IgE-t and specific IgE (IgE-s) were measured for the main inhalant allergens; IgE-s in class 0 for all allergens (66.2%) characterized non-atopy. The reference values were estimated by means of linear regression using a 50% random subsample of non-atopic subjects. Two non-atopic subsamples were examined so that one subsample could be used to establish reference IgE-t values, and these values were compared to those in the second non-atopic subsample to validate the findings. Sensitivity and

specificity for atopy were assessed on the other 50% of non-atopic and on all atopic subjects. The 95th percentile of IgE-t reference values in non-smokers was 148 kU/l in women and 169 kU/l in men, while it was 194 and 220 kU/l in female and male smokers, respectively: serum IgE-t above the 95th percentile identifies <32% and above the 99th percentile <20% of atopic adults (low sensitivity), but a serum IgE-t below the 95th percentile identifies >90% and below the 99th percentile identifies >95% of non-atopic adults (good specificity). Due to the adequate specificity, IgE-t values exceeding the normal limits confirm a suspected atopic status; however, because of the low sensitivity, values below the cutoff seem not to exclude an atopic status with sufficient accuracy.

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Introduction

Allergic sensitization mediated by immunoglobulin E (IgE) is the basis of allergic diseases, and elevated total IgE (IgE-t) – in spite of some well-known limitations – was frequently included as a diagnostic criterion of allergic diseases and other IgE-mediated disorders [1–4]. The usefulness of IgE-t values in this respect depends on the establishment of reliable reference values for the particular population. The determination of reference values can

Table 1. Distribution of the subjects examined according to center and country

Center	n	%
Belgium	511	7.6
South Antwerp	296	4.4
Antwerp City	215	3.2
Germany	512	7.6
Hamburg	259	3.8
Erfurt	253	3.7
Spain	1,332	19.7
Barcelona	207	3.1
Galdakao	360	5.3
Albacete	290	4.3
Oviedo	246	3.6
Huelva	229	3.4
France	818	12.1
Pessac	126	1.9
Grenoble	279	4.1
Montpellier	126	1.9
Paris	287	4.3
Italy	432	6.4
Pavia	103	1.5
Turin	157	2.3
Verona	172	2.5
UK	702	10.4
Cardiff	195	2.9
Ipswich	255	3.8
Norwich	252	3.7
Iceland: Garðabær	464	6.9
Norway: Bergen	502	7.4
Sweden	1,063	15.7
Göteborg	336	5.0
Umeå	309	4.6
Uppsala	418	6.2
Switzerland: Basel	424	6.3
Total	6,760	100.0

be difficult due to problems in defining and selecting non-atopic subjects, the considerable overlap of IgE values between atopics and non-atopics and the wide variety of factors that influence total IgE values such as gender, age, race, smoking habits, exposure to environmental pollutants and some non-atopic disorders [2–5].

In the literature, the reference value of IgE-t (1.5–144 kU/l) was established almost 2 decades ago [6]. There is ample evidence that this value may vary according to the place of birth and background exposure [3, 7–10]. Thus, if the diagnosis of allergy is based on IgE-t, it is imperative that the cutoff value is derived from the most recent and geographically defined normalized reference values for that locality.

The aim of this study was therefore to measure total IgE in a non-atopic European population of apparently healthy young adults, in order to establish reference values for that population and to assess whether the level of normality obtained could be useful in the clinical diagnosis of atopy and allergic diseases.

Materials and Methods

Subjects

The designs of the European Community Respiratory Health Survey (ECRHS) I and II have been published in detail previously [11, 12]. In the ECRHS I, conducted in 1990–1992, each participant was sent a brief questionnaire (stage 1), and from those who responded a random sample was selected to undergo a more detailed clinical examination (stage 2). In addition, a ‘symptomatic sample’, reporting symptoms of waking with shortness of breath, asthma attacks or using asthma medication in stage 1, was also studied. In the ECRHS II, conducted in 1998–2002, subjects who had participated in stage 2 of the ECRHS I were invited to participate in the follow-up. This analysis includes data from European centers in the ECRHS II (table 1) and excludes the United States and Australia.

Questionnaire

Symptomatic subjects were classified according to the following definitions, considering the 2000 questionnaire: allergic rhinitis in the case of an affirmative answer to the question: ‘Do you have any nasal allergies including hay fever?’; asthma (ever) in the case of an affirmative answer to the question: ‘Have you ever had asthma?’ and ‘Was it confirmed by a doctor?’; current asthma, in the case of an affirmative answer to the question: ‘Have you had an attack of asthma in the last 12 months?’. Subjects were classified according to their smoking habits as: smokers, if they were current smokers and had smoked at least one cigarette per day or one cigar a week for 1 year and during the last 6 months; the remainder were classified as non-smokers.

Total and Specific IgE

Serum IgE-t and specific IgE (IgE-s) to cat, *Dermatophagoides pteronyssinus*, *Cladosporium* and timothy grass were measured using the Pharmacia CAP System.

In the 1992 ECRHS survey, in all centres IgE-s was measured against the same allergens and against local allergens. Because local allergens did not add any further information they were excluded from the new ECRHS survey.

The measurement ranges for IgE-t and IgE-s were 2–2,000 kU/l and 0.35–100 kUA/l, respectively. The results were subdivided into classes from 1 to 6 following the recommendations of the European Academy of Allergology and Clinical Immunology: <0.35 kUA/l = class 0; ≥0.35 and <0.70 kUA/l = class I; ≥0.70 and <3.50 kUA/l = class II; ≥3.50 and <17.5 kUA/l = class III; ≥17.5 and <50.0 kUA/l = class IV; ≥50.0 and <100 kUA/l = class V, and ≥100 kUA/l = class VI. The subjects were considered to be atopic if they had a positive (≥0.35 kUA/l, or IgE-s class 0 or higher) determination for at least one allergen. IgE-s results were regarded as positive if ≥class I.

Table 2. Distribution of IgE-s classes by allergen considered in the whole sample

Allergens	IgE class					
	0	≥ 1	≥ 2	≥ 3	≥ 4	≥ 5
House dust mites, n	5,449	1,380	1,085	612	270	69
%	80.6	20.4	16.1	9.1	4.0	1.0
Cat, n	5,919	872	685	343	120	31
%	87.6	12.9	10.1	5.1	1.8	0.5
Timothy grass, n	5,389	1,468	1,298	876	408	97
%	79.7	21.7	19.2	13.0	6.0	1.4
<i>Cladosporium</i> , n	6,648	114	72	31	13	2
%	98.3	1.7	1.1	0.5	0.2	0.0
IgE-s _{max} class, n	4,407	2,353	2,021	1,300	529	180
%	65.2	34.8	29.9	19.2	7.8	2.7

IgE-s_{max} class = the maximum class among all allergens tested.

Regarding IgE-t, the Pharmacia CAP-IgE method, which is calibrated against WHO IgE reference serum 75/502, has a detection range of 2–2,000 kU/l. For samples with an IgE value exceeding the upper limit, a nominal value of 2,050 kU/l was assigned for the purpose of statistical analysis. For samples with IgE values below the detection limit, a nominal value of 1 kU/l was assigned for the purposes of statistical analysis.

During the first ECRHS survey in 1992, all the subjects had a skin prick test (SPT) carried out using Phazet (Pharmacia Diagnostics, Uppsala, Sweden). The allergens selected in all centers included: *D. pteronyssinus*, cat, birch, timothy grass, *Parietaria judaica*, olive, ragweed, *Cladosporium herbarum* and *Alternaria alternata*. Each area could add up to two additional allergens of local importance. In the year 2000, SPT were not repeated because Phazet was no longer commercially available; therefore, all subjects with a positive SPT in 1992 and a negative IgE-s measurement in 2000 were excluded from the analysis [11].

Statistical Analysis

All data were analyzed with STATA 8. The distribution of IgE-s values was calculated according to class: we assigned an IgE-s (maximum IgE-s class, IgE-s_{max}) which was considered to be the highest class among all the allergens tested. We considered subjects with IgE-s_{max} reaction = class 0 to be non-atopic. For analysis purposes IgE-s class 4 and higher were grouped together. The 95th percentile of IgE among subjects with IgE-s class 0 was calculated from the results of multiple regression analysis.

In order to have independent samples for estimating predicting equations and validating them, we took a random sample (A) of 50% of non-atopic subjects; we worked out the regression equation considering this 50% sample with log (IgE-t) as dependent, smoking (yes/no), sex (females/males), age (<25 years), computing robust standard errors considering centers as clusters. The variables with negligible and statistically non-significant effects were removed from the model.

Considering the interest for one tail (high) of the distribution, from the regression equation we estimated predicted values and the 95th (and 99th) percentile as cutoff point for normal IgE values adding to the predicted value 1.64 (and 2.56 times) the square

root of the regression mean square error (regression standard deviation).

Validation and Analysis of the Clinical Usefulness of IgE-t in Allergy Diagnosis

We computed the classification of the IgE-s class by the two levels of confidence (specificity) reference values in the 50% (sample B) of non-atopic subjects not used for estimation, and all atopic subjects. In these samples, we computed sensitivity, specificity, predictive values and receiver-operator characteristic areas for the two levels of reference values versus the IgE-s class considering as 'positive' subjects with IgE-s_{max} class ≥ the cutoff value considered.

To assess the diagnostic implications of the reference IgE-t value we analyzed the ability of reference values in predicting the probability of various symptoms in atopic or non-atopic subjects compared with subjects without symptoms in the whole population (sample A + sample B + atopic) classifying by IgE-t ≤ or > the cutoff point estimated at 95th percentile by means of logistic regression analysis.

Results

Table 1 shows the distribution of the subjects among centers and countries. Of the 7,034 adults included in the study, 274 had a positive SPT in the 1992 survey and a negative radioallergosorbent test in 2000 and were therefore excluded from the study. The remaining 6,760 people were composed of 3,428 males (50.7%) and 3,332 females (49.3%).

Table 2 shows the distribution of IgE-s values by the allergen considered. The subjects with IgE-s values < class 1 range from 98.3% for mold to 79.7% for timothy grass. Considering atopic subjects with IgE-s > class 0 for at least one allergen tested, we detected 2,353 atopic sub-

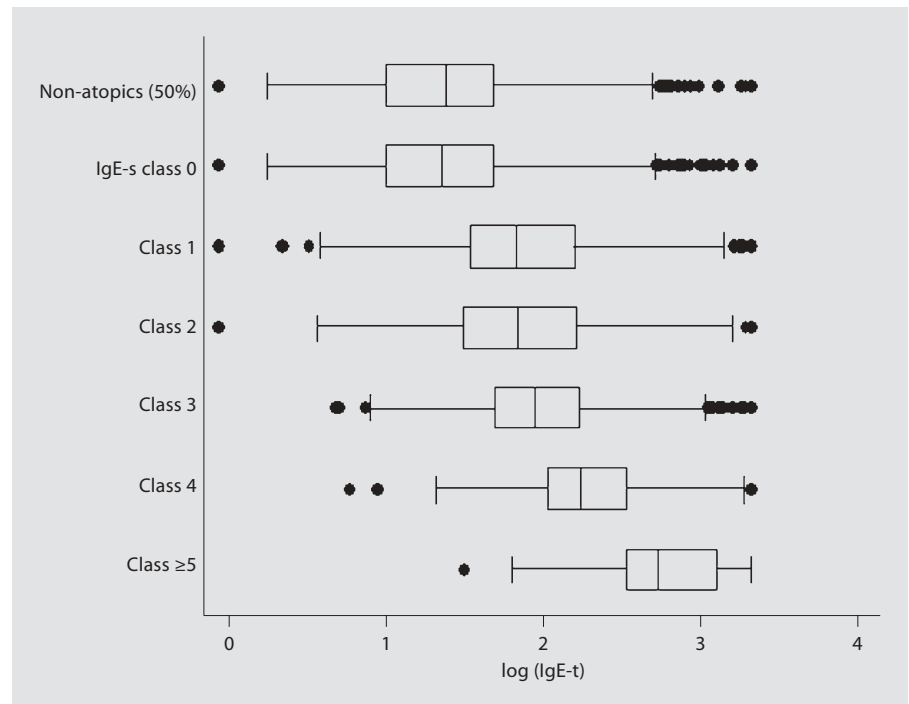


Fig. 1. Distribution of log IgE-t by IgE specific class splitting class 0 into two approximately 50% random samples of non-atopics used for estimation purposes and IgEs class 0 (50% remained of non-atopics) to 5 for validation.

jects (34.8%); 10.2% had two or more positive allergens; 2.9% had three, and 29 (0.4%) had all.

The IgE-t among non-atopics ranged from <2 to >2,000 kU/l. The distribution of IgE values was highly right skewed, but became normally distributed after log transformation. In the whole sample, the geometric mean of IgE was 41.3 kU/l (geometric SD = 4.3, 95% confidence interval, CI, 39.9–42.7). In subjects with IgE-s class = 0, the IgE-t mean was 23.8 (geometric SD = 3.5, 95% CI 22.9–24.7).

Reference Values

The group of subjects with IgE-s in class 0 was split into the two random subsamples A and B, and was approximately 50%: the A subsample (2,249 subjects) was composed of 45.6% males, had a mean age of 43.5 years (± 7.2) and a mean log IgE-t concentration of 1.375 (± 0.53), i.e. a geometric mean of 23.7; the B subsample (2,158 subjects) consisted of 45.6% males, had a mean age of 43.2 years (± 7.0) and mean log IgE-t concentration of 1.368 (± 0.56), i.e. a geometric mean of 23.3.

Figure 1 shows the distribution of log IgE-t by IgE-s class in the two subsamples of non-atopic and atopic subjects. There is a wide distribution of IgE values in non-atopic subjects ranging between the two scale extremes.

We estimated the regression equation considering the subsample A of non-atopic subjects with log IgE-t as de-

Table 3. Results of regression analysis of IgE-t in log (kU/l) versus smoking habits and gender using a 50% subsample of non-atopic subjects: mean, 95th and 99th percentiles of total IgE (kU/l) by sex and smoking habits

log (IgE)	B	95% CI
Male	0.056	0.01–0.10
Smoking	0.116	0.07–0.16
Constant (α)	1.275	1.24–1.31

Regression SD = 0.54624

		Mean	95th percentile	99th percentile
Non-smokers	Females	19	148	300
	Males	21	169	341
Smokers	Females	25	194	392
	Males	28	220	446

B = Regression coefficient.

pendent, smoking (yes/no), sex (females/males) and age (<25 years) computing robust standard error considering centers as clusters.

Table 3 shows the results of the regression analysis. Age had a small but statistically non-significant effect

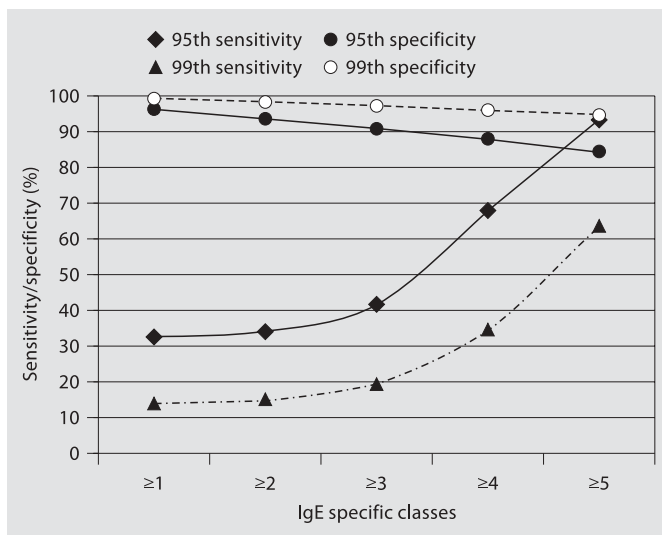


Fig. 2. Sensitivity and specificity of the two cutoffs (9th and 99th percentile) for total IgE normal value by IgE-s class in the 50% of the sample used for validation.

($p \leq 0.5$) and was excluded from the model. Males have higher IgE-t values than females and smokers have a significantly higher concentration than non-smokers. Table 3 also reports the mean estimated IgE-t by sex and smoking habits and the 95th and 99th percentiles as the upper normal threshold values.

The cutoff to classify normal IgE was considered the 95th percentile; the 99th percentile has to be considered a level with higher specificity (values exceeding the 99th percentile are 'certainly' abnormal values); IgE levels between both values should be considered borderline or uncertain. Applying these criteria to the whole sample, using these values 85.8% of subjects were classified as having normal, 8.6% as uncertain and 5.6% as abnormal IgE.

Validation and Analysis of the Clinical Usefulness of IgE-t in Allergy Diagnosis

The following analyses were conducted on the sample excluding the subjects used for estimation (subsample A, 50% of non-atopic and all atopic subjects). Figure 2 shows the validity of different cutoffs for IgE reference values in predicting atopy and defined the following different levels of IgE-s concentrations (classes). Using the 95th percentile as the cutoff of normal values, sensitivity ranges from 32.4% considering as atopic subjects with IgE-s class ≥ 1 , to 93% for class ≥ 5 ; the specificity ranges from 96 to 84% in the same IgE-s intervals. Using the 99th percentile

Table 4. Odds ratios and 95% CI of having abnormal IgE-t for symptoms

	OR	95% CI
Non-atopic subjects		
Asthma	1.21	0.72–1.95
Asthma diagnosed	1.22	0.71–1.99
Current asthma	1.94	0.96–3.58
Drugs for asthma	1.35	0.56–2.78
Allergic rhinitis	1.13	0.77–1.63
Allergic dermatitis/eczema	0.98	0.73–1.32
Atopic subjects		
Asthma	1.69	1.42–2.00
Asthma diagnosed	1.81	1.52–2.15
Current asthma	1.90	1.53–2.36
Drugs for asthma	2.14	1.72–2.65
Allergic rhinitis	1.03	0.87–1.22
Allergic dermatitis/eczema	1.12	0.95–1.32

as the normal cutoff, the specificity is 94% for IgE-s class 5 but the sensitivity is $<65\%$. High IgE-t values are very specific for all IgE-s classes but very poor regarding sensitivity: a lot of subjects with a high IgE-s class could have values of IgE-t <99 th percentile; on the contrary, only few subjects with high IgE-s values have low IgE-t.

Table 4 shows odds ratios with 95% CI for IgE-t ≥ 95 th percentile in symptomatic subjects by atopic status: the normal limits of IgE-t are associated with asthma during the patient's life and doctor-confirmed asthma and drugs for asthma only in atopic subjects. Current asthma (asthma attacks in the last 12 months) is associated with the IgE level in both atopic and non-atopic subjects, but the association is statistically significant for atopic patients only. Allergic rhinitis and eczema are not significantly associated with IgE beyond the normal limits either in atopic or in non-atopic subjects.

Discussion

Ever since Zetterstrom and Johansson [6] established the reference value of IgE-t for non-atopic adults (1.5–114 kU/l), this range was widely applied for the diagnosis of atopy or allergy. Our results show that the reference values in the European population are slightly higher than the values suggested by Zetterstrom and Johansson [6] and others [13]. The difference could be due to the

geographic restriction or to the wider age ranges of the population examined in those studies. Nevertheless, in contrast to the other studies, in the present study symptomatic non-atopic subjects were not excluded from the analysis: actually, the purpose was to identify reference values in a laboratory test potentially able to distinguish between normal and abnormal values and, possibly, between atopic and non-atopic, as symptom identification is a clinical and not a laboratory task. Other studies, with a protocol similar to the present one, found not dissimilar values in the same age range, considering the lack of controls for smoking habits and their being limited to the Dutch population [14].

The reasons for the large overlap in serum IgE-t between atopic and non-atopic subjects, although not surprising, is unclear. Apart from atopy, a number of other conditions are known to cause increased IgE-t levels. These include parasitic infections (especially by helminths) [15], immunodeficiencies (e.g. Wiskott-Aldrich syndrome) [16] and some neoplasms [17]. However, since the population on which our reference value determination was based was a random sample of the general European young adult population, with expected low prevalence of the previous conditions, it is more likely that the elevated IgE-t levels represented a general feature to which genetic and/or environmental factors may contribute [18, 19]. We also have to consider that our classification of atopy was based on a limited battery of allergens and we cannot exclude that a proportion of non-atopic subjects with IgE-t levels beyond the reference value could be due to sensitization to allergens that were not included, although the allergens used are the most representative ones in Europeans [14].

However, another potential explanation is the cross-sectional nature of this analysis and, although IgE sensitization to allergens is relatively stable, you may expect some of the non-atopics with high IgE-t to become atopic sometime in the future.

Although gender and smoking habits explain only a small proportion of IgE-t variability in non-atopic subjects, the reference values obtained in this study are dependent on gender and smoking: males and smokers had significantly higher values than females and non-smokers, respectively; IgE-t had no relationship with age in linear regression analysis. These results are in agreement with other reports published in the literature [3, 4, 14, 20, 21].

Studies that do not confirm the effects of gender or smoking in non-atopic subjects are generally based on samples with insufficient sample size to detect this small

effect as statistically significant [6, 9] or are not adjusted for atopy. However, although the gender effect is small, accounting for it improves estimation precision.

Immunological changes in relation to smoking are well known [20–22] and two hypotheses have been proposed to explain the relationship between smoking and IgE: a direct effect on IgE regulation at the cellular level and an indirect action which may lead to an increased permeability of airways to allergens [23]. The demonstration that a small IgE increase in smokers is independent of the atopic status could strengthen the direct effect hypothesis.

With regard to the lack of an age effect, although it is well known that IgE-t values increase from infancy to adolescence [19, 20], the trend in adulthood is controversial [3, 14, 21]. The lack of correlation of IgE-t with age in our study may be partly due to the limited age range that we studied (25–50 years).

Considering the ability of IgE-t to discriminate between atopic and non-atopic subjects, we could have some difficulty in defining atopy itself. However, IgE-t levels at the 95th percentile seem to have a sufficient combination of sensitivity and specificity only defining as atopic the subjects with a high IgE-s value (class 4 or more), although the low prevalence in this group generates a very low positive predictive value. For subjects with low or moderate values of IgE-s (classes 1–3), despite the elevated specificity (most non-atopics have values lower than the limit) and positive predictive value (most subjects with values of IgE-t higher than the limit are atopic), the sensitivity and (then) the negative predictive value are unacceptably low (most atopics in class <4 are not detected by the proposed limits and an important number of subjects with normal IgE are atopic). Therefore, IgE-t values higher than the normal limits at the 95th percentile suggest the presence of atopy, but values under the limits can exclude with reasonable likelihood only subjects with very high values of IgE-s. Obviously, due to the wide overlap between the two populations of atopics and non-atopics with low IgE-s class, if we use higher percentiles for the 'normal' definition, we produce a useless increase in specificity and positive predictive value, while at the same time lowering sensitivity and the negative predictive value in the high IgE class. As remarked in the results, if we define the cutoff for normal values at higher values (>99th percentile) and only consider as atopic the subjects with a very high IgE-s class (≥ 4), the classification error is not acceptable due to the very low sensitivity.

Considering the cross-classification of symptomatic (asthma, rhinitis and dermatitis) and non-symptomatic subjects, atopics and non-atopics with the reference values of IgE-t, IgE-t values higher than the reference values were predictive of asthmatic (and no other) symptoms only for atopic subjects but low sensitivity was confirmed. The lack of association for allergic rhinitis and allergic dermatitis/eczema could be due to the not sufficiently valid definition of these conditions in a study designed to collect asthma and asthma-like symptoms. This result suggests that IgE-t is linked more to atopy than *directly* to symptoms.

In conclusion, the study has shown that normal IgE-t levels in young European adults are, although slightly, gender and smoking status dependent and higher than those reported to date. The very wide spread of the values severely limits their predictive value in allergy diagnosis.

IgE-t values surpassing the normal limits confirm a suspected atopic status, but borderline values or values below the limits apparently do not to exclude an atopic status with sufficient accuracy, at least for low IgE-s classes. Thus, if it is doubtful that IgE-t values would be useful in discriminating atopy from non-atopy or allergic subjects in the general population (for example in epidemiological studies or for screening purposes), they may be of value in more selected populations (i.e. symptomatic subjects suspected of being atopic) to confirm an atopic status. It may be useful, however, to indicate that the probability of sensitization and IgE-t values beyond the limits should prompt the clinician to conduct further investigations in patients with a negative specific-IgE test or a positive one in a low class for a common inhalant allergen panel.

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