GUIDELINES

Guidelines on the Clinical Usefulness of Determination of Specific Immunoglobulin E to Foods

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Abstract

The diagnostic gold standard for food allergy is challenge with the culprit food, particularly in double-blind placebo-controlled challenge. This approach involves risks and consumes both time and resources. A more efficient system would be desirable. The detection of serum specific immunoglobulin E (sIgE) against the culprit food enables us to establish sensitization, although this is not always accompanied by clinical reactivity. Age, symptoms (immediate/late reaction, local/systemic reaction), concomitant condition (eg, atopic dermatitis, pollinosis) and selection sample criteria (eg, presence of symptoms related to ingestion, positive skin prick test result) can influence the detection and concentration of IgE against foods. We analyze the clinical usefulness of sIgE determination in light of studies in which oral food challenge is used as the diagnostic method. We review clinical usefulness at diagnosis and in the decision to reintroduce the food, as well as the prognostic value of the determination of IgE to foods.

Key words: Specific IgE. Food allergy. Diagnosis. Prognosis.

Resumen

El patrón oro en el diagnóstico de la alergia alimentaria es la provocación con el alimento en cuestión, particularmente en doble ciego y controlada con placebo. Este método diagnóstico implica riesgos y un elevado consumo de tiempo y recursos. Sería deseable un sistema que nos ahorrara un buen número de ellas. La detección de IgE sérica específica frente al alimento causal permite identificar la existencia de sensibilización frente a ese alimento, pero no siempre se acompaña de reactividad clínica. Edad, clínica producida por la alergia alimentaria (reacción inmediata/tardía, reacción local/sistémica), patologías concomitantes a la alergia alimentaria (dermatitis atópica, polinosis…) y criterio de selección de la muestra (presencia de síntomas en relación a la ingestión del alimento, prick test positivo,…) son aspectos que pueden influir en la frecuencia de detección y concentración de IgE frente a alimentos. En este documento se pretende analizar la utilidad clínica de la determinación de IgE específica a la luz de los estudios realizados en los que la provocación oral con alimentos es considerada como método diagnóstico. Se revisa la utilidad clínica en el momento del diagnóstico, en la decisión de reintroducir el alimento, así como el valor pronóstico de la determinación de IgE a alimentos.

Palabras clave: IgE específica. Alergia alimentaria. Diagnóstico. Pronóstico.

Introduction

The prevalence of self-reported food allergy varies from 3% to 33% [1]; however, prevalence established by open or double-blind challenge is much lower [2], varying between 1% and 10.8% [1]. The diagnostic gold standard for food allergy is challenge with the culprit food, particularly double-blind placebo-controlled challenge. This approach involves risks and consumes both time and resources. Given the number of candidates for oral challenge testing, a more efficient system would be desirable. Furthermore, although diagnostic challenges are the gold standard, they are not systematically undertaken in normal clinical practice. Of the immunologic mechanisms underlying food allergy, the most well known is specific immunoglobulin (Ig) E to foods. The detection of serum specific IgE (sIgE) against the culprit food enables sensitization to be established, even if this is not always accompanied by clinical symptoms, which are essential for the term food allergy to be applied.

It cannot be denied that determination of sIgE offers poor reproducibility due to the variability of the biological source and lack of standardization in the extracts. Therefore, it frequently yields both false negatives and false positives. Nevertheless, this test is habitually requested by clinical allergists.

The aim of the present study was to review the clinical usefulness of sIgE determination in the diagnostic process, given evidence from studies in which oral challenge with foods was used as the method of diagnosis.

Sources of Variability

Analytical Method

Different commercial techniques use different standards and different units of measurement; therefore, it is difficult to compare results [3]. Even assays using reference reagents calibrated against the 75/502 World Health Organization (WHO) standard, whose units are comparable, do not necessarily yield overlapping or interchangeable results [4,5]. Thus, in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), yield varies from one commercial assay to another [3,6]. This also occurs when cutoff points are modified.

Foods Tested

The biochemical composition of the food extracts can influence sIgE determination, as follows:

- Extracts from plant foods frequently have a low protein content and poor biological activity, which may give rise to false negatives.
- The presence of proteolytic enzymes can degrade allergenic molecules (eg, Mal d 1) and give rise to false negatives. This is a more serious problem in extracts for skin prick testing.
- The phenomenon of immunologic cross-reactivity may appear in 3 clinical situations: a) situations with usual clinical relevance (eg, between fish or between crustaceans); b) situations with inconstant clinical relevance (eg, pollinosis and plants); and c) situations with no usual clinical relevance (eg, pollinosis due to grasses and cereals). Situations b and c frequently give rise to false positives in clinical terms, even when they correspond to a real immunologic state.

Study Population

Age, clinical symptoms caused by the food allergy (immediate/late reaction, local/systemic reaction), concomitant illness (eg, atopic dermatitis, pollinosis), and selection criteria (eg, presence of symptoms related to ingestion, positive skin prick test result) can all influence detection and concentration of IgE against foods.

Sensitivity and specificity depend on the technique used (method of analysis and allergenic source) and can be expressed as follows: sensitivity = TP/(TP+FN) and specificity = TN/(TN+FP) where TP represents the number of cases with a positive challenge test result and positive sIgE, FN represents patients with a positive challenge and negative sIgE, TN represents patients with a negative challenge test result and negative sIgE, and FP represents patients with a negative challenge and positive sIgE. The positive predictive value [TP · PREV / TP · PREV + FP · (1-PREV)] and negative predictive value [TN · (1-PREV) / TN · (1-PREV) + FN · PREV] depend on the prevalence (PREV represents positive challenge tests/total number of patients tested), which again varies depending on the criteria used to establish a test as positive and the population studied. Thus, at least for milk, egg, and soy, the PPV is higher for immediate reactions than for late reactions, and both the PPV and NPV are greater in children under the age of 2 years than in older children [7].

When estimating the probability of a positive diagnosis of allergy to a specific food in a particular patient, apart from the probability inherent in each patient's clinical history, we can base our judgment on the sIgE value, which we must interpret bearing in mind the sources of variability mentioned above.

Clinical Usefulness of Determination of sIgE to Foods in the Diagnosis of Food Allergy

A study carried out in Spain [2] among children and adults with food allergy showed that when foods (mainly fruits and nuts) were taken together and the sIgE was determined using CAP with a cutoff point of 0.35 kU_A/L, determination of sIgE has a sensitivity of 84%, a specificity of 43%, a PPV of 50%, and an NPV of 80%.

In general, determination of sIgE to animal foods offers better yields (Table 1) than to plant foods (Table 2). In any case, the figures provided in the tables should be taken as an approximate guide, especially those corresponding to the predictive values calculated from the prevalence of a particular study, which, depending on the study design, will reflect more or less accurately the real prevalence. In these cases, it would be more appropriate to use values not influenced by the prevalence

Table 1. Diagnostic Yield of Specific Immunoglobulin E to Animal Foods

Food	N	Age	Selection Criterion	Associated Disorder	Positive Oral Challenge Response	Method	Cutoff Point	S, %	SP, %	PPV, %	NPV, %	Ref
Cod	11	Adults	SFA cod		I	RAST CAP ML	0.35 PRU/mL 0.35 kU_A/L 1.43 SU/ml	100 100 100	67 33 100	96[a] 91[a] 100[a]	100[a] 100[a] 100[a]	6
Cod	10	Adults	SFA cod		I	RAST	0.35 PRU/mL	100	87			39
Milk Egg white	19	Adults	SFA milk and/or egg		I milk I egg	RAST	0.35 PRU/mL	100 100	87 79			40
Milk Egg white	21	Adults	SFA milk and/or egg		I milk I egg	RAST CAP ML MATRIX	0.35 PRU/mL 0.35 kU_A/L 1.43 SU/mL 0.25	100 100 100 89	33 33 33 17	43[a] 43[a] 43[a] 71[a]	100[a] 100[a] 100[a] 40[a]	3
Milk Egg	60	Children (3 mo-48 mo)	SFA gastrointestinal	Family history of atopy 53%	Milk: I 32% L 68% Egg: I 26% L 74%	CAP milk CAP egg	0.35 kU_A/L 0.35 kU_A/L	23 32	74 67	54 67	42 32	41
Egg	33	Children (5 mo-4.75 y)	FA, with no prior ingestion of egg, SPT/IgE egg 21/33 positive	Other food allergy (eczema 61%)	I (93%) L (14%)	RAST	0.35 PRU/mL	85	68	66	86	42
Egg white	81	Children <2 y	SFA egg	AD 43% BA 57%	I	CAP	0.35 kU_A/L	91	77	94	68	21
Egg Milk	126 109	0.6-17.9 y	SFA egg SFA milk	AD 100% BA 50%	I (<2h)	CAP egg CAP milk	0.35 kU_A/L 0.35 kU_A/L	98 100	45 30	84 57	88 100	43
Egg Milk	227 398	1 mo-16 y	SFA egg SFA milk	DA 88%	I 67% L 63%	CAP egg CAP milk	0.35 kU_A/L 0.35 kU_A/L	97 83	51 53	80 63	89 76	44
Milk	170	Children <1 y	SFA milk	AD 23%	I	CAP milk	0.35 kU_A/L	72	62	60	73	8
Egg	108	14 mo-13 y	SFA egg	AD 94% BA 26%	I	CAP	0.35 kU_A/L	97	29	69	86	28

Abbreviations: AD, atopic dermatitis; BA, bronchial asthma; CAP, CAP system; FA, food allergy; I, immediate; L, late; MATRIX, Matrix food aero; ML: Magic lite; NPV, negative predictive value; PPV, positive predictive value; PRU, Phadebas RAST unit; RAST, Phadebas RAST; Ref, reference of source study; S, sensitivity; SFA, suspected food allergy; SP, specificity; SPT, skin prick test.
[a] Values calculated from the prevalence data of the sample studied.

Table 2. Diagnostic Yield of Specific Immunoglobulin E to Plant Foods

Food	N	Age	Selection Criterion	Associated Disorder	Positive Oral Challenge Response	Method	Cutoff Point	S, %	SP, %	PPV, %	NPV, %	Ref
Melon	53	Adults	SFA melon	FA vegetables 34% Pollinosis 34%	I	CAP	0.35 kU_A/L	53	62	44	70	[45]
Kiwi	45	6-64 y	SFA kiwi	Children 90% atopic disease	I (38% only OAS)	CAP	0.35 kU_A/L	61	83	92[a]	36[a]	[46]
Brazil nut	56	4-83 y	SFA and/or SPT/IgE positive	AD 75% BA 71% AR 88%	I	CAP	0.35 kU_A/L	84	55	88	47	[47]
Wheat	39	<2 y	SFA wheat with clinical symptoms AD/GI	AD 92%	I 23% L 77%	CAP	0.35 kU_A/L	18[a]	93[a]	84[a]	40[a]	[48]
Wheat	27	14-60 y	SFA wheat with I clinical symptoms	Pollinosis to gramineae 52% FA vegetables 26%	I	CAP	0.35 kU_A/L	85 75[b]	27 50[b]	57 86[b]	58 33[b]	[49]
Wheat Soy Peanut	87 31 41	0.6-17.9 y	SFA wheat SFA soy SFA peanut	AD 100% BA 50%	I (<2h)	CAP wheat CAP soy CAP peanut	0.35 kU_A/L 0.35 kU_A/L 0.35 kU_A/L	90 76 90	51 47 29	35 35 55	94 84 75	[43]
Wheat Soy	178 189	1 mo-16 y	SFA wheat SFA soy	AD 88%	I 67% L 63% C 19%	CAP wheat CAP soy	0.35 kU_A/L 0.35 kU_A/L	79 69	38 50	41 22	77 88	[44]
Mustard	30	2-20 y	SFA any food and SPT mustard positive	AD/BA/U/ AE/GI	I 6/7 L 1/7	CAP	0.35 kU_A/L	83[a]	24[a]	9[a]	94[a]	[50]

Abbreviations: AD, atopic dermatitis; AE, angioedema; AR, allergic rhinitis; BA, bronchial asthma; C, combined; CAP: CAP system; FA, food allergy; GI, gastrointestinal; I, immediate; L, late; NPV, negative predictive value; OAS, oral allergy syndrome; PPV, positive predictive value; Ref, reference of source study; S indicates sensitivity; SP, specificity; SFA, suspected food allergy; SPT, skin prick test; U, urticaria.

[a] Values calculated from the prevalence data from the sample studied.

[b] Patients with pollinosis have been excluded.

Table 3. Improvement in Diagnostic Yield of the Specific Immunoglobulin E Determination by Modifying the Cutoff Point

Food	N	Age	Selection Criterion	Associated Disorder	Positive Oral Challenge Response	Method	Cutoff Point	S, %	SP, %	PPV, %	NPV, %	Ref
Egg Milk Peanut Soy Wheat Fish	126 109 41 111 87 20	0.6-17.9 y	SFA egg SFA milk SFA peanut SFA soy SFA wheat SFA fish	AD 100% BA 50%	I (<2 h)	CAP egg CAP milk CAP peanut CAP soy CAP wheat CAP fish	3.4 kU_A/L 5.8 kU_A/L 10.7 kU_A/L 5 kU_A/L 8.1 kU_A/L 1.8 kU_A/L	82 80 76 68 70 85	84 81 88 63 73 88	94 80 94 28 25 71	62 81 62 90 95 94	[43]
Peanut	157	Mean , 7 y (1-16 y)	SFA peanut or positive SPT with doubtful reaction or without prior ingestion	AD 40% BA 45%		CAP peanut	15 kU_A/L	28	97	91	53	[51]
Egg Milk Peanut Soy Wheat Fish	75 62 68 25 23 8	3 mo-14 y	SFA egg SFA milk SFA peanut SFA soy SFA wheat SFA fish	AD 61% BA 50%	I	CAP egg CAP milk CAP peanut CAP soy CAP wheat CAP fish	6 kU_A/L[b] 32 kU_A/L[b] 15 kU_A/L 65 kU_A/L[b] 100 kU_A/L[b] 20 kU_A/L[b]	64 34 57 24 13 25	90 100 100 99 100 100	96 100 100 86 100 100	39 44 36 89 78 76	[52]
Saracen wheat	28 patients, 16 controls		Patients: positive oral challenge Controls: asymptomatic with positive SPT			CAP	1.26 kU_A/L	93	93	80	98	[53]
Hazel nut	78	14-64 y	SFA hazel nut	Pollinosis 100% (90% birch)	I (76% OAS)	CAP	0.70 kU_A/L[c]	75	16	92	5	[54]
Brasil nut	56	4-83 y	SFA and/or positive SPT/IgE	AD 75% BA 71% AR 88%	I	CAP	1 kU_A/L[c]	35	100	100	33	[47]
Milk	170	Children < 1 y	SFA milk	AD 23%°	I	CAP milk	0.70 kU_A/L[a]	74	71	67	77	[8]
Egg white	81	<2 y	SFA egg	AD 43% BA 57	I	CAP white	0.43 kU_A/L[a]	>80	>80			[21]
Celery	32	13-55 y	SFA celery	Pollinosis 100%	I (50% SAO)	CAP	0.70 kU_A/L[c]	73	38	90	17	[55]
Egg white	56	6 mo-5 y	AD	AD 100%	I (<2h)	ML white CAP white	<2 y, 3.3 SU/mL >2 y, 8.8 SU/mL <2 y, 0.8 SU/mL >2 y, 0.8 SU/mL	82 90 73 89	82 89 75 75	82 89 89 80	68 85 51 86	[56]

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; BA, bronchial asthma; CAP, CAP system; I, immediate; ML, Magic lite; NPV, negative predictive value; PPV, positive predictive value; OAS, oral allergy syndrome; Ref, reference of source study; S indicates sensitivity; SFA, suspected food allergy; SP, specificity; SPT, skin prick test.

[a] Optimum decision points calculated using receiver operating characteristic curves.

[b] Cutoff points taken from the bibliography.

[c] Cutoff points established arbitrarily.

Table 4. Specific Immunoglobulin E Levels with Diagnostic Value

Food	N	Age	Selection Criterion	Associated Disorder	Positive Oral Challenge Response	Method	PPV = 90%	PPV = 95%	Ref
Egg Milk Peanut Fish	126 109 41 20	0.6-17.9 y	SFA egg SFA milk SFA peanut SFA fish	AD 100% BA 50%	I (<2 h)	CAP egg CAP milk CAP peanut CAP fish	2 kU_A/L 23 kU_A/L 9 kU_A/L 9.5 kU_A/L	6 kU_A/L 32 kU_A/L 15 kU_A/L 20 kU_A/L	43
Milk Egg	398 227	1 mo-16 y	SFA milk SFA egg	AD 88%	I 67% L 63% C 19%	CAP milk CAP egg	< 1 y, 25.8 kU_A/L >1 y, NC <1 y, 4.2 kU_A/L > 1 y, 6.7 kU_A/L	NC NC <1 y, 10.9 kU_A/L >1 y, 13.2 kU_A/L	44
Milk	170	<1 y	SFA milk	AD 23%	I	CAP milk	2.5 kU_A/L	5 kU_A/L	8
Milk Egg	969	Mean, 1.3 y	SFA milk SFA egg	AD 64% BA 18%		CAP milk CAP egg		<1 y, 13 kU_A/L 1-2 y, 23 kU_A/L >2 y, 30 kU_A/L <1 y, 5.8 kU_A/L 1-2 y, 38.6 kU_A/L >2 y, 57.3 kU_A/L	57

Abbreviations: AD, atopic dermatitis; BA, bronchial asthma; C, combined; CAP, CAP system; I, immediate; L, late; NC, not calculable; PPV, positive predictive value; Ref, reference of source study; SFA, suspected food allergy.

of the disorder, such as the probability ratios or values detected in 95% of the study sample.

The availability of quasi-quantitative assays allows the cutoff point to be changed depending on the food, the population studied, and the objective of the study (diagnosis, follow-up). Table 3 shows the yields obtained when the cutoff points for a particular method were changed individually for each food. The new points can be established arbitrarily or using receiver operating characteristic (ROC) curves, which allow the optimum decision point to be fixed where both the sensitivity and specificity values for the technique are at their maximum levels.

Furthermore, logistic regression may be used to calculate sIgE to a particular food, which in a specific population is associated with the probability of clinical reactivity chosen at the time of diagnosis (PPV between 90% and 95%) (Table 4). This information helps to reduce the need for oral challenge tests. It must be stressed that sIgE concentrations lower than these cutoff points do not allow the clinical relevance of this food to be ruled out, since the NPVs associated with these diagnostic decision points are usually low.

Several studies show that patients with food allergy confirmed by challenge tests have sIgE concentrations that are significantly higher than those of patients with a negative challenge test result [7-9]. However, the possible relationship between sIgE levels against a particular food and the severity of the reaction caused by ingestion of that food remains controversial. Sicherer et al [10] found a poor correlation between triggering doses, severity of reaction, and sIgE concentrations to different foods in a study of children with atopic dermatitis. Similar results were found in a European study [11] carried out on soy-allergic patients (children and adults, 97% with another associated atopic disease [atopic dermatis, 33%; asthma, 66%; and rhinoconjunctivitis, 67%]) and in the study by Flinterman et al [9] in which no correlation was detected in peanut-allergic children. In contrast, Hourihane et al [12] found that in adults, and to a lesser extent in children, IgE levels to peanut did correlate with the severity of the reaction in challenge tests performed at low doses of this food. Similarly, Peeters et al [13], in a series of peanut-allergic adults, found that those who reacted at low doses in the challenge test had sIgE levels to peanut that were higher than those who reacted at high doses.

Usefulness of the Clinical Decision to Reintroduce the Food

Children, particularly infants, commonly overcome food allergy. Quantification of sIgE to the food during follow-up might help establish exactly when it should be reintroduced, thus minimizing the frequency of challenge tests and their risks. Several studies have been carried out from this viewpoint. Again, the results, decision points established, and the probability of overcoming the allergy associated with a given concentration of sIgE can only be extrapolated to the same clinical and age groups. In a study of children with atopic dermatitis and food allergy, Niggemann et al [14] found no differences in sIgE levels to the culprit food or in disease progression when comparing patients with persistent or transitory food allergy.

In children aged 1 to 11 months diagnosed with allergy to cow milk proteins on the basis of clinical history, positive skin prick or sIgE results (CAP), and oral challenge with immediate response, Boyano et al [15] describe sIgE concentrations

with a 90% and 95% probability of positive challenge results during follow-up. These decision points are greater as age at evaluation increases. sIgE levels to milk and casein at 36 months were the most informative as regards whether the allergy to milk persisted or was overcome.

In patients with egg allergy, immediate reaction, and no history of atopic dermatitis, Crespo et al [16] found that sIgE levels to egg white and the probability of a positive result in a rechallenge test during follow-up were directly proportional. These authors recommend delaying rechallenge when IgE values against egg white are greater than 1.2 kU_A/L. Shek et al [17] analyzed the relationship between clinical progression and sIgE levels measured by CAP in patients allergic to egg and/or milk. Patients diagnosed before the age of 4 are more likely to overcome their allergy, the sooner the reduction in sIgE occurs and the greater its magnitude.

Perry et al [18] propose performing the challenge test to reintroduce the food after an avoidance diet in children when the probability of tolerance is ≥50%, which in their series (associated diseases: atopic dermatitis, 58%; asthma, 48%; rhinitis, 43%; allergy to more than 1 food, 77%) occurred at 2 kU_A/L for milk, egg, and peanut. Similar results have been described in another series of children diagnosed with allergy to peanut [19,20]. In a study carried out in patients diagnosed in infancy with allergy to nuts or sensitization with no prior ingestion, oral challenge tests were performed in 39 children over the age of 4 with no history of reaction in the previous year and sIgE levels of <10 kU_A/L. The results show that 2 kU_A/L was the concentration with an NPV of 70%.

Prognostic Value of the Determination of IgE to Foods

The prognostic value of determining specific IgE in food allergy can be analyzed from several perspectives. Firstly, some studies examine whether determination of sIgE to a particular food at the time of diagnosis is related or not to the probability of the patient overcoming this allergy in the future. In this sense, Boyano et al [21] analyzed the relationship between the clinical progression of egg-allergic children under the age of 2 with immediate reaction and sIgE levels to egg white (CAP) at diagnosis. They found that, only in the children with a history of skin reactions, the lower the initial level of IgE to egg white, the greater the probability of achieving tolerance. Savage et al [22] found that it is unlikely that children allergic to egg with sIgE of >50 kU_A/L become tolerant. Vanto et al [23] monitored the clinical progression of milk-allergic children with immediate or late clinical manifestations for 4 years. Eighty-two percent of the children who achieved tolerance had IgE levels to milk <2 kU_A/L at diagnosis, and 71% of those in whom the allergy persisted had IgE levels to milk of ≥2 kU_A/L.

The persistence of food allergy has been associated with sensitization to certain food allergens. Thus, IgE sensitization to casein appears to be more predominant in older children who have not overcome allergy to cow milk proteins [24], and its determination may improve the predictive values of clinical persistence, particularly in children over 3 years of age [25]. Similarly, sensitization to ovomucoid appears to be related to the persistence of egg allergy [26] and a lower probability of tolerating hard-boiled eggs than in individuals who are not sensitized to this allergen [27,28]. A further step would be to identify the epitopes of an allergen that are recognized by the IgE of a particular patient, since sensitization to specific linear epitopes of casein [29-31], ovomucoid [32], and Ara h 1 and Ara h 2 [33] have proven to be of prognostic interest as regards whether allergy to milk, egg, and peanut will persist or be overcome in the future. Sensitization to specific molecules from a food source may have implications for the risk of severe reactions; therefore, determination of sIgE to these purified allergens is of prognostic interest for the risk run by the allergic

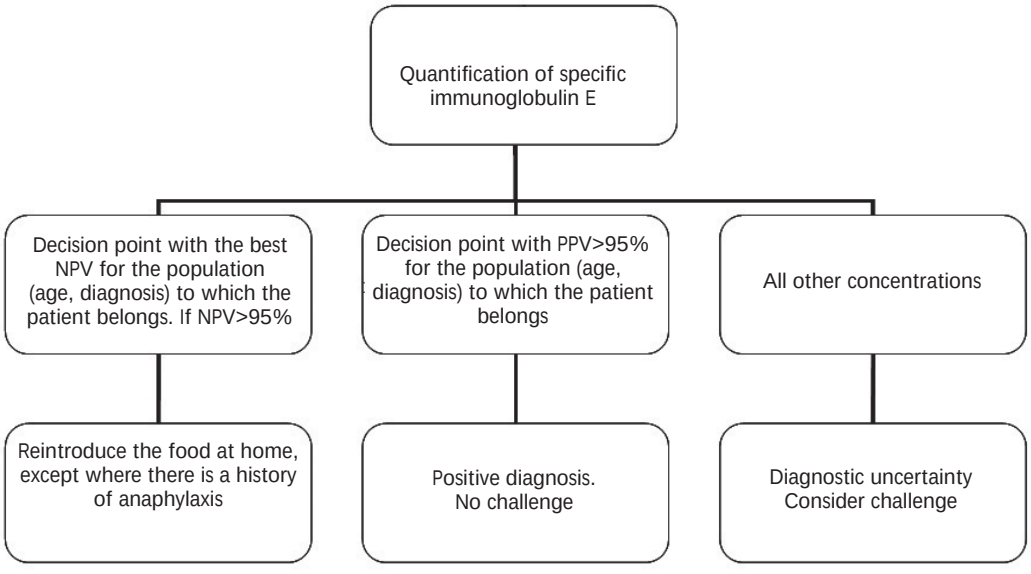

Figure. Algorithm for the diagnostic interpretation of specific immunoglobulin E values to foods

patient with future exposures. Thus, for example, sensitization to lipid transport proteins in patients allergic to Rosaceae [34-36], to 5-ω gliadin in wheat-allergic patients [37], and to class 1 chitinases in patients with latex-fruit syndrome is associated with a high risk of severe reactions. In contrast, sensitization exclusively to Bet v 1 and/or profilin involves a low risk of systemic reaction. Furthermore, knowledge of IgE reactivity against different purified allergenic molecules that can be obtained using the so-called diagnosis by components allows a prognosis to be made regarding the presence or absence of risk of certain cross-reactivity patterns with a known molecular basis.

In conclusion, the determination of sIgE to foods may be of value for the diagnosis, prognosis, and progression of an allergic disorder. For the diagnostic interpretation of sIgE to a particular food using a standardized quasi-quantitative technique (with reference reagents calibrated against WHO standards) in a particular patient, the algorithm in the Figure could be followed.

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