Practice Parameter: Clinical Guidelines for Serum Specific IgE in Allergy Practice

Indian Academy of Pediatrics – Allergy and Applied Immunology Chapter

Compiled in October 2025; Next revision due in October 2028

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Introduction

An accurate diagnosis coupled with optimal therapy forms the basis of appropriate management of allergy. Clinical history forms the cornerstone of allergy diagnosis. It is augmented by a thorough physical examination and laboratory tests in vivo and/or vitro whenever required.

Sensitization occurs when a person is exposed to allergens, leading to cross-linking of allergen-specific immunoglobulin E (sIgE); subsequent exposure may lead to clinical symptoms. Allergic sensitization is characterized by the presence of IgE antibodies specific to the allergens that are ingested, absorbed or inhaled. Allergen specific IgE antibodies are found in bound and free form in a sensitized individual.

Skin prick test (SPT) is the gold standard test for detection of sIgE and detects bound sIgE. It is commonly used as first line given its good sensitivity, less turnover time and cost-effectiveness. Where SPT is not possible or indicated, an alternative is invitro testing to detect sIgE to the allergen. In this document we will discuss only the invitro tests for detection of Serum Specific IgE.

Serum IgE tests

Total IgE: It is important to understand that total IgE is the total amount of IgE present in the blood. It is nonspecific and can be elevated in several conditions but not limited to allergic diseases, parasitic infections, neoplastic diseases, and immunodeficiency disorders. Hence its use is limited in diagnosis of specific allergies.
However, it is useful measure where anti IgE treatment is considered and in conditions such as Allergic fungal rhinosinusitis (AFRS), Eosinophilic airway diseases.

Serum Specific IgE (sIgE): This IgE binds only to that specific allergen hence is indicative of sensitization. It only detects circulating free sIgE to that specific allergen. Depending on the assay and technique used, tests can detect sIgE to the whole allergen (Serum specific IgE) or to individual components of the allergen (Component resolved diagnostics).

The decision as to which test to use for sIgE detection must be considered based on a detailed clinical assessment on an individual patient basis.

Table 1: Comparison of Serum sIgE and Skin Prick Test

	Serum sIgE	SPT
Unaffected/ independent of medications	Yes	No
Unaffected/ independent of skin status	Yes	No
Trained personnel needed	No	Yes
Quantitative results kUA/L	Yes	No
Time factor	1-7 days	15-30 minutes
Cost factor	More expensive	Less expensive
Recent anaphylaxis (<4 weeks)	Yes	No
Usefulness in motivating Parents/ Patients	Obscure	Dramatic

Blood testing for specific IgE will be helpful in the following situations:
1. Identification and quantification of allergen sIgE
2. Prediction of outgrowing or tolerance to food allergens
3. As an adjunct for the decision on allergen immunotherapy
4. Patients at high risk of anaphylaxis

Different factors influencing this decision are detailed in table 2

Table 2: Indications of sIgE testing

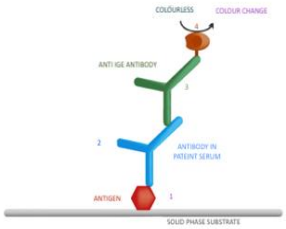
1. Patient related	a. Area of skin not favorable to do skin prick test like in patients of eczema and urticaria. b. Inability to stop the medications that will interfere with the skin prick test. c. Anaphylactic episodes in the previous 4 weeks d. Patient unwilling for the test despite counseling e. Extremes of ages (especially infants < 6 months) f. Poor access to skin prick test allergens
2. Allergen specific	The relevant allergen extracts are not available for skin prick test but are for In-vitro testing
3.Progress/prognosis	a. Before the challenge, especially for food allergies. A negative SPT and a negative in vitro test are both used to confirm before the challenge. b. Specific situations where detailed analysis of components is required for prognostication, especially in food allergies c. To know cross-reactivity and its clinical relevance, especially in oral allergy syndrome
4. Geography.	Patient is from an area where there is no access to

	skin prick test material or personnel versed with doing skin prick test (and are unable to travel to a place having these); then, *in vitro* tests can be considered

Basic Methodology of the Immunoassays

The immunoassays are the most prevalent tests in use for invitro sIgE detection. There are a few inter-methodological variations of immunoassays. Methodology used in measuring sIgE are variants of the classic sandwich technique.
They have a reaction site, antigen (allergen) bound to the reaction site, test serum, anti-IgE antibody, and a labelling agent for the anti-IgE.

1. Antigen is bound to the reaction site
2. sIgE in test serum binds to the antigen
3. Enzyme-labelled anti-IgE antibody binds to the Fc portion of sIgE to form a complex
4. Allergen-IgE-anti-IgE complex incubated with reagent leads to a change in colour.



The intensity of the colour or fluorescence is measured quantitatively and expressed as kUA/L

The allergen used in immunoassays can be derived from an allergen extract or a recombinant molecule. An extract can have both allergenic and nonallergenic substances. Some of these are cross-reactive carbohydrate determinants (CCD). CCD may react with the anti-IgE thus lead to false positive or disproportionately high reading. Greater availability of purified extracts has meant that the newer generation sIgE tests have fewer confounding factors hence better reliability and reproducibility.

Cross-reactivity in allergic reactions occurs when the proteins in one substance are like proteins in another. Hence, both have a similar epitope, and hence, there activity too is similar. This can often lead to confusion. There is also an issue of cross-reactivity within the assays. CCD-positive sera show binding even with no allergen sIgE in that sample.

Measurement of sIgE can be achieved with single reagents (single plex) or with a pre-defined panel of a few molecules which are tested simultaneously (multiplex).

Different techniques of measuring sIgE

a. Radioallergosorbent assays (RASTs) – (Discontinued since 2010)

b. Enzyme-linked immunosorbent assays (ELISAs) – relatively simple and inexpensive compared to FEIAs

c. fluorescent enzyme immunoassays (FEIAs) (Immunocap)

d. Chemiluminescent assays

Currently the assays that have been validated and in use are Immunocap and Immunoblot technique. Immunocap is largely a single plex test where one or more allergens are chosen

based on history. Immunoblot is a multiplex test which comes as a strip of set combination of allergens. There are several blood 'allergy tests' prevalent, many of which are non-validated hence of questionable value. At the time of writing this document Immunocap is perceived as "reference standard" for in vitro sIgE testing.

Interpretation of test results.

A positive sIgE test indicates *sensitization* (the presence of IgE antibodies) but *not* necessarily clinical *allergy* (a reaction upon exposure)

A test result is expressed as kUA/L. The present cutoff for a positive report is 0.1kUA/L. However, it is important to understand higher sIgE levels correlate with a higher probability of true positive test, but there are no absolute cutoffs that apply universally. Equally important is to note a higher value does not indicate more severe allergy.

As the sensitivity has increased there is higher rate of false positive results with sIgE. This must be kept in mind while interpreting results. Result interpretation depends largely on clinical history and its correlation with the test. Often it is essential to take a second history to confirm or exclude allergies after the test. Based on the combined interpretation of the sIgE results and the clinical data, the clinician estimates the likelihood that the child has a true IgE-mediated allergy to the suspected allergen(s). Probability Outcomes can be categorized into High, Moderate/Unclear, Low/Unlikely categories**.**

High Probability of Allergy: Confirm Clinical Diagnosis & Develop Comprehensive Management Plan: If the sIgE results strongly support the clinical history of a reaction, the diagnosis of IgE-mediated allergy is made clinically, and management is done accordingly.

Moderate/Unclear Probability: Consider further assessment: If the sIgE results are positive but the clinical history is equivocal, or if there is a discrepancy, further history /testing may be needed.

Low Probability of Allergy OR Allergy Unlikely: Consider Alternative Diagnoses: If the sIgE results are negative or very low, and the clinical history does not strongly suggest IgE-mediated allergy, reevaluate diagnosis considering other potential causes for the child's symptoms (e.g., GERD, infectious gastroenteritis, viral-induced wheezing, non-allergic rhinitis)

Special Considerations

Food Allergy: Food allergies can be IgE mediated or non-IgE mediated. In non-Ig E-mediated allergies, there is no allergen sIgE present in the serum. Hence, in these individuals, *in vitro* testing does not help in the detection/confirmation of allergy. Oral food challenge remains the gold standard for these individuals. Furthermore, even in IgE-mediated food allergies, there is no reliable single cutoff value for all food allergens.

Component-resolved diagnostics (CRD): This is very specialized test and is indicated only in a select group of patients' should never be used as a screening test. It involves microarray testing using recombinant allergens and antigenic components of major allergens and to

assess the precise antigenic epitopes specific to the patient. This can augment in detailed diagnosis and prognostication. It also helps in diagnosing sensitization to some insect venoms and foods and as a means of predicting cross-reactivity between food and pollen allergens. Interpretation of a CRD test result can be very complex and confusing if done inappropriately and without adequate training, hence should only be done when specific indications are present

Table 3: Dos and don'ts while pursuing sIgE tests

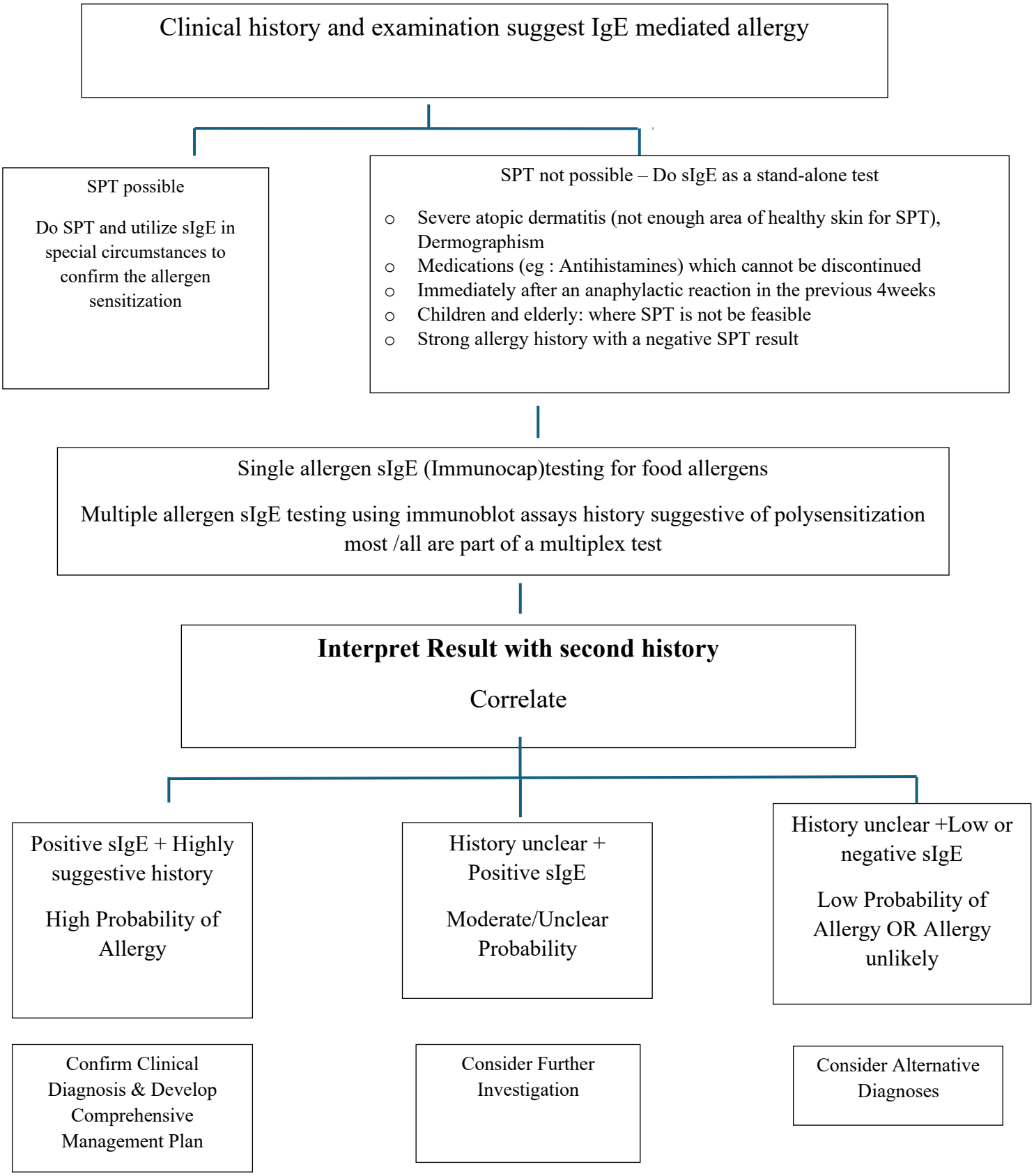
- Should never be used as screening test for allergies.

- Clinical assessment and correlation is to be done by the physician, the treatment should not be based on the results of any single diagnostic test.
- Immunotherapy should be based solely on the result of a sIgE test.
- Serum sIgE are of no value in investigation or management non-IgE mediated allergies.
- The degree of positivity sIgE results is not a surrogate marker of severity of allergic reaction.
- If there are no IgE mediated symptoms, using sIgE results as a guide may lead to inappropriate dietary avoidance
- Use of multiplex recombinant allergens should be restricted to only indicated cases as multiple allergen positivity indicates only sensitization, not clinical allergy.

Suggested Reading

1. Nagarajan SA, Nayak SH. *Invitro* diagnosis of allergic diseases. J Pediatr Pulmonol 2023;2:S119-24.

2. Ansotegui IJ, et al IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J. 2020 Feb 25;13(2):100080. doi: 10.1016/j.waojou.2019.100080. Erratum in: World Allergy Organ J. 2021 Jun 17;14(7):100557.


Clinical history and examination suggest IgE mediated allergy
SPT possible
Do SPT and utilize sIgE in special circumstances to confirm the allergen sensitization
SPT not possible – Do sIgE as a stand-alone test
Severe atopic dermatitis (not enough area of healthy skin for SPT), Dermographism
Medications (eg : Antihistamines) which cannot be discontinued
Immediately after an anaphylactic reaction in the previous 4weeks
Children and elderly: where SPT is not be feasible
Strong allergy history with a negative SPT result
Single allergen sIgE (Immunocap)testing for food allergens
Multiple allergen sIgE testing using immunoblot assays history suggestive of polysensitization most /all are part of a multiplex test
Interpret Result with second history
Correlate
Positive sIgE + Highly suggestive history
High Probability of Allergy
History unclear + Positive sIgE
Moderate/Unclear Probability
History unclear +Low or negative sIgE
Low Probability of Allergy OR Allergy unlikely
Confirm Clinical Diagnosis & Develop Comprehensive Management Plan
Consider Further Investigation
Consider Alternative Diagnoses