

How to interpret skin prick tests and serum-specific IgE in children and young people with food allergy

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Accepted 21 June 2021

ABSTRACT

Food allergy is common, it can lead to significant morbidity and negatively impacts on quality of life; therefore, it is vitally important we get the diagnosis right. However, making the diagnosis can be complex. Clinical history is the most important diagnostic tool and subsequent investigation may help confirm the diagnosis. The investigations available to most paediatric departments are skin prick testing and specific IgE so we will focus on these. Within this article we explore the evidence related to targeted testing and how to interpret these within the clinical context.

INTRODUCTION

Allergy is an adverse hypersensitivity reaction initiated by immunological mechanisms subdivided into IgE-mediated and non-IgE-mediated reactions.¹ Allergic symptoms range from mild to severe with anaphylaxis being the most severe clinical manifestation.² Food allergy is common with up to 5% of infants in the UK affected.³ It negatively impacts on quality of life therefore it is vitally important we get the diagnosis right.⁴

The basis of development of IgE-mediated allergic disease is the production of allergen-specific IgE. When the body encounters an allergen, antigen-presenting cells process the allergen, and in the right microenvironment, that is, presence of interleukin 4, 5 and 13, for example, in eczematous skin a shift occurs toward Th2 cell production and consequently B cell production of IgE targeted towards the specific allergen. The presence of specific IgE (sIgE) demonstrates sensitisation.² This IgE binds to mast cells throughout the body and if re-exposure occurs, binding of antigen to IgE can cause mast cell degranulation and release of chemical mediators including

histamine resulting in an allergic reaction. Not everyone who is sensitised will develop an allergic reaction on re-exposure to the allergen.

Clinical history is the most important diagnostic tool and subsequent investigations may help confirm the diagnosis. The EATERS method is a useful framework for establishing an allergy history.⁵ The investigations available to most paediatric departments are skin prick testing (SPT) and sIgE.

A positive SPT or sIgE result does not differentiate between sensitisation and food allergy.^{2,6,7} Furthermore, a child with clinical allergy may have negative results. The gold standard test is a double-blind placebo-controlled oral food challenge but with limited resources this is often not feasible.²

SKIN PRICK TESTING

Dr Charles Blackley in 1873 described the first skin test by placing allergen on grazed skin identifying pollen as the cause of hay fever.^{8,9} The scratch test was subsequently replaced with the SPT by Sir Thomas Lewis in 1924.¹⁰ SPT is used widely as a primary diagnostic tool in detecting IgE-mediated reactions. SPT is inexpensive, minimally invasive and results are available within 15 min.⁸

HOW TO PERFORM A SPT

Consent should be obtained due to the risk of a systemic reaction.¹¹ SPT is usually performed on the flexor aspect of the forearm, alternatively in infants it can be performed on their back.

To standardise the test and prove validity, a negative (saline) and positive control (histamine solution) must be used. A positive control must measure more than 3 mm. A negative should be less than 3 mm, this helps distinguish children



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To cite: Ferris K, Cowan M, Williams C, et al. *Arch Dis Child Educ Pract Ed* Epub ahead of print: [please include Day Month Year]. doi:10.1136/archdischild-2020-320562



Figure 1 Skin prick test performed on forearm, demonstrating positive control, negative control and testing of four allergens of which one is positive.

with dermographism, where pressure causes mast cell activation.¹¹

A small drop of allergen is placed on the skin and then the skin pierced with a standardised lancet to introduce the allergen. At least 2 cm must be left between each prick to avoid contamination and false positive results¹¹ (figure 1).

SPT results can be affected by the quality of the allergen extract¹²; thus, standardised allergen extracts are recommended.⁶ Some standardised fruit and vegetable extracts produce a high rate of false negative results and it is not always possible to create stable extracts so in these circumstances a prick-prick technique is performed.⁸ Prick-prick involves inserting the lancet into the fruit/vegetable and then pricking this directly onto the child's skin. Prick-prick tests are useful when the history is suggestive of allergy but the extract SPT is negative.¹³

When an allergen is introduced into the epidermis of the skin, sIgE bound to mast cells is cross-linked resulting in mast cell degranulation and histamine release.⁸ This histamine produces a weal and flare response. The weal is measured to quantify sIgE to that allergen.¹³ The visualisation of a positive SPT may impact the patient's behaviour which may be important for education.⁸

SPT can be performed on children from birth through to adulthood.^{6 8} Systemic allergic reactions including anaphylaxis to SPT are rare, but need to be considered. A trained healthcare professional must be in attendance with emergency medication and resuscitation equipment available.⁸

Measuring the SPT

After 15 min, the SPT can be measured. First, measure and record the positive and negative controls then the allergen extracts.

Measure the weal at its longest diameter and the extent 90° to the first measurement. The result is recorded in millimetres as either two measurements or the mean of the two measurements.¹¹ The flare around the weal is not measured.⁸ An alternative more accurate method is to scan the size of the entire weal which will calculate its actual size.¹⁴

SPT have high sensitivity but low specificity.¹⁵ A SPT result of 3 mm or more indicates sensitisation to the allergen; however, in infants less than 2 years of age, a smaller weal may be considered to be a positive response.¹¹ Not everyone who is sensitised will have clinical allergy. The 95% positive predictive values (PPV) for several foods have been determined to allow more accurate interpretation of results.^{2 7 15 16} SPT results of ≥8 mm for cow's milk, ≥7 mm for egg and ≥8 mm for peanut are strongly associated with a positive reaction during food challenge. In infants less than 2 years of age, these results are smaller with a PPV of 6 mm for cow's milk, 4–5 mm for egg and 4 mm for peanut.^{2 15 16}

The SPT value does not correlate with the severity of the allergic reaction or the threshold for reaction.¹⁵

It is possible for a child with a negative SPT to have a clinical reaction so results must be interpreted alongside the history.

IMPORTANT CONSIDERATIONS

SPT should be avoided in patients who are unwell or have poorly controlled asthma as this increases the risk of a systemic allergic reaction.¹⁵ SPT relies on the patient having a clear patch of skin for testing and can be difficult to perform in children with severe eczema.⁸

To minimise false negative results, antihistamine medication should be stopped for 3–5 days prior to testing.¹³ If this is distressing for the child, use sIgE as an alternative. Other medications such as oral and topical steroids, omalizumab and antidepressants may impact on the SPT result.⁸

Mast cell anergy may occur following anaphylaxis and SPT should be delayed for 6 weeks to allow for mast cell recovery to avoid false negative testing.¹³

SPECIFIC IGE

A complementary diagnostic tool is in vitro measurement of IgE antibody which is especially useful in patients who cannot undergo SPT.^{8 17}

In 1967, measurement of total IgE was first described.¹⁸ It was soon discovered that total IgE levels could not be considered a reliable marker of allergy status¹⁹ as elevated IgE levels may be found in a variety of atopic conditions such as eczema as well as non-allergic conditions. This led to the introduction of testing for specific IgE (sIgE) antibodies. The patient's serum is incubated with the allergen in question and sIgE from the patient binds to the allergen. This is identified by fluorescently labelled anti-IgE antibody.² The sIgE antibodies to the allergen can then be quantified.

sIgE has high sensitivity but poor specificity for diagnosing food allergy when the arbitrary cut-off value of 0.35 kU/L is used; however, employing 95% PPV improves the specificity.^{7 20} For example, a child who has a sIgE of ≥ 15 kU/L (PPV) for peanut has 95% chance of having peanut allergy.^{7 14} A result of less than 0.35 kU/L may be used to rule out a diagnosis of food allergy due to its high negative predictive value.

Many children have results that fall between 0.35 kU/L and the PPV for that allergen and must be interpreted in the context of the clinical history.^{7 20} Like SPT, the PPV for sIgE can vary with age for various allergens.¹⁶ The quantitative result of the sIgE does not correlate with the severity of the allergic reaction or the threshold for reaction.¹⁵

ADVANTAGES AND DISADVANTAGES OF SIGE

Advantages to measuring sIgE include no risk of systemic allergic reactions so they can be performed in a range of clinical areas and do not need staff trained in resuscitation or equipment available. There is no interference from medications including antihistamines and tests are not contraindicated in dermatological disease such as severe eczema or impacted by dermatographism.⁸ Some units have had to rely on sIgE testing during the COVID-19 pandemic when there may have been difficulty in facilitating SPT. sIgE can be performed to a range of allergens from a single blood sample.

Disadvantages in measuring sIgE include the need for venepuncture and the delay in results being available. The major disadvantage is the rate of false positive results making interpretation difficult.

OTHER TESTS AVAILABLE

Component resolved diagnostics (CRD) measures IgE to specific food proteins (rather than whole extract) and may be of diagnostic value in peanut and hazelnut allergy.¹⁵ CRD is particularly useful in differentiating oral allergy syndrome to allow for risk stratification.

Basophil activation test (BAT) is a functional assay that assesses IgE function. BAT is not yet widely available, cannot be used in isolation and must be reserved for specific cases only.^{7 20}

WHEN A CHILD OR YOUNG PERSON HAS NEGATIVE SPT/SIGE RESULTS, CAN I EXCLUDE ALLERGY?

No, as a child/young person with allergy may have negative test results. The most important diagnostic tool is an allergy-focused history. So if the history is positive and testing negative then continued avoidance of the allergen must be recommended. A diagnostic food challenge in hospital may be considered to confirm this.

False negative SPT results can be caused by poor quality allergen extracts, medications such as those with antihistamine effects, during the period of mast cell anergy following anaphylaxis (within 6 weeks of the reaction) or if the positive histamine control is weak or absent.

Allergy tests look for IgE-mediated allergy so remember your patient may have non-IgE-mediated allergy, this may be differentiated in the history eliminating the need for testing. Non-IgE allergy is diagnosed following an allergy-focused history, resolution of symptoms following complete dietary elimination and return of symptoms on reintroduction.

WHEN A CHILD OR YOUNG PERSON HAS POSITIVE SPT/SIGE RESULTS, DOES THIS CONFIRM A DIAGNOSIS OF ALLERGY?

Although a positive test result makes the diagnosis of allergy more likely, remember a positive SPT/sIgE cannot differentiate between sensitisation and food allergy. Sensitisation means there is sIgE to the allergen but no symptoms on re-exposure, whereas a patient with allergy has sIgE and symptoms on re-exposure.^{2 6 7} A diagnosis can only be confidently made if you have a positive allergy history. Allergy testing should be specific and only in the context of a positive history. If you have a history of proven tolerance of the allergen and regular consumption, then testing is not required.

False positive results are common with testing, they can occur during SPT when there is dermatographism, severe eczema or contamination from adjacent skin pricks. sIgE is notorious for producing false positive results making interpretation difficult particularly in patients with severe atopy.

A CHILD HAS BEEN COMING TO MY CLINIC FOR SEVERAL YEARS, I HAVE BEEN MEASURING THEIR SPT/SIGE OVER TIME AND THEIR RESULTS ARE NOW NEGATIVE, WHAT DO I DO NOW?

Food allergies may resolve over time with milk and egg being the most common foods that can be outgrown.¹⁵ At this point, you can discuss with the child and their parents/guardians that they could be considered for an oral food challenge to assess tolerance. This decision is patient specific and must be made alongside the child/young person and their family.

SKIN PRICK TESTING (SPT)

AND

SPECIFIC IGE

SHOULD ONLY BE CONSIDERED IN THE
CONTEXT OF A POSITIVE ALLERGY HISTORY

SPT	SPECIFIC IGE
IgE mediated allergy	IgE mediated allergy
First line investigation	Alternative diagnostic tool
Immediate results in clinic (15-20 minutes)	Results take time
Small risk of systemic allergic reaction	No risk of systemic allergic reaction
Trained staff and resuscitation equipment must be available	Performed by trained phlebotomy staff
Need to stop antihistamines pre SPT	Don't need to stop antihistamines
Child should be well. Eczema and asthma should be stable	Can be performed safely in severe eczema or asthma
Can test different allergens simultaneously- limited by space	Can test different allergens on one blood sample
Well tolerated	Requires venepuncture

Figure 2 Summary infographic—important considerations for skin prick testing and specific IgE.

CONCLUSION

The diagnosis of IgE-mediated food allergy requires a considered clinical approach centred on an allergy-focused history. Targeted SPT or sIgE can then be performed but must be interpreted with caution and within the context of the history (figure 2). The gold

standard for diagnosing food allergy is a double-blind placebo-controlled oral food challenge; however, this is often difficult to achieve in practice therefore use of testing may support the diagnosis.^{2 15}

Contributors KF conceptualised the idea. MC performed a literature search on SPT and developed this section which was then reviewed by SM, CG and KF. CW and KF performed a literature search on sIgE and developed this section. All sections were reviewed, edited and assembled by KF. SC reviewed and edited the full manuscript. Final review was conducted by all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

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