

PRACTICE

RATIONAL TESTING

Diagnosis of immediate food allergy

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College in Qatar, and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 10 month old girl with a history of eczema was brought to the emergency department with urticaria and angioedema without respiratory or circulatory features to suggest anaphylaxis (see glossary). Ten minutes before the symptoms appeared she had eaten some lightly cooked (scrambled) egg. The emergency department doctor administered oral antihistamines and instituted close clinical monitoring. Within 30 minutes symptoms had resolved, and the child was discharged after a six hour period of observation. The doctor explained the likely diagnosis of an egg allergy and recommended avoidance of foods containing egg. An appointment with the GP to consider further investigation or onward referral to a paediatric allergy service was advised. When consulting their GP the next day, the parents asked about tests to confirm egg allergy and whether an adrenaline auto-injector was necessary.

What is the next investigation?

Before allergy testing is carried out a focused history is essential (box 1). Urticaria and angioedema (see glossary) are compatible with an immediate hypersensitivity reaction to food but can also occur spontaneously without any allergic trigger. In immediate (IgE mediated) food allergy the allergen exposure should have a close temporal relation with the onset of symptoms.¹ Symptoms will typically begin within seconds/minutes of exposure to the allergen and resolve before 12 hours. In this case, symptoms began within 10 minutes and the total duration of symptoms was two hours.

The next appropriate investigation is to validate the clinical suspicion of egg allergy by performing skin prick or specific IgE testing. Access to these tests for generalists can vary between services and, in some instances, will first require

referral to specialist allergy services. Though both methods of testing were assessed by the National Institute for Care and Health Excellence (NICE) in the 2011 guideline for the diagnosis and assessment of food allergy in children,² many of the studies reviewed were of poor quality. The guideline recommends these tests in the appropriate setting and when there is adequate competency in the interpretation of results. For many non-specialists this interpretation can require the advice of experienced allergy practitioners.

In our scenario, the GP measured specific IgE to both egg white and egg yolk, the results of which were 7.52 kU/L and 0.19 kU/L, respectively (reference range 0-0.35 kU/L), and did not request a "food panel" to five common food allergens offered by the local laboratory. Panel testing detects specific IgE to several of the most commonly implicated allergens. This screening approach is problematic and can give rise to unexpected positive results that can be difficult to interpret.

Specific IgE testing: limitations and difficulties in interpretation

Detectable specific IgE does not necessarily imply an allergy.¹ Patients can be sensitised, meaning that they have raised serum concentrations of specific IgE to an allergen without associated immediate symptoms when exposed. The higher the specific IgE, the more likely it is that the test result will be clinically relevant. Despite this, the level of specific IgE does not predict the severity of symptoms. Calculation of specific IgE concentrations with 95% positive predictive values (table 1¹) has been used to improve diagnostic accuracy.¹ These values are typically calculated from patients with confirmed food allergy and, if used rationally (guided by the history), can lead to an improved certainty of the clinical diagnosis. In the case above the specific IgE results suggest a greater than 95% certainty that the diagnosis of egg allergy considered before the tests is correct.

Key points

- Before you consider allergy testing, take a focused history: ask about the suspected allergen, symptoms, and their timing in relation to suspected allergen exposure
- Skin prick and specific IgE testing should be used to diagnose immediate food allergy only when the clinical history supports this
- Select only the specific allergens suspected in the clinical history. The use of specific IgE food panels or a blanket screening approach is likely to yield positive results that are difficult to interpret
- Positive results of specific IgE or skin prick testing without clinical reactivity denote sensitisation and dietary restriction is not recommended
- Unnecessary dietary restriction increases the risk of nutritional deficiencies and parental/patient anxiety

Box 1: Key questions in an allergy focused history*Was there an exposure to a suspected allergen?*

The most common allergens in children are egg, peanut, and milk. In adults, peanut, tree nut, fish, and shellfish are most common

How soon after exposure did symptoms begin?

Symptoms typically begin within minutes of exposure but can take up to two hours

What were the reported symptoms and were they suggestive of an allergic reaction?

Symptoms of an allergic reaction include immediate oral pruritus and swelling, urticaria, abdominal pain, vomiting, throat tightness, stridor, cough, respiratory distress, drowsiness, and collapse

Were there additional cofactors present?

Some allergic reactions need the addition of cofactors before the reaction is clinically apparent. Specific examples include infection, alcohol, exercise, and use of non-steroidal anti-inflammatory drugs (NSAIDs)

Has there been uneventful exposure to the potential allergen before or after the reaction?

Ask about how the food was prepared (raw versus cooked), and consider a dose dependent threshold for reactivity. Consider whether the implicated food has been correctly identified

Is a non-allergic explanation possible?

Did urticaria and angioedema persist despite avoidance of the reputed allergen? Has the same allergen been eaten since without adverse outcome? Spontaneous urticaria and angioedema should be considered in these circumstances

The most common pitfall with specific IgE testing is the assumption that a positive test result confirms clinical allergy. Incorrect use of specific IgE as a screening test, without a compatible history, can lead to food allergy being erroneously diagnosed.³ The consequences of incorrect diagnosis can include an unnecessarily restricted diet and patient/parental anxiety. Case reports have even described the loss of tolerance to foods because of prolonged inappropriate exclusion, leading to anaphylaxis on re-introduction.⁴ Conversely, a negative specific IgE result can be used to inappropriately refute a diagnosis of allergy. A common example of this includes allergy to fruit and vegetables where the diagnostic performance characteristics of specific IgE testing are poor. In recent years, component resolved diagnostics, which detect specific IgE to epitopes (those sites of an allergen to which antibody binds, such as Gal d1 in egg), have been investigated as an additional diagnostic and prognostic tools.⁵ The clinical utility and cost effectiveness have not yet been fully evaluated and remain controversial, and the use of component resolved diagnostics should be restricted to specialists. Requests for specific IgE testing must be tailored to the clinical history and involve an appreciation of its limitations.

Skin prick testing: limitations and difficulties in interpretation

Skin prick testing identifies in vivo sensitisation to allergens. It can be performed in an outpatient setting and involves the epicutaneous introduction of allergen extracts with a standardised lancet.⁶ Typically the volar aspect of the forearm, or the back in small infants, is used. The site is then inspected 15 minutes later and compared with suitable positive and negative controls. A weal 3 mm greater in diameter than the negative control is considered a positive test result⁴; smaller yet

still important weals can be observed in infants. Again, accurate interpretation of results requires an appropriate clinical history. Skin prick tests can fail to show sensitisation when antihistamines are used concurrently, and training in measurement and interpretation of results is required. In some cases, such as with fruit and vegetables, skin prick testing with fresh allergen is desirable as the performance of the distilled extract is poor. The choice of specific IgE or skin prick testing should be individualised to the patient and reflect the advantages and limitations of each test and the available expertise of the doctor involved (table 2).⁷

Oral food challenge testing

The ideal test to confirm or refute the diagnosis of immediate food allergy is the double blind placebo controlled food challenge carried out by specialist allergy services.⁸ Blinded challenges allow confident identification of clinical allergy and exclude asymptomatic sensitisation and functional symptoms. This investigative strategy is particularly important when the history and test results are ambiguous. In practice, specialist centres routinely provide unblinded challenges, although access to these resource intensive investigations might be rationed in some healthcare systems. Various protocols exist to perform these tests, but all challenge protocols include the administration of increasing quantities of a proposed allergen under medical supervision. Direct mucosal exposure (allergen held to lip) is the first stage of the challenge before titrated oral ingestion. In certain cases, after risk stratification by experienced practitioners, home challenges might be recommended.⁹ Failure to directly provoke symptoms will confidently exclude an allergy in most cases.

Outcome

Based on the history and specific IgE results, the GP diagnosed egg allergy. By avoiding blanket/panel allergy testing, the GP avoided the common pitfall of detecting multiple, clinically irrelevant, low level positive specific IgE results. She did not prescribe an adrenaline auto-injector given the absence of anaphylaxis or severe comorbid conditions—such as poorly controlled asthma—and the low incidence of life threatening reactions to egg.⁹ For other allergens, an adrenaline auto-injector can be considered in the absence of life threatening features if there are comorbid conditions or the allergen is difficult to avoid or has a high associated risk of anaphylaxis (such as with peanut). A written management plan was agreed with the parents, clearly setting out the use of antihistamines for skin limited reactions after accidental exposure, and reasons to seek emergency help. Although this was the first exposure to scrambled egg (lightly cooked), the GP noted that the child had previously eaten baked egg (well cooked) uneventfully and thus advised avoiding raw and lightly cooked egg in the diet, but continuing previously tolerated well cooked egg. She discussed the question of onward referral with the local paediatric allergy service. They agreed that specialist assessment was not required at this stage as symptoms were limited to the skin, the child did not have asthma, and the diagnosis was clear (box 2). Referral for a home based challenge to less well cooked egg, when the child reached 3-4 years, was planned, with the parents' agreement.

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Box 2: Which patients with egg allergy should be referred to an allergy clinic?¹⁰

Children with systemic symptoms consistent with a severe reaction

Children who have poorly controlled asthma or use inhaled glucocorticoids regularly

When the diagnosis is uncertain

Persistent egg allergy (beyond age 6-8)

Egg allergy with another major food allergy

Glossary

Urticaria: Synonymous with hives; itchy, red, raised weals with central pallor. Individual lesions last for less than 24 hours and fade leaving normal skin

Angioedema: A swelling of the deeper layers of skin or mucous membranes. While this can affect any part of the body, the lips, face, tongue, digits, and genitals are the most common sites

Anaphylaxis: A rapidly evolving life threatening allergic reaction frequently characterised by hypotension and bronchospasm and often accompanied by flushing, urticaria, and/or angioedema

Acute spontaneous urticaria and angioedema: Urticaria and angioedema without an allergic trigger. Frequently this happens in children because of a viral infection. It is suggested by the absence of a suitable history consistent with an immediate (IgE mediated) allergy (reproducible rapid onset of symptoms related to allergen exposure; see box 1) and the persistence of symptoms over several days/weeks, even when a reputed allergen has been avoided. If symptoms last beyond six weeks, it is termed chronic spontaneous urticaria and angioedema

Tables

Table 1| Specific IgE concentrations with 95% positive predictive values in children and infants^{*1}

Allergen	At mean age 5	In infants aged <2
Egg	7 kUA/L	2 kUA/L
Milk	15 kUA/L	5 kUA/L
Peanut	14 kUA/L	Not clearly established

kUA/L=allergen specific KU/L

Table 2| Advantages and disadvantages of skin prick and specific IgE testing of investigation of allergy*

Specific IgE testing	Skin testing
Sensitive	Often greater sensitivity than specific IgE
Widely available	Available in centres with appropriate reagents, equipment, and trained staff
Results can take days to weeks	Results in 15 minutes, visible to patients
No interference from drugs	Antihistamines, β blockers, and some antidepressants can interfere with results
Standardised laboratory assay	Observer dependent
Interference from high total IgE can cause positive results without clinical allergy	No interference from high total IgE

*Adapted from the ASCIA manual: Skin Prick Testing for the Diagnosis of Allergic Disease.⁸