Laboratory Testing for Total IgE and Specific IgE

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Scope

The aim of this guideline is to provide indications for testing for Total IgE and Specific IgE which can be used by clinicians and laboratories, including circumstances where testing is not required. These guidelines apply to adult and children.

Key recommendations for Clinical Users

Total IgE

Laboratory testing for total IgE should be reserved for

- Patients in whom allergic bronchopulmonary aspergillosis (ABPA) is suspected (1)
- Patients in whom omalizumab therapy for asthma is being considered (2)

Testing for total IgE does not contribute much to an allergy focussed evaluation, which relies on an accurate history, and it should not be used as a "screening" test. (3).

A normal total IgE does not exclude clinical allergy and **does not invalidate a request for specific IgE.** In contrast the incidental finding of a raised total IgE without a specific history of allergic symptomatology is rarely an indication for referral to an allergy specialist.

Total IgE may assist in the interpretation of weakly positive specific IgE results, where a markedly elevated total IgE (e.g in widespread eczema) may result in weakly positive specific IgE that are not clinically relevant and are not associated with symptoms.

Specific IgE

An allergy focussed clinical history, eliciting details of possible IgE mediated hypersensitivity symptoms and the circumstances in which symptoms occur is the basis for deciding which if any specific IgE test(s) should be requested. Such a history should also document known tolerance of certain allergens in the diet or environment, which then should not be included in any focussed specific IgE testing

Specific IgE testing cannot replace an allergy focussed history

The results of specific IgE cannot be accurately interpreted unless testing was based on an allergy focussed history.

Specific IgE are tests of sensitisation which are used to support a clinical diagnosis of allergy. Positive specific IgE may be seen in people who tolerate the food/potential allergen in question, and positive tests should NOT be used in isolation to provide clinical advice.

Specific IgE testing provides similar, although not identical, information to Skin Prick Testing; but may be particularly valuable in assessing some groups of patients (patients taking antihistamines, eczema/dermographism).

For certain labile allergens (e.g. fresh fruit such as kiwi, apple) the specific IgE has lower sensitivity than Skin Prick testing

Patients should NOT be tested for specific IgE to foods which are not associated with possible IgE mediated symptoms.

Key recommendations for Laboratories

Total IgE should be reported with an age related reference range

A normal total IgE does not exclude clinical allergy and **does not invalidate a request for specific IgE.** Total IgE should NOT be used to determine whether to proceed to specific IgE testing. Significant allergy may be present with a normal total IgE, and conversely an elevated total IgE may be found in those with only minor allergies, or even just an atopic tendency.

To aid clinical interpretation, it is recommended that the laboratory should add on the total IgE if a positive result is obtained for specific IgE. (4).

Testing should be performed using a method supported by data on which to determine clinically relevant decision points.

Food mix tests are Not Recommended because of the occurrence of both false positive and false negative results. It is not a useful screening tool. Testing to individual specific IgE should be performed.

Report specific IgE as numerical values KUA/L

Background and Epidemiology

Allergic disease is rapidly becoming more common. Typical manifestations are asthma, rhinitis, eczema, food allergy and anaphylaxis, venom allergy. Approximately 50% of young people have a diagnosis of an atopic disease (5), and the prevalence of food allergy is over 5% in children (6) and 1-2% in adults. The majority of children will outgrow milk and egg allergy, however only 20% will outgrow peanut allergy, which now affects 1 in 50 children (2). Hence the number of adults with food allergy is expected to rise significantly over the next decade.

Food allergy typically causes symptoms within an hour of ingesting the implicated food, (occasionally up to 2 hours) and with rare exceptions occurs every time the food is eaten, and not if the food is avoided. Symptoms usually include urticaria with or without angioedema and may include bronchospasm, acute gastrointestinal disturbance, laryngeal oedema or hypotension.

Relatively few foods account for most IgE mediated allergic reactions in both children and adults.

- In children these include egg, milk, peanut, tree nuts, kiwi, fish
- In adults these include peanut, tree nuts, fish, shellfish, fruits.
- Seeds (e.g. sesame) and fruits (e.g. kiwi) are emerging allergens.

NB Soya and wheat are very rarely allergenic in either children or adults

Specific IgE testing is often incorrectly referred to as “allergy testing. However a positive specific IgE is only a demonstration of sensitisation (which is actually defined as simply having specific IgE. Allergy is having specific IgE and symptoms on known exposure).

The clinical diagnosis of allergy is supported by demonstrating sensitisation to the putative allergen (either by measuring specific IgE or by skin prick testing) (4). Patients who have experienced severe allergic reactions should be referred for specialist allergy/immunology assessment. However while awaiting an appointment, testing to appropriate allergens may be of value.

It is important to be aware that many people are sensitised to, but tolerant of foods. In the absence of symptoms related to food ingestion, testing for specific IgE should not be performed, and if performed in error, patients should NOT be advised to avoid foods which they tolerate, purely on the basis of a laboratory test.

It is now recognised that avoidance of foods purely on the basis of sensitisation, such as the presence of specific IgE, may be associated with a significantly increased risk of developing allergy (4). Hence testing for sensitisation should only be performed based on an allergy focussed history. Frequently, even if a food has previously been tolerated without symptoms, the anxiety caused by a positive test result may lead to inappropriate elimination from the diet, and potential loss of tolerance.

Specific IgE tests cannot help investigate non-allergic food intolerance, coeliac disease or headache.

Ireland has one of the highest rates of allergic asthma internationally. Identifying relevant aeroallergens may help improve symptom control, but does not replace the need for appropriate asthma medication.

There is not a role for specific IgE testing to food allergens in the management of asthma in either adults or children.

Total IgE

Total IgE is elevated in most, but not all, patients with atopic disease (rhinitis, allergic asthma, eczema, food allergy, etc). IgE may also be raised during parasitic infection, however this is rare in the Western world. However measuring total IgE is rarely useful in allergy diagnosis, and gives no additional information compared to asking the patient if they have any allergic disease (ref). Monitoring total IgE is of value in monitoring patients with or at risk of allergic bronchopulmonary aspergillosis such as those with cystic fibrosis or severe asthma (1).

Omalizumab is a monoclonal antibody against IgE, preventing it's binding to mast cells, which is used to treat allergic asthma and also chronic spontaneous urticaria. Dosing in asthma (but not chronic spontaneous urticaria) is related to total IgE level, requiring measurement of this analyte prior to prescribing this treatment for asthma (2). Of note, chronic spontaneous urticaria/angioedema is a non-allergic form of urticaria and/or angioedema and measurement of total or specific IgE is not indicated in this condition

Hyper-IgE syndrome is a very rare hereditary primary immunodeficiency characterised by extensive eczema, skin infections, deep seated pulmonary infections with Staph aureus, and skeletal and dental abnormalities. Typically total IgE is over 2,000 IU/mL in this condition. However this finding is not specific, as total IgE levels of several thousand are much more frequently seen with uncomplicated, extensive or especially poorly controlled eczema**.** **(**Families can be mistakenly motivated to seek allergy "screening" instead of intensifying topical care of eczema)

Total IgE Testing

Who to Test

- Patients at risk of ABPA, or in whom ABPA is suspected
- Patients with allergic asthma, where treatment with omalizumab is under consideration
- Laboratories should add a total IgE to results for a specific IgE which is weakly positive to assist in interpretation

Who Not to Test

Measurement of total IgE is not indicated in the investigation of atopic allergic disease or urticaria, as it does not aid diagnosis or management

Who to Re-Test

- Repeat testing is reasonable in patients being monitored for ABPA (1)

Who Not to Re-Test

- Repeat testing is of no value in patients being treated with omalizumab. Changes in total IgE levels are not related to the clinical outcome of therapy (2).

Specific IgE Testing

Who to Test

When taking an allergy focussed history, you need to establish:

- What happens?: anaphylaxis, asthma, rhinitis, urticaria, angioedema
- When do symptoms happen?
- Is there any apparent immediate trigger?
- For food allergic symptoms, which of the common food allergens does the patient tolerate without symptoms (egg, milk, peanut, tree nuts, sesame, fruits, fish, shellfish)
- Are there any particular circumstances (such as exercise) involved?

Anaphylaxis

(Food, drug, insect venom, food-exercise, idiopathic). Please refer the patient to a paediatric or adult allergy/clinical immunology centre for full clinical assessment which will include specific IgE and skin testing where appropriate.

Component testing:

Specific IgE positivity to allergen components (e.g. peanut components Ara-h 1, 2, 3, 8, 9) has little bearing on clinical management outside of specialist clinic setting and research studies. They do not automatically predict more severe (anaphylactic) reactions.

Venom Allergy

Specific IgE to bee and wasp venom is not useful as a screening tool.

Asthma and Rhinitis

In asthma and rhinitis testing for inhalant allergens is useful.

- House dust mite, grass pollen, tree pollen, cat or dog
- Plus other animals or moulds (alternaria, cladosporium, aspergillus) if relevant.
- Again, individual testing is more useful than panels in selecting allergens to avoid.

*** Drug Allergy**

- Drug allergy can usually be diagnosed clinically, and testing is only indicated where there is genuine uncertainty about whether an allergy is present
- There are very few specific IgE tests available to drugs.
- The sensitivity of drug specific IgE testing is poor, even in patients with a history of an immediate allergy. Sensitivity is better within 1 year of reaction, but in the case of penicillin allergy, is still only about 20% sensitive.
- Specific IgE measurement is not useful for delayed hypersensitivity reactions.

Who Not to Test

- Specific IgE tests cannot help investigate non-allergic food intolerance, coeliac disease or headache.
- There are no specific IgE tests to additives or colourants.
- Specific IgE cannot help investigate contact allergic dermatitis (patch testing, by a dermatologist may be of value).
- Specific IgE tests are not helpful in the investigation of chronic spontaneous urticaria.

Who to Re-Test

- In children, retesting previously positive food specific IgE on an annual/biannual basis may be helpful to monitor for resolution of food allergy.
- In children or adults, previously negative food specific IgE should only be repeated if new symptoms, temporally related to the food in question develop, or if the test negative foods have not been introduced, as is routinely advised in paediatric allergy clinics.
- Repeat testing for aeroallergen-specific IgE is rarely helpful, and should only be considered if new symptoms develop

Specimen and Ordering information

All requests (electronic and paper) and specimens must adhere to the laboratories standard requirements. In order to comply with accreditation standards, laboratories cannot accept or process samples which do not meet minimum standards.

No special patient preparation or specimen precautions are required.

Total IgE or Specific IgE levels are NOT affected by antihistamine therapy

How to Test

IgE is present in very small amounts in serum compared to IgG, A and M. Immunochemical techniques with enhanced sensitivities (such as fluorescent detection techniques; enhanced surface binding) are required to detect physiologically relevant concentrations

A limited number of tests should be performed, based on the allergy-focussed history. Requests for a large number of tests, without clinical justification should not be processed until adequate clinical details are provided.

Testing should be performed using a method supported by data on which to determine clinically relevant decision points.

When a weakly positive specific IgE result is obtained, a total IgE should be added on, to aid interpretation.

An urgent service is not required.

Interpretation of tests

Total IgE

In patients with clinical features of ABPA, investigation of specific immunological reactivity is indicated when total IgE is > 1,000 IU/mL, or more than double the baseline value (1).

When omalizumab is used to treat asthma, the total IgE should be used in the nomogram to calculate the appropriate dosing regimen (2).

Markedly elevated total IgE levels may be seen in patients with severe eczema.

Specific IgE

All specific IgE tests must be interpreted in the context of an allergy focussed history. It is the responsibility of the requester to ensure that specific IgE is **NOT** ordered to foods which the patient can tolerate, as this frequently causes anxiety, and if the patient stops eating the food in question, clinical allergy may develop and there may be adverse nutritional consequences.

Interpretation of specific IgE tests chosen on the basis of an allergy-focussed history is usually straightforward, however if there is doubt as to whether there is clinical allergy, a challenge should be performed in an appropriate setting.

When used indiscriminately specific IgE tests may be associated with false positive results Interpretation of a broad battery of tests where several positive results are obtained which are not clearly related to symptoms is complex and time consuming, and may require multiple challenge tests to clarify. This is time-consuming for both the patient and specialist teams, and involves considerable cost for the patient and the health service.

False negative results may occur, but these are rare.

For certain labile allergens (e.g. fresh fruit such as kiwi, apple) the specific IgE has lower sensitivity than Skin Prick testing

Recommendations for National Laboratory Information System (MedLIS)

An order entry form may assist with demand management.

Results of specific IgE tests should be reported numerically.

Consultation Plan and History

This guideline was prepared in consultation with all consultant members of the Irish Association of Allergy and Immunology (IAAI).

It is recommended that consultation with the ICGP and Irish Thoracic Society by included prior to publication

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