Review Article

AN INTRODUCTION TO LABORATORY INVESTIGATIONS FOR ALLERGIC CONDITIONS

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ABSTRACT

A wide range of laboratory investigations are available for the confirmation of atopy and the identification of a specific allergenic trigger causative of the patient’s symptoms. In order to appropriately manage the patient, improving the patient’s quality of life and reducing the burden on the health system, early diagnosis of allergy and identification of the allergic trigger is needed. In order to accomplish this, the clinician needs a thorough clinical history of the patient to select the most appropriate test, but also a knowledge of the test-principles and local availability of tests. This feature provides a broad overview of the principles of allergy investigations. Its purpose is to assist the general practitioner and primary healthcare workers in a meaningful, cost-effective selection of allergy investigations.

INTRODUCTION

A variety of tests have been developed over the past years that focus on the various components of the allergic response. It is often difficult for the general practitioner to keep up-to-date with the latest trends in the industry, as well as with the latest guidelines for various disciplines. Due to the variety of tests available, medical practitioners may have difficulty in selecting the appropriate allergy test.

There are various factors that may influence the healthcare professional in selecting allergy tests. These include:

- Patient factors including vague symptoms and non-specific signs;
- The experience and training background of the clinician, specifically in allergic conditions;
- Availability of specific types of allergy tests;
- Cost of allergy tests.

The early diagnosis of allergy and identification of the allergic trigger is needed to appropriately manage the patient, improve the patient’s quality of life, and reduce the burden on the health system.1

WHY TEST FOR ALLERGIES?

In spite of many consensus documents and research that has proven the importance of allergy testing, especially in childhood, there are still different opinions amongst healthcare providers as to whether to “treat” or “test”.2 The so-called “treaters” are usually healthcare workers that are only allowed a limited budget for diagnosing and treating a patient. By not wasting costs on expensive allergy tests, more money can be spent on pharmacotherapy for the symptomatic treatment of the clinically diagnosed allergic condition. The allergy is often not confirmed in these cases (or excluded), and appropriate therapy cannot be initiated. It may lead either to a missed differential diagnosis, or worsening of the allergic condition. In opposition are the “testers” who will argue that management of an allergic patient can be more effective and focussed if the suspected allergen causing the symptoms is identified. They will carefully select appropriate allergy investigations based on the patient’s clinical history and examination.1 Instead of wasting money on symptomatic pharmacotherapy, management can then be focused on e.g. avoidance measures, desensitisation therapy, etc. There is also a third group of clinicians, “tick and treat”. This group of healthcare workers are often forced by patients to do extensive allergy tests, not history driven (“tick” multiple tests on pathology form). The allergy results in these cases are also often misinterpreted. The end result is often a huge bill from the pathologist’s office, and patient with poor quality of life, as they have to unnecessarily avoid specific foodstuffs or their favourite pet. Ideally any allergy test request should be balanced with an appropriate clinical history and examination. This may then ensure a cost-effective identification of the allergen, as well as the appropriate management of the allergic condition, improve the patient’s quality of life, prevent complications and worsening of allergic condition.

WHICH ALLERGY TEST SHOULD THE CLINICIAN CHOOSE?

Laboratory investigations (‘Allergy testing’) serve only to confirm or exclude the clinical diagnosis of allergy and to
identify an allergic trigger suspected on the basis of the patient’s clinical history. The clinical history and physical examination remain the most essential part of the diagnosis of allergic diseases.3 A variety of tests have been developed that detect the various elements of allergic pathophysiology. Measurements of total serum IgE levels, detection of allergen specific-IgE antibodies, measurement of biochemical mediators, and examination of tissues and secretions for eosinophils are the most common laboratory investigations for allergic conditions utilised by the clinicians.

The different allergy tests can broadly be classified into two groups, according to the mechanism of allergic disease (Table 1):

- **IgE-mediated** (Type I or immediate hypersensitivity) allergy tests. This group includes tests such as total IgE, allergen specific-IgE, skin prick tests and allergen component specific-IgE tests. Most of the inhalant allergies are IgE-mediated, whereas approximately 50-60% of food allergies and less than 5% of drug allergies are IgE-mediated.

- **Non IgE-mediated** (Type III & IV or delayed hypersensitivity) allergy tests. This group includes tests such as basophil activation tests (CAST), T-cell mediated tests such as MELISA and skin patch testing.3

Alternatively allergy investigations can also be classified as:

- **In vitro**: All blood tests – IgE based, basophil activation tests, T-cell mediated tests;
- **In vivo**: Skin prick tests, skin patch tests, intradermal tests, food challenge tests.3

Not all allergy tests are available at all laboratories, and some are only available at specialised centres. Sometimes the choice of test will depend on availability of the test, as in the case of inhalant allergen sensitisation testing (Skin Prick Test versus specific-IgE tests). Another factor to consider is specimen stability. The delayed immune response tests, such as the basophil activation test, and the MELISA, should be analysed within 24 hours, usually only at a main laboratory, thus transport and time of specimen collection should be taken into account.

**SUMMARY**

Different allergy tests are offered by clinical laboratories to aid in the diagnosis of an allergy. Knowledge of the available allergy tests together with a careful, exposure-specific patient history may lead to cost-effective allergy test requests, with a subsequent beneficial outcome of the patient.

**ABBREVIATIONS AND EXPLANATION OF VARIOUS IN VITRO AND IN VIVO ALLERGY TEST METHODS:**

BAT: Basophil Activation Test.

CAST: Cellular Antigen Stimulation Test, also called BAT. Different reference ranges and units apply to different methods/laboratories.

ECP: Eosinophil Cationic Protein.

ImmunoCAP®: A commercial immunoassay for measuring specific-IgE (ThermoFisher, Sweden). Most publications and clinical decision points are based on ImmunoCAP® immunoassay methods. sIgE results are reported in kIU/L.

ISAC®: Immuno Solid-phase Allergen Chip (ThermoFisher, Sweden) measures allergen components semi-quantitatively in ISU units.

MELISA: MEmory Lymphocyte Immune-Stimulation Assay.
**TABLE I: LIST OF MOST COMMONLY AVAILABLE ALLERGY INVESTIGATIONS**

<table>
<thead>
<tr>
<th>TEST</th>
<th>EXPLANATION OF TEST</th>
<th>SPECIAL PRECAUTIONS</th>
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<tr>
<td>Total IgE</td>
<td>Increased total IgE levels can suggest allergy as a cause of symptoms, but has limited specific diagnostic value. There is a large degree of overlap between IgE levels in persons with and without allergic disease, limiting the utility of total IgE in diagnosing allergy. Specific clinical situations in which total IgE levels may be helpful include: Parasitic infections, allergic broncho pulmonary aspergillosis, hyperimmunoglobulin E syndrome and occasionally haematological malignancies; Evaluation of patients eligible for anti-IgE treatment (Omalizumab).</td>
<td>The IgE antibody based test is not influenced by medications with antihistamine properties.</td>
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<tr>
<td>Phadiatop® inhalant screen</td>
<td>The Phadiatop ImmunoCAP® assay is the most reliable in vitro test to screen for possible sensitisation to inhalant allergens. A positive test should be followed by a panel of common inhalant allergen specific skin prick tests or an ImmunoCAP® specific-IgE test to the relevant individual allergens. Phadiatop® is the brand name of the Thermofisher inhalant screen. Other manufacturers may use different names, and include different allergens in the screen mixture.</td>
<td>Specimen type: IgE antibodies are measured in serum (blood collected in a yellow or red top tube).</td>
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<tr>
<td>ImmunoCAP® screen mixes</td>
<td>Specific-IgE against a mixture of the most common food allergens, e.g. nut mix (fx1), seafood mix (fx2), cereal/wheat mix (fx3) or paediatric food mix (fx5) or pollen mixes. A positive result reliably indicates that the patient has allergen specific-IgE to one or more of the constituent allergens incorporated in the allergen mix, and should be followed with an individual ImmunoCAP® test to identify the responsible allergen.</td>
<td>The IgE antibody based test is not influenced by medications with antihistamine properties.</td>
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<tr>
<td>Individual specific-IgE</td>
<td>Specific-IgE against a mixture of the most common food allergens, e.g. nut mix (fx1), seafood mix (fx2), cereal/wheat mix (fx3) or paediatric food mix (fx5) or pollen mixes. A positive result reliably indicates that the patient has allergen specific-IgE to one or more of the constituent allergens incorporated in the allergen mix, and should be followed with an individual ImmunoCAP® test to identify the responsible allergen.</td>
<td>The IgE antibody based test is not influenced by medications with antihistamine properties.</td>
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<tr>
<td>Immuno Solid-Phase Allergen Chip (ISAC®)</td>
<td>The ISAC® comprehensive allergy profile test for specific-IgE to 112 allergen components from 51 sources. This test is recommended for multisensitised patients. It may add additional diagnostic information by predicting cross reactivity and the risk for severe reactions, as well as additional information on the heat stability and biodegradability of allergens.</td>
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<tr>
<td>Skin Prick Tests (SPTs)</td>
<td>SPT are used to identify immediate IgE-mediated hypersensitivity against a group of allergens by measuring the histamine response to an allergen. The wheal reaction is measured after 15-20 minutes, compared to histamine (positive) and negative (saline) controls. SPT should be offered only by trained and experienced personnel, using quality reagents, in a setting where systemic reactions can be managed accordingly.</td>
<td>Drugs with antihistamine properties may interfere with the test, and should be discontinued 2-3 days prior to the SPT. The abstinence time period depends on the half-life of the drug.</td>
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<td>Skin Patch Tests</td>
<td>The suspected contact dermatitis allergens are placed in small finn chambers and kept in place on the patient’s skin for 48 hours with hypoallergenic tape. The patches (allergens) are removed after 48 hours, after which the reactions are then evaluated immediately, at 72 and 96 hours for a reaction. The standard skin patch test (Trolab®) include 45 allergens, but different patch test panels can be set up per patient history, (e.g. sunscreen, hairdressing, etc).</td>
<td>The patient should discontinue systemic glucocorticosteroids for a period of 2-6 weeks. The abstinence period depends on the type of steroidal drug, the dose and the chronicity of use.</td>
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<td>CAST tests/ Basophil activation tests</td>
<td>Food additive- and drug allergies are most often non IgE-mediated and diagnosis can be confirmed by measuring the basophil activation after stimulating the cells in vitro with the allergen in question. Standardised reagents are also available for other allergens, (e.g. food, inhalant), that may cause delayed immune reactions. Basophil activation tests are also being evaluated for IgE-mediated allergic reactions.</td>
<td>Specimen type: Whole blood. CAST - blood collected in purple (EDTA) or green (heparin) top tubes. The antiagulant differ between laboratories and CAST test methods. MELISA – whole blood in light blue (citrate) tubes. These specimens should be arranged with the laboratory beforehand, as specimens should be analysed preferably within 24 hours for accurate results.</td>
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<td>MELISA Lymphocyte stimulation test</td>
<td>Indicated mainly for metal allergies, e.g. amalgam in prosthesis/dental implants, and some drug and food allergies by measuring the lymphocyte proliferation after in vitro stimulation with the allergen in question.</td>
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<td>Eosinophils</td>
<td>Serum tryptase can be used as a marker of mast cell activation in anaphylaxis, and to diagnose systemic mastocytosis. Histamine and tryptase, amongst others, are released from mast cells during activation, but the short half-life of histamine renders it impractical as marker for anaphylaxis. The half-life of tryptase is approximately 90 minutes.</td>
<td>Specimen type: Serum (blood collected in a yellow or red top tube). Collect specimens directly after reactions, after 2-4 hours, and after 12 hours for a basal level.</td>
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<td>Tryptase</td>
<td>Elevated eosinophils, eosinophil derived substances (i.e. ECP) in body fluid are indicators of allergic inflammatory conditions.</td>
<td>Specimen type: nasal smear/sputum/ bronchial secretion, etc.</td>
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Phadiatop®: Phadia Differential Atopy Test is a multi-allergen inhalant screening test (ThermoFisher, Sweden – previously Phadia).

RAST: Radio-Allergo Sorbent Test. The first immunoassays used to measure specific-IgE’s employed radiolabeled indicators, which has since been replaced by enzyme labels. The name ‘RAST’ is sometimes still used to refer to specific-IgE tests.

Specific-IgE: Specific-IgE (sIgE) refers to the measurement of a group of IgE antibodies in the blood that recognises a specific allergen. Different test methods and manufacturers of sIgE assays are available.

SPT: Skin Prick Test.

Total IgE: The total IgE immunoassay quantitate the total concentration of IgE antibodies in the patient’s serum in kIU/L units.

Tryptase: Also called mast-cell tryptase. It is used as a marker of mast cell activation.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflict of interest.

REFERENCES

PRODUCT NEWS

OMNAIR® NASAL SPRAY FOR ALLERGIC RHINITIS.

OMNair Nasal Spray (50 μg ciclesonide) is indicated for:
• The treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.
• The treatment of nasal symptoms associated with perennial allergic rhinitis in adults and children 12 years of age and older.

OMNair Nasal Spray (120 puff metered spray), is a topical glucocorticosteroid (ciclesonide) delivered as the first and only hypotonic suspension to ‘stick and stay’.1,2,3

OMNair Nasal Spray offers multiple benefits in the treatment of Allergic Rhinitis (AR) such as:
1. A hypotonic formulation which enhances the uptake of ciclesonide as well as it providing a favourable hydration effect 3
2. A 24 hour significant and sustained tNASS reduction with effects on all main Allergic Rhinitis symptoms (runny nose, itchy nose, sneezing and nasal congestion)4,5
3. Proven efficacy in long term studies6
4. A fast onset of action; works from 1 hour7
5. A favourable safety and tolerability profile. Less than 1 % is available systemically while
6. 99 % is protein bound
7. A convenient once daily dosage to enhance compliance

REFERENCES