consensus document

GUIDELINE FOR DIAGNOSTIC TESTING IN ALLERGY - UPDATE 2014

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1. ALLERGY

Allergy is a hypersensitivity reaction initiated by immunological mechanisms. Allergy can be antibody- or cell-mediated. In the majority of cases the antibody typically responsible for an allergic reaction belongs to the IgE isotype, and these individuals may be referred to as suffering from an IgE-mediated allergy.[1]

ATOPY

Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, such individuals may develop the typical symptoms of asthma, rhinoconjunctivitis or eczema.[1]

Atopic individuals must have clinical symptoms. Some 30-40% of individuals in developed countries are allergic, but only a proportion of these have atopic diseases, which include asthma (5-10%), rhinitis (10-20%) and food allergy (1-3%).

In population studies allergic diseases peak at different ages. Food allergy and atopic eczema are predominant in early childhood, whereas asthma shows a biphasic peak and rhinitis peaks in the second or third decade.

Atopic diseases manifest as hyper-responsiveness in the target organ, whether skin, nose, lung or gastrointestinal tract. This hyper-responsiveness may have both IgE-mediated and non-IgE-mediated components. The situation is further complicated because allergen exposure in allergic subjects may increase target organ hyper-responsiveness, which results in exaggerated symptoms on exposure to non-specific irritants (tobacco smoke, changes in temperature, etc.) in these subjects. Increased non-specific responsiveness lowers the threshold for symptoms on subsequent allergen exposure.

2. WHY TEST

- To identify and avoid trigger allergens
- To be able to provide relevant and effective therapy
- Allergens can be identified for allergen immunotherapy/ desensitisation. Immunotherapy is the only disease-modifying therapy available for allergies
- To identify patients whose symptoms cannot be attributed to allergy. This prevents the following:
  - Unnecessary drug therapy
  - Unnecessary allergen avoidance that may be expensive, harmful (restrictive diet) or upsetting (removal of pets)

3. ALLERGEN AVOIDANCE

- Allergen avoidance can prevent severe reactions (e.g., seafood allergy)
- Allergen avoidance can decrease and control a patient's symptoms
- A patient may be sensitised to an allergen, but be asymptomatic with low exposure. This patient has a tolerance to a specific allergen, but when exposed to high levels of allergen, he/she may lose tolerance and become symptomatic
- Individuals with sensitisation to multiple allergens may experience more severe symptoms after exposure to these allergens

4. DIAGNOSTIC APPROACH

Definitive allergy diagnosis ***depends primarily on the clinical history.*** The history, aided by a physical examination, should guide objective testing of IgE sensitivity. Either skin tests or allergen-specific serum IgE measurements may be used to focus on the following questions:

- Is the patient allergic?
- Does allergy contribute to the patient's symptoms?
- What are the clinically relevant allergens?

There should be a high index of suspicion of allergy in

patients presenting with symptoms of asthma, rhinitis or eczema, particularly if there is an associated personal or family history of atopy.

On the basis of a positive history, a limited number of skin-prick tests (SPTs) or specific IgE measurements to commonly prevailing aero-allergens (Table I) or foods should be performed to confirm or exclude atopy.

Some foods commonly provoke allergic reactions. They include cow's milk, egg and peanut in infants and young children, and fish, shellfish, peanuts, tree nuts, fruit and spices in older children and adults.

Physical examination may determine which organs are involved. When both the clinical history and results of SPTs (or specific IgE) are negative, a diagnosis of allergy is less likely.

A positive history and positive tests help in rationalising treatment, initiating specific allergen avoidance measures and selecting appropriate immunotherapy.

4.1 SKIN-PRICK TESTING

SPTs with allergen extracts are the favoured method of *in vivo* testing for IgE-mediated sensitivity. Testing for a limited number of common allergens (Table I) may confirm or exclude atopy. The quality of extracts is important for reliable results.

Table I: Prevailing aero-allergens in South Africa[3]

All regions	House-dust mites (Der p 1 and Der f 1)
	Rye and Bermuda grass
	Aspergillus, Alternaria, Cladosporium
	Cat and Dog
Western Cape	Oak and plane tree pollen, Blomia tropicalis
	Epicoccium fungal spore
	Cockroach
Gauteng	Tree pollens including cypress
Farming areas	Zea mays pollen
	Horse
	Blomia tropicalis
Health care worker	Latex chlorhexidine
Grain industry	Storage mites, wheat and rye

Standardised commercial extracts are currently available for most common inhalant allergens and for some food allergens. Some patients with a documented food allergy on history fail to react to these extracts but may react to fresh extracts of the food,[2,3] e.g., fruits, celery,[4] shellfish and fish.[5,6,7,8]

Results of SPTs must always be expressed in a quantitative manner (measurement of wheal and flare in mm.), that can be interpreted by other practitioners. SPTs must be performed in a setting where personnel and equipment are available for resuscitation as there is a small but definite risk of anaphylaxis.[9]

4.2 BLOOD TESTS *(IN VITRO)*

Total IgE was initially used as a screening test for allergic disease, but it has limitations. IgE is elevated in allergic diseases and in non-allergic conditions, e.g., parasitic infestation. As many as 50% of IgE-mediated allergic patients have a total IgE within the normal range. *The predictive value of this test is limited in allergy diagnosis, but may be useful to exclude rather than prove allergy, when the history is convincing, but SPT/Specific IgE is negative.* It is not recommended as a screening test for Atopy.

Specific IgE measures allergen-specific IgE in patient serum. In the case of inhalant allergens, a level of >0.35 kU/l is considered positive (sensitivity 60-80%, specificity 90%). For food allergy, the cut-off value is >0.35, but clinical reactivity is age dependant and interpretation is guided by history.[10,11] The respective advantages/disadvantages of SPTs vs specific IgE are shown in Table II.

REMEMBER: Allergen Specific IgE measures sensitisation, but not necessarily clinically relevant allergy. Low levels of allergen specific IgE should be interpreted cautiously and in conjunction with history.

Cross reactions may occur between certain allergens. Cross-reactive peptides may be clinically relevant, but some pan allergens e.g., CCD's (Cross-reactive Carbohydrate Derivatives) are usually not clinically relevant. It is important that test results are always correlated with the clinical findings. Individual IgE's are available to some of these cross-reactive allergens, e.g., CCD, PR-10, profillin, lipid transfer protein. (Components)

4.3 MULTI-ALLERGEN IgE ANTIBODY SCREENING ASSAYS

The multi-allergen screen for aero-allergens is the

Phadiatop[12] (Thermo Fisher, Uppsala) and for foods the Fx5 (Thermo Fisher, Uppsala).

Phadiatop is usually reported as positive or negative. A positive test indicates that the patient may be sensitive to one or more of the following inhalants: *house-dust mites, grass pollens, mould, cat, and dog.*

The ***Fx5*** is a food screening test. A level of >0.35 kU/l is considered positive and indicates that the patient may be sensitive to one or more of the following foods: *cow's milk, egg white, fish, wheat, peanut, and soya*.

A negative multi-allergen screen reduces the probability that IgE mediated allergic disease is the cause of the patient's clinical problems.

DIAGNOSTIC TESTS OF UNPROVEN VALUE[13,14,15,16]
These tests are of unproven value, expensive and are not endorsed by the Allergy Society of South Africa.

- Neutralisation provocation (Miller) tests - based on multiple skin tests (environmental allergens like smoke, petrol, tobacco, etc.)
- Leukocytotoxic tests
- Hair analysis
- Vega testing (a 'black box' electrical test) - based on the addition of extracts to a chamber contained within an electrical circuit completed by the patient
- Applied kinesiology - based on muscle weakness
- Auricular cardiac reflex testing - based on pulse rate
- ALCAT
- IgG measurements

4.4 MAST CELL TRYPTASE

The serum level of β-tryptase can be useful as a marker of mast cell activation in the definitive diagnosis of anaphylaxis.[17] Tryptase levels peak at 45-60 minutes and may remain elevated for several hours (up to 24 hours).[18]

Ideally, three serial measurements should be performed:
- The first soon after the reaction
- The second a few hours later
- A baseline level 24 hours later
- Tryptase may even be measured post-mortem, if anaphylaxis is suspected.

4.5 CAST TESTING

Some patients may develop symptoms due to sensitivity to various foods, food additives (colorants, flavourants or preservatives) or medications, which are not IgE mediated. This may occasionally occur to aeroallergens as well. These chemical sensitivities may be confirmed by CAST testing (cellular antigen stimulation test) and should be discussed with a specialist/ laboratory.[19, 20, 21] These reactions are sulfido leukotriene mediated.

4.6 COMPONENT RESOLVED TESTING

Natural allergen sources may contain many different proteins, but only a few of them are allergenic. Some of these protein components are species-specific, but some occur in multiple allergen sources (cross-reactive components).

The identification of these allergenic proteins has led to the development of a new concept in allergy diagnosis, namely component-resolved diagnostics.

Component resolved allergy testing allows the clinician to identify potential disease-eliciting molecules, predict cross-reactivity, severity of reactions and the probability of the development of tolerance.

This knowledge can be used to advise patients on appropriate avoidance measures, reduce the number

Table II: SPT vs. specific IgE

SPT	Specific IgE
Inexpensive	More expensive
Immediate results	Delay in results
Problem if urticaria/eczema present	Not influenced by skin disease
Blocked by Antihistamines	Not affected by drugs
Small risk of anaphylaxis	No risk of anaphylaxis
Educational value	
Limited range of allergens	Wider range of allergens

of food challenges and identify the relevant allergen for specific immunotherapy.

Component resolved allergy testing should not be used as a screening test or a first-line test, but as a second-line test in poly-sensitised patients to distinguish genuine sensitisations from cross-reactions. This is particularly important when selecting patients for specific immunotherapy, as selection of truly eligible patients who should respond well to immunotherapy, as well as the identification of the primary sensitising allergen, are important for optimal and cost-effective patient management.

The other major use for component resolved testing is in patients with food allergies, where it can be used to improve risk assessment, which improves recommendations for allergen avoidance and decreases the need for provocation testing.

Allergen component testing is available as individual

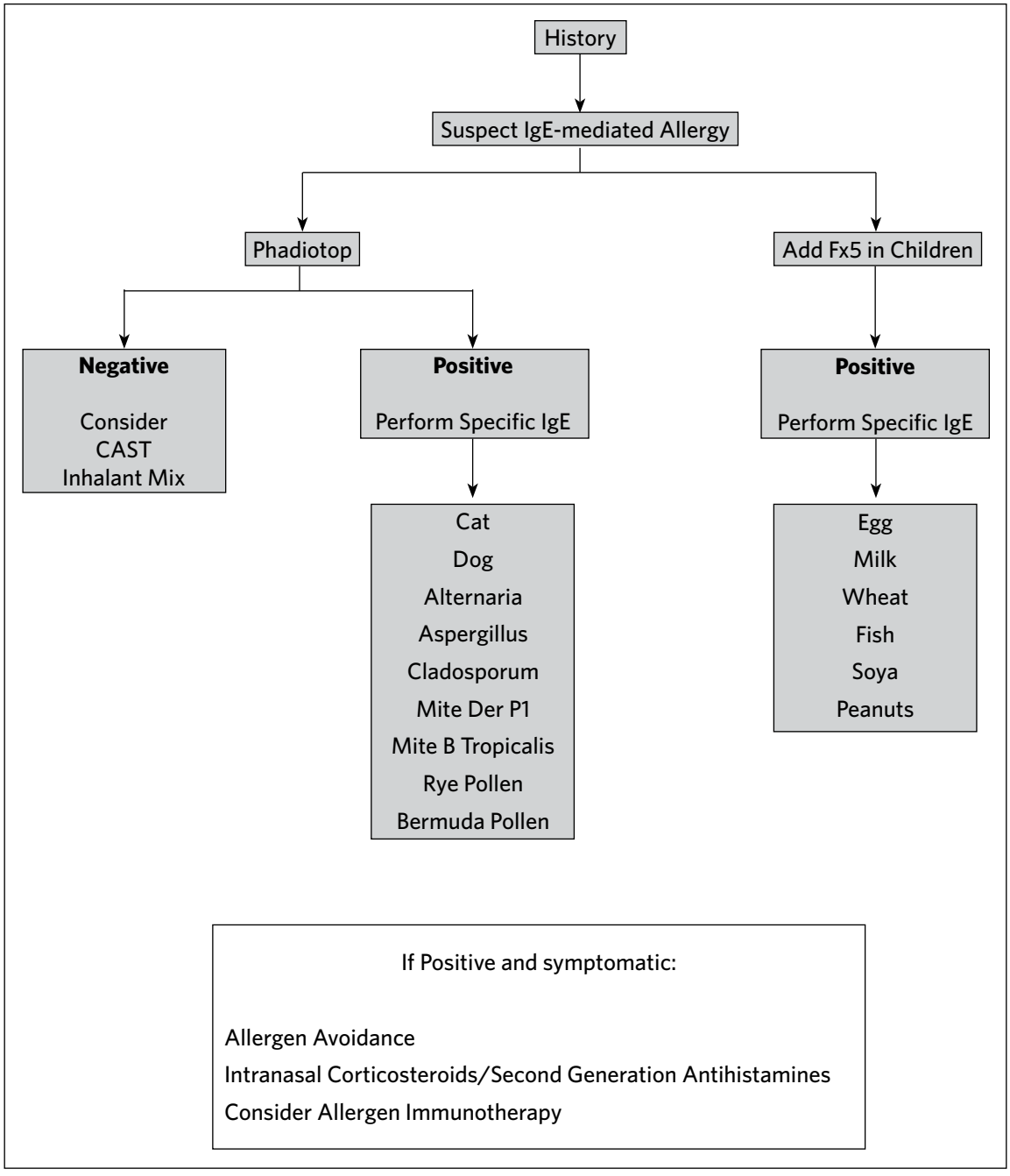

Figure 1. Diagnostic Algorithm for in-vitro Inhalant Allergy Testing.

components on platforms like the ImmunoCAP (Phadia, Uppsala) or on multiplex platforms like the ImmunoCAP Immuno-Solid Phase Allergen Chip (ISAC) containing 112 different allergen components.[22]

CONFLICT OF INTEREST

The author D Hawarden is the vice-chairman of the Allergy Society of South Africa and declares no conflict of interest in the production of this document.

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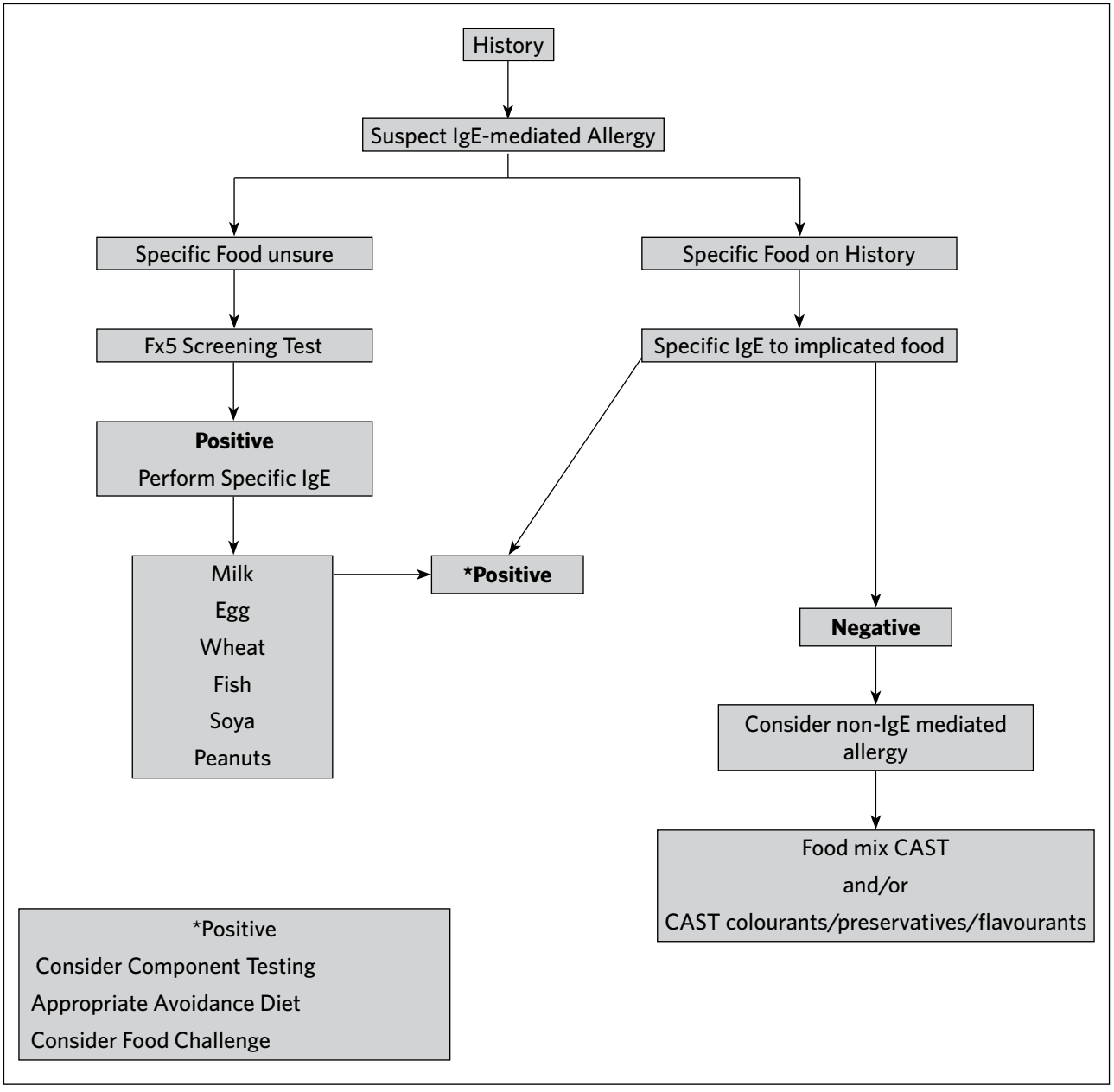

Figure 2. Diagnostic Algorithm for in-vitro Food Allergy Testing.

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ethics CPD questionnaire

DANGER AT THE FRONTIER: SOCIAL MEDIA AND ETHICS

CPD QUESTIONS: Indicate True or False

True/False

1. It is acceptable to post photographs of patients online, provided they consent to this.

2. Medicine and social media share the following features: privacy and confidentiality.

3. Professionalism is the contract that doctors have with society, to use their skills and knowledge in the best interests of their patients.

4. Self-regulation is an integral part of professionalism.

5. It is acceptable for a doctor to "friend" a patient on social media, provided the privacy settings are high.

6. LinkedIn and ResearchGate are examples of professional social networking sites.

7. It is better to remain anonymous when posting medical information to a social networking site, as the source cannot be traced back to its point of origin.

8. Consultants should not "friend" junior doctors, as this may blur professional boundaries.

9. **Choose the single best answer:** Which of the following is NOT a key principle embodied in the concept of medical professionalism?
   (a) Physicians subordinate their patients' interests to their own interests;
   (b) Physicians adhere to high ethical and moral standards;
   (c) Physicians exercise accountability for themselves and for their colleagues;
   (d) Physicians reflect upon their actions and decisions.

10. **Choose the single best answer** regarding the recommendations for doctors who use social media:
    (a) Only write about specific patients;
    (b) Only accept "friend requests" from patients you no longer see;
    (c) State your qualifications and credentials accurately;
    (d) It is permissible to offer medical advice to non-patients.