

A PRACTICAL DIAGNOSTIC APPROACH TO FOOD ALLERGIES

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ABSTRACT

Any abnormal reaction resulting from the ingestion of a food could be considered an adverse food reaction, and not necessarily a food allergy. In the evaluation of a patient with a history of an adverse reaction to food, one must consider the broad differential diagnosis before labelling the patient as 'allergic' to a foodstuff. The classification of adverse reactions to food is discussed, and different test modalities, with a practical diagnostic approach to food allergies, are outlined in this article.

INTRODUCTION

Any abnormal reaction resulting from the ingestion of a food could be considered an adverse food reaction.¹ In the evaluation of a patient with a history of an adverse reaction to food, one must consider the broad differential diagnosis before labelling the patient as 'allergic' to a foodstuff.

Adverse food reactions can be broadly divided into toxic and non-toxic reactions (Figure 1).¹ Toxic substances in food may affect any exposed individual, whereas non-toxic reactions are highly individual, and depend on genetic, epigenetic and environmental factors. Non-toxic reactions are grouped into i) immune mediated and ii) non-immune mediated reactions. The term food allergy is reserved for adverse reactions that involve the immune system. The term food intolerance is generally used in relation to non-immune mediated reactions. While the scientific basis of toxic and allergic (immune mediated) reactions to food is well established, the non-immune mechanism of some types of food intolerance is less well defined.^{1,2}

CLASSIFICATION OF FOOD ALLERGY

Food allergy may be due to IgE-mediated, non IgE-mediated or a combination of IgE- and non IgE-mediated reactions. Clinically it can involve the skin, gastrointestinal tract, respiratory tract and/or cardiovascular system. The prevalence of food allergy varies from 1 to 10% in children less than 5 years of age, dropping significantly in the adult population, as some allergies are outgrown.^{3,4}

A. IgE-MEDIATED FOOD ALLERGY:

The best characterised food allergies involve the IgE-mediated immune mechanism. A failure to develop oral tolerance to food allergens (antigens) may lead to an excessive production of IgE-antibodies to the specific food. IgE-mediated allergies present typically within minutes to hours after ingestion of the specific food. Patients typically present with the following symptoms or conditions³:

- Generalised: anaphylaxis, food dependent exercise-induced anaphylaxis;
- Cutaneous: urticaria, angioedema, flushing, acute contact urticaria;
- Gastrointestinal: oral allergy syndrome, gastrointestinal anaphylaxis, colic, vomiting & diarrhoea;
- Respiratory: acute rhino-conjunctivitis, allergic asthma.

The prevalence of food hypersensitivity is the greatest during the first few years of life. In infancy and childhood the most common food allergens include egg, milk, fish, wheat, soya and peanut. In older children and adults the range of food allergens causative of hypersensitisation broadens to include seafood, tree nuts and fruits. Most children develop tolerance to food allergens by the age of 5-6 years, except in the majority cases of peanut, tree nut and seafood allergy.²

The diagnosis of an IgE-mediated allergy remains a clinical exercise dependent upon a clinical history, selective *in vivo* tests (skin prick tests) or *in vitro* measurement of food specific-IgE (sIgE), appropriate exclusion diet, and blinded provocation. To screen for food hypersensitivity against

TABLE I: THE "BIG 8" FOOD ALLERGENS AND IMMUNOCAP® (RAST) FOOD GROUP TESTS

INDIVIDUAL sIgE	THE BIG 8 FOOD ALLERGENS	Egg white, Milk, Fish, Wheat, Peanut, Soya, Shellfish, Tree nuts
GROUP TESTS	Mixed nuts (Fx1)	Mix of Peanut, Hazel nut, Brazil nut, Almond, Coconut
	Mixed seafood (Fx2)	Mix of Cod fish, Shrimp, Blue mussel, Tuna, Salmon
	Mixed cereal (Fx3)	Mix of Wheat, Oat, Maize, Sesame seed, Buckwheat
	Paediatric food mix (Fx5)	Mix of Egg white, Milk, Fish, Peanut, Soy and Wheat

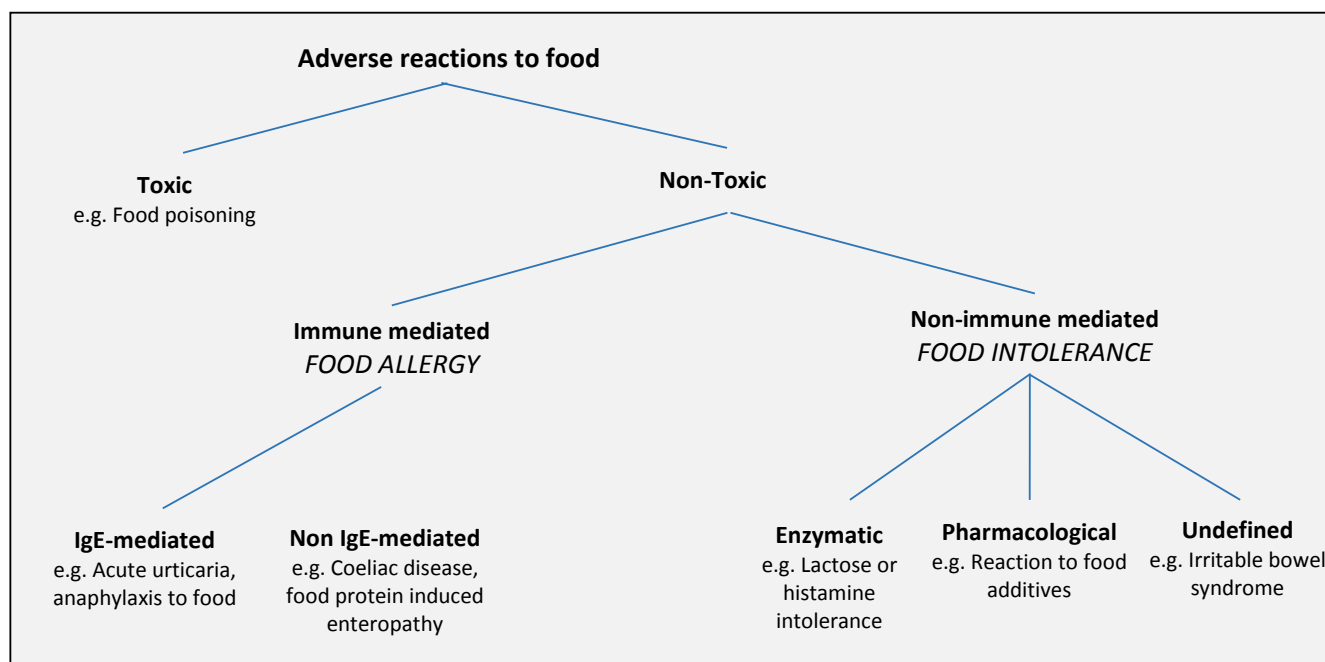


Figure 1: The classification of adverse food reactions, as initially proposed by the EAACI-Position paper on Adverse Reactions to Food^{1,2,3}

specific food groups, the ImmunoCAP® sIgE (RAST) group tests for food mixes may be used (Table I). A positive ImmunoCAP® sIgE food mix test will give the clinician a good indication of which group of individual allergens should be tested for. With a high index of suspicion of a specific food allergen, it will be more cost-effective to request an individual sIgE test instead of group tests.

Presumptive diagnosis of food allergy based on sIgE test results is not acceptable, as the presence of sIgE antibodies only indicates sensitisation to the specific food. Over one quarter of all patients with positive sIgE antibodies to food will unnecessarily alter their eating habits based on misinterpretations of food sIgE blood tests. There are no specific diagnostic cut-off values for sIgE. The higher the sIgE concentration, the higher the likelihood of clinical allergy. However, some food allergens may produce clinical reactivity at low concentrations, therefore the importance of clinical correlation. Published decision points at 95% positive predictive values (PPV) are listed in Table II.^{5,6,7} In cases where the sIgE concentration exceeded the 'decision point' (95% PPV), the chance of being clinically allergic to that specific food substance is 95% for that specific individual. It is worthwhile to note that the 95% PPVs in most studies were determined using the ImmunoCAP® immunoassays. There is currently no standardisation between sIgE methods, therefore different cut-off points will be applicable with different methods.

CROSS-REACTIVITY OF IgE-MEDIATED FOOD ALLERGIES:

The presence of sIgE in a patient's blood may be due to antibodies to a protein specific to a food source, or due to antibodies formed against a protein that are present in food related sources (cross reacting antibodies). Sensitisation to certain fruit or vegetables is often asso-

ciated with sensitisation to other foods belonging to the same or closely related botanical family. Another example of cross-reactivity is that of inhalant allergens and food allergens. Patients with sensitisation to common inhalants such as pollen and house dust mites, have the possibility of reacting to food allergens that cross-react with the inhalant allergens.⁸ Cross-reacting allergens may not always be of clinical relevance, and therefore the food group should not be eliminated from a patient's diet without clinical correlation, or confirmation with an elimination diet.

B. NON IgE-MEDIATED FOOD ALLERGY:

Non IgE-mediated allergic reactions are less well defined than IgE-mediated reactions. The diagnosis of these conditions remains a challenge, as the clinical picture is not as obvious as the IgE-mediated allergies, and laboratory investigations are not always suitable. These reactions usually occur hours to days after exposure to the food allergen. Typical manifestations of non IgE-mediated allergic conditions include:⁹

- Gastrointestinal: food protein-induced enterocolitis (FPIES), allergic proctocolitis, coeliac disease, gastrointestinal motility disorders;
- Cutaneous: contact dermatitis, dermatitis herpetiformis;
- Respiratory: pulmonary hemosiderosis (Heiner's syndrome).

TABLE II: 95% PPV FOR FOOD SPECIFIC-IgE BY IMMUNOCAP®^{5,6,7}

FOOD	SPECIFIC-IgE IN KU/L
Egg	> 7 (> 2 for infants and toddlers)
Milk	> 15 (> 7 for infants and toddlers)
Peanuts	> 14
Fish	> 20
Tree nuts	> 15
Wheat	> 80
Soy	> 65

TABLE III: CELLULAR ALLERGEN STIMULATION TESTS (CAST) TESTS AVAILABLE FOR FOOD ADDITIVES

PRESERVATIVES	Tartrazines, sodium benzoate, sodium nitrite, potassium-metabisulphite, sodium salicylate, monosodium glutamate, potassium sorbate, etc.
FOOD COLOURANT GROUP I	Quinoline yellow, Sunset yellow FCF, Cromotrope B, Armaranth, New coccine, etc.
FOOD COLORANT GROUP II	Erythrosine, Patent blue V, Indigo carmine, Brilliant black, etc.

Cow's milk and soy protein are the most common food allergens indicated in FPIES and allergic proctocolitis syndromes in infants and children. Food containing gluten is associated with autoimmune conditions such as coeliac disease and dermatitis herpetiformis. Food induced contact dermatitis is often seen in an occupational setting amongst food handlers that handle raw fish, shellfish, meat, eggs and spices. Non IgE-hypersensitivity to cow's milk, and infrequently to egg and pork, are responsible for the rare syndrome of food-induced pulmonary hemosiderosis. Hidden allergens such as food ad-

ditives (Table III) may also be responsible for some of the non IgE-mediated food reactions.

Diagnosis of the non IgE-mediated cases involve a high clinical index of suspicion (history), elimination diets, skin patch testing, cell-mediated *in vitro* tests, biopsy and histology, and serology in the case of coeliac disease.

C. COMBINED IgE- AND NON IgE-MEDIATED FOOD ALLERGY:

Both IgE- and non IgE-immune mediated mechanisms are involved in allergic conditions presenting with:

- Cutaneous: atopic dermatitis, contact dermatitis;
- Gastrointestinal: allergic eosinophilic oesophagitis and gastroenteritis;
- Respiratory: asthma.

Diagnosis is based on patient's history, together with demonstration of food sIgE antibodies, cell-mediated reactivity to specific food, occasionally allergen specific patch tests, elimination diets and oral food challenges.

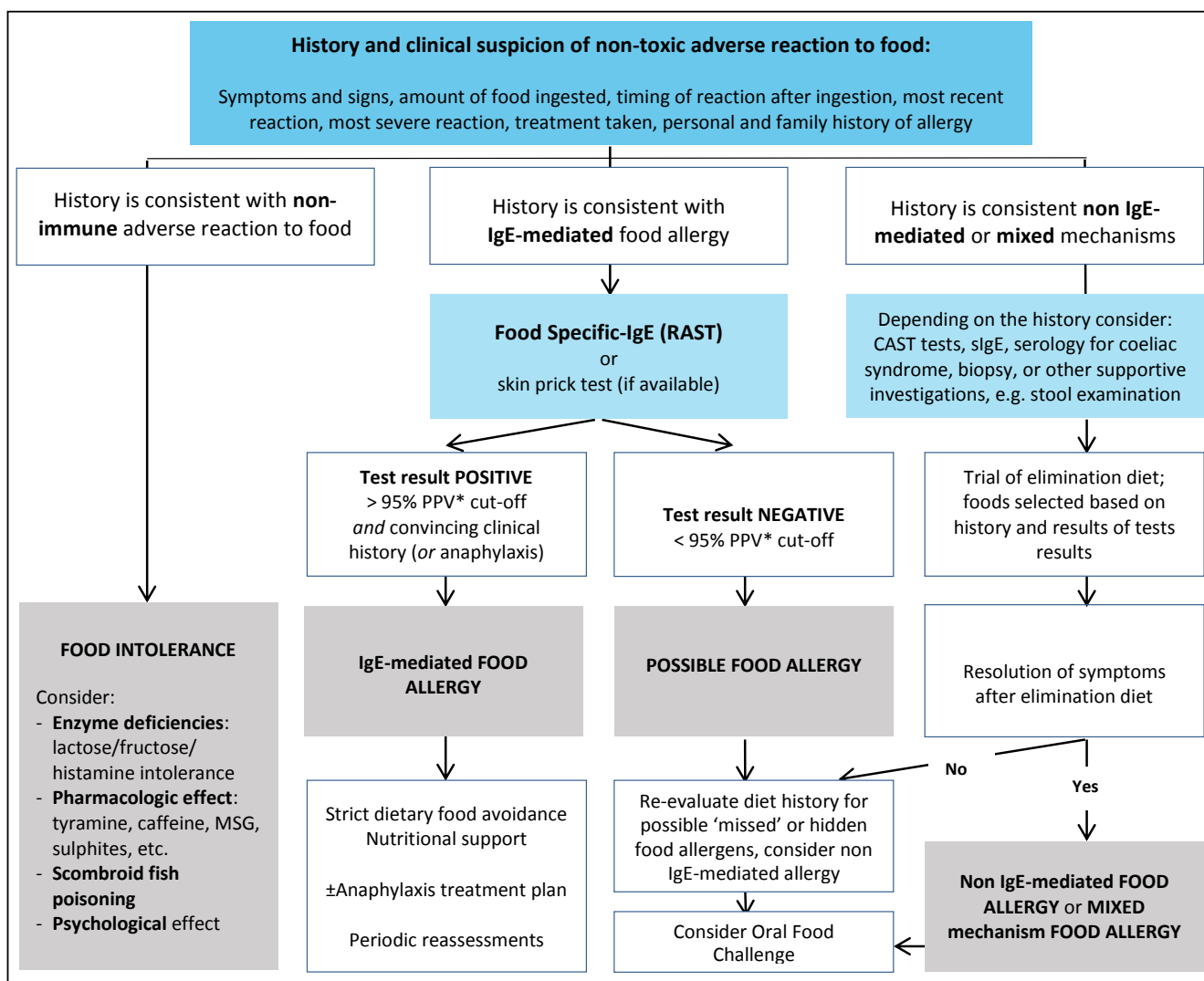


Figure 2: Diagnostic algorithm for investigation of non-toxic adverse food reactions (*95% PPV in Table II.)

TABLE IV: EXAMPLES OF NON-ALLERGIC ADVERSE REACTIONS TO FOOD

CONDITION	SYMPTOMS	MECHANISM
LACTOSE INTOLERANCE	Bloating, abdominal pain, diarrhoea.	Lactase enzyme deficiency.
FRUCTOSE INTOLERANCE		Fructose enzyme deficiency.
HISTAMINE INTOLERANCE	Diarrhoea, nausea & vomiting, headache, nasal congestion, itching of eyes and nose, wheezing, hypotension, tachycardia, urticaria, pruritus, flushing, etc.	Inhibition or deficiency of the diamine oxidase (DAO) enzyme , leading to an accumulation of histamine. Foods rich in histamine: Cheeses, processed meat, some fish, yeast extracts, tomato ketchup, alcohol, etc. Foods with histamine releasing properties: citrus, papaya, strawberries, pineapple, tomato, spinach, chocolate, peanuts and tree nuts, fish, shellfish, pork, egg white, additives, liquorice, spices, etc.
SCOMBROID FISH POISONING	Flushing, angioedema, hives, abdominal pain, symptoms similar to histamine intolerance.	Fish from the <i>Scombridae</i> family, i.e. tuna and mackerel (dark meat fish) contain large amounts of histidine, which is converted to histamine by bacteria in spoiled fish .
TYRAMINE	Migraine.	Pharmacologic effect in susceptible individuals.
CAFFEINE	Tremors, cramps, diarrhoea.	Pharmacologic effects of caffeine in susceptible individuals.
MONOSODIUM GLUTAMATE	Asthma, 'Chinese restaurant syndrome', urticaria.	Pharmacologic effects of glutamate in susceptible individuals.
PANIC DISORDER	Subjective reactions upon smelling or seeing the specific food.	Psychological .

FOOD INTOLERANCE

Food allergy must be distinguished from a variety of adverse reactions to foods that do not have an immune basis but may resemble it in clinical manifestations. Mechanisms of adverse reactions include pharmacologic effects to substances such as caffeine and tyramine and enzyme deficiencies causing lactose intolerance or histamine sensitivity. The mechanisms for some of the food intolerances remain unclear. The diagnosis of food chemical intolerance is largely based on history and elimination diets.

INVESTIGATIONS FOR FOOD ALLERGY

The diagnosis of food allergy is largely based on the clinical history and physical examination (Figure 2). Based on the clinical history, laboratory investigations may be considered. Elimination diets and provocation testing may also be utilised in the diagnosis of food allergy. Laboratory investigations available for food allergy testing depend on the immune mechanism involved, and the availability of the tests:

- **Immediate/IgE-mediated reactions:** food specific-IgE or skin prick tests;
- **Delayed/cell-mediated reactions:** basophil activation tests (CAST) or skin patch testing.

There are many other 'diagnostic' allergy tests, performed by non-accredited laboratories and health practitioners. Examples include IgG-measurements against a variety of food groups, Vega testing and ALCAT, to name just a few. These tests are not currently recommended by the Allergy Society of South Africa (ALLSA).¹⁰

SUMMARY: INVESTIGATIONS FOR FOOD ALLERGY

In all cases of suspected food allergy, as with all allergy testing, a full clinical history is indispensable in order to

facilitate appropriate and cost effective test requests. A positive sIgE test merely indicates sensitisation against the allergen, and the diagnosis needs to be confirmed by a clear clinical history, or by supervised food challenge testing. Not all food allergies are IgE-mediated, and a delayed sensitivity mechanism test should be considered in selected cases, especially in food additives. Alternative, non-accredited tests such as IgG testing against food allergens are not recommended.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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