An approach to the Diagnosis of an Allergy
Ampath offers a referral clinic to assist clinicians with the diagnostic workup of problematic patients with allergies and immunodeficiencies. At this clinic a complete history is obtained, the patient is examined and the necessary diagnostic tests are performed. A detailed report of the history, clinical findings and diagnostic tests, as well as advice on management is sent to the clinician after the consultation. Patients follow up with the original referring clinician for further management.

Other special services offered are allergen immunotherapy/desensitisation, drug allergy testing, prick-prick testing with fresh foods and patch testing.

Clinics are available in Hatfield and in Garsfontein, Pretoria and appointments can be made at: (012) 423 0575/67 (Hatfield) or (012) 369 6112 (Garsfontein) Referral letters are required. Patients should be asked to discontinue antihistamines 3 days and systemic corticosteroids 2 weeks prior to appointments.

Advice on allergy test interpretation: (012) 678 0613/4

Dr Cathy van Rooyen, Dr Sylvia van den Berg, Dr Louise Murray

Edition 3
August 2014
AN INTRODUCTION TO
ALLERGY DIAGNOSIS
WHAT IS AN ALLERGY?

An allergy is a hypersensitivity reaction initiated by the immune system. Allergy can be antibody- or cell mediated. 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. Individuals suffering from a cell-mediated allergy are referred to as suffering from a non-IgE mediated allergy. Reactions not initiated by the immune system are not allergy and cannot be detected by allergy tests. Examples of these are lactose intolerance, sensitivity to caffeine and other intolerances.

WHY SHOULD ALLERGY TESTS BE DONE?

- To identify and avoid trigger allergens.
- Allergens can be identified for allergen immunotherapy/desensitisation, the only disease-modifying therapy available for allergies.
- To be able to provide relevant and effective therapy.
- To identify patients whose symptoms cannot be attributed to allergy, which prevents unnecessary drug therapy or avoidance.

HOW DO I DIAGNOSE ALLERGY?

Allergy diagnosis depends primarily on the clinical history. The history, aided by a physical examination, should guide which allergy tests are ordered. Try and answer the following questions before ordering allergy tests:

- Is the patient allergic?
- What are the clinically relevant allergens?
- Does allergy contribute to the patient’s symptoms?
- What is the suspected mechanism of allergy?

There should be a high index of suspicion of allergy in patients presenting with symptoms of asthma, rhinitis, eczema or anaphylaxis, particularly if there is an associated family history of allergy.

IgE mediated allergic reactions usually occur within 5-20 minutes after exposure, but may occur up to 2 hours later depending on the allergen and route of exposure. Patients experience classical allergy symptoms, which may include itching, redness, hives, swelling, hay fever, wheezing and anaphylaxis.

Non-IgE mediated allergic reactions may present like IgE mediated reactions, but may also cause delayed reactions. Reactions may be dose-dependent and cumulative, therefore patients don’t always react after each exposure. This is particularly true for cellular reactions caused by basophils.

Cellular reactions mediated by T-cells are delayed and symptoms only occur after 24 hours (usually 2-3 days). Symptoms are often skin or mucosal rashes and eruptions, chest symptoms and conjunctivitis.

INDIVIDUAL ALLERGENS ADD UP TO SYMPTOMS:

Identifying the obvious allergen is not always enough e.g., pollen during pollen season. Knowing all relevant allergens is a prerequisite for giving your patients comprehensive allergen avoidance advice and thereby pushing the patient below the symptom threshold.

- Up to 80% of allergy patients are poly sensitized, i.e., allergic to more than one allergen.
- The average primary care patient is sensitized to three, and often more, allergens.
WHICH ARE THE MAIN ALLERGENS THAT I SHOULD CONSIDER?

On the basis of a positive initial history, testing for the most common food or aero-allergens should be performed to confirm or exclude atopy.

AERO-ALLERGENS:

Patients should be screened for allergies to aero-allergens by using a Phadiatop (specific IgE / RAST allergen mix for common aero-allergens) or a panel of aero-allergen skin prick tests (SPT). If a specific aero-allergen is suspected from the clinical history, testing to that specific allergen should be requested. An inhalant mix CAST can also be ordered when a non-IgE (basophil) mediated allergy is suspected. If screening tests are used, it should specifically be requested that individual allergens be done if the initial screen is positive, so the causative allergen can be identified.

The most common aero-allergens throughout South Africa are house dust mite (d. pteronyssinus and d. farinae), grass pollen (Bermuda and Rye grass), moulds (Alternaria and Cladosporium), cat and dog. Tree and weed pollens tend to differ regionally and as most of our allergenic trees are cultivated, it depends on the planting trends in the patient’s environment. If these allergens are considered, a tree mix or weed mix is recommended.

The most sensible approach is by using tree pollen mixes, e.g. Tree mix 1 (olive, willow, pine, eucalyptus, acacia, maleleuca) or Tree mix 2 (Oak, elm, plane, willow, cottonwood). Individual tree pollen IgE testing can be requested separately should a specific culprit tree be suspected from the patient’s history. The most common allergenic tree pollens in South Africa are plane tree, oak, olive, cypress, eucalyptus, pine, acacia, willow, poplar, mulberry, elm, ash and elder. Some indigenous trees like stinkwood and karee are also thought to be allergenic, but allergy tests to these pollens are not currently available.
THE FOLLOWING ALLERGENS SHOULD BE CONSIDERED AND REQUESTED INDIVIDUALLY BASED ON THE PATIENT’S CLINICAL HISTORY AND GEOGRAPHICAL ENVIRONMENT:

| GAUTENG: Also consider tree pollens like plane, acacia, oak, cypress |
| WESTERN CAPE: Also consider German cockroach and epicoccum fungal spores. |
| HIGHVELD, FREESTATE AND NORTH WEST: Also consider maize pollen, Eucalyptus tree pollen (perennial symptoms) and weed pollens like cosmos and khakibos (weed mix IgE) |
| KWAZULU NATAL: Also consider cockroach |
| FARMING AREAS: Also consider maize and wheat pollen, storage mites, other animal danders (e.g. horse and cow), p. notatum (mould found in vineyards), pine and eucalyptus (plantations), etc. |

FOOD ALLERGENS:

Patients should be screened for allergies to food allergens by using a food mix IgE (RAST) for common food allergens or a panel of food allergen skin prick tests (SPT). If a specific food allergen is suspected from the clinical history, testing to that specific allergen should be requested. If an allergy to food colourants and preservatives is suspected, a CAST tests for colourants and preservatives can be requested. A food mix CAST can also be ordered when a non-IgE (basophil) mediated allergy is suspected.

Some foods commonly provoke allergic reactions; they include cow’s milk, egg, soya and peanut in infants and young children, and fish, shellfish, peanuts, tree nuts, wheat, fruit and food additives like colourants and preservatives in older children and adults.

*All laboratory tests should be correlated with the clinical history.*

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

The mechanism of pathogenesis should be considered when allergy tests are requested, as well as the most appropriate allergen selection. Initial or screening tests should be used to make the initial diagnosis and identify the offending allergens. More specialised tests should be used to predict the severity of allergy, relevant cross-reactivity vs. primary sensitisation and the likelihood of allergy resolution.

If the initial tests are negative and the clinical history is not very suggestive of allergy, one can exclude allergy with a high degree of confidence and no specific treatment for allergy is indicated. Other diseases mimicking allergy should also be considered, e.g. reflux, cystic fibrosis, anatomical abnormalities, ciliary dyskinesia, primary immunodeficiencies, Wegener’s granulomatosis, Coeliac’s disease, etc. If the patient history is suggestive of allergy, another allergen or another mechanism of allergy should be considered, as well as other diseases mimicking allergy.
WHICH TESTS ARE AVAILABLE TO DIAGNOSE ALLERGY?

IgE MEDIATED ALLERGY TESTS

TOTAL IgE

Total IgE was initially used as a screening test for allergic disease, but it has limitations. It is useful to exclude rather than prove IgE mediated allergy, when the history is convincing, but SPT/Specific IgE is negative. Some pointers for interpretation are that lower IgE levels are found in children and the aged with IgE mediated allergy, and that IgE levels may be normal when allergy only affects a small target organ, e.g. the nose. Total IgE may also be increased in other conditions, e.g. parasitic infections, lymphoma, liver disease, vasculitis (Churg-Strauss syndrome), Allergic Broncho-pulmonary Aspergillosis, Hyper-IgE syndrome, etc.

SPECIFIC IgE (ImmunoCap®)

These tests are also commonly known as RAST tests, although the methodology has changed to Enzyme immunoassays and are performed on the ImmunoCap® in Ampath. Specific IgE measures allergen-specific IgE to allergens in patient serum. These tests are reliable for the diagnosis of inhalant allergies, but not always that reliable for food and drug allergies. Specific IgE tests can be ordered to single allergens or as multiple allergen screening tests. Allergen Specific IgE measures sensitization, but not necessarily clinically relevant allergy. Low levels of allergen specific IgE should be interpreted cautiously and in conjunction with the clinical history.

Cross reactions may occur between certain allergens due to shared proteins, e.g. allergen components found in pollens as well as foods of plant origin. This will lead to multiple positive specific IgE tests, although the patient may not react clinically to all of these allergens. Testing IgE to specific allergen components can help to identify primary sensitisation and cross-reactions. This will be further discussed under allergen component testing.

INTERPRETATION OF ImmunoCap® TEST RESULTS

The higher the specific IgE antibodies, i.e. sensitization, the higher the risk for symptomatic allergy.

FACTORS TO CONSIDER FOR A FINAL DIAGNOSIS:

- Age
- Allergen load
- Previous symptoms
- Degree of atopy
- Type of sensitizing allergens
- Other triggering factors

Positive test results:

>0,10 KuA/L indicates sensitization. In infants, even very low levels may indicate risk for symptomatic allergy.
AN INTRODUCTION TO ALLERGY DIAGNOSIS

MULTI-ALLERGEN IgE ANTIBODY SCREENING ASSAYS

These tests are useful when a patient provides an equivocal history for allergic disease (making it difficult to pinpoint with reasonable certainty which allergens to test for). The multi-allergen screen used for aero-allergens is the Phadiatop and for foods the Fx5. The 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, tree pollens, weed pollens, mould, cat, and dog. The Fx5 food mix screen consists of 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.

IgE TO ALLERGEN COMPONENTS

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 allergen component names include their scientific acronym and number (e.g. Ara h 2 means the second allergen from Arachis hypogaea or peanut).

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 also be used to advise patients on appropriate avoidance measures, reduce the number 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 components as specific IgE (RAST) tests or as multiplex assays like the Immuno-Solid Phase Allergen Chip (ISAC) containing 112 different allergen components. There is only a limited amount of component allergens available as single specific IgE (RAST) tests.
NON-IgE MEDIATED ALLERGY TESTS

CAST TESTING / BASOPHIL ACTIVATION TESTING:

Basophils have IgE receptors on their cell surfaces, therefore they may be activated either directly or via specific IgE in the patient’s serum. While protein allergens are usually required for IgE binding, basophils may also be activated directly by small molecular weight allergens. Some patients may develop symptoms due to sensitivity to various food additives (colourants, flavourants or preservatives) or medications, which are not IgE mediated. Basophil mediated allergy may include an immediate or a delayed allergic response. Prominent symptoms are rhinitis, asthma, gastrointestinal symptoms and urticaria. Reactions may also be dose-dependent and cumulative.

Basophil mediated allergy can be measured by Cellular Allergen Stimulation test (CAST), which identifies particular basophilic activation markers by flow-cytometry after stimulation by a particular allergen. A wide range of commercial allergens are available, which include foods, inhalants, colourants, preservatives, venoms, latex and drugs. If commercial drug allergens are not available, it is possible to use actual drugs as allergens, provided there is no cellular toxicity. Different dilutions of the drugs are used and results are correlated with patient controls. Several screening tests are available, most notably food and inhalant screens and even drug allergy screens, e.g. a general anaesthetic allergy screen.

MELISA TESTING / T-CELL PROLIFERATION ASSAYS:

T-cell mediated reactions are delayed allergic reactions and can typically be classified as type IV Gel and Coombs Hypersensitivity reactions. Patients most often present with skin reactions like maculopapular rashes, ocular symptoms, respiratory symptoms, oral lichen planus and loosening of dental and orthopaedic metal prostheses, but other symptoms may also occur, depending on the type of exposure. The most common allergens causing T-cell mediated allergy are drugs, metals, latex and food. MELISA (Memory Lymphocyte Immunostimulation assay) tests or Lymphocyte proliferation assays can be used to diagnose T-cell mediated allergy. Lymphocyte proliferation is measured after stimulation with allergens for 5-6 days by detection of radioactive markers and morphological examination of lymphoblasts.

OTHER TESTS USEFUL IN ALLERGY DIAGNOSIS:

MAST CELL TRYPOTASE

The serum level of β-trypotase can be useful as a marker of mast cell activation in the definitive diagnosis of anaphylaxis. Tryptase levels peak at 45-60 minutes and may remain elevated for several hours (up to 24 hours). Ideally, three serial measurements should be performed: the first soon after the reaction, the second a few hours later, and a baseline level 24 hours later.

NASAL MUCUS EXAMINATION:

Nasal smears can be stained for eosinophils to distinguish between allergic or eosinophilic rhinitis and vasomotor rhinitis. This is a cheap and useful tool when the diagnosis of allergic rhinitis is uncertain.
AN INTRODUCTION TO ALLERGY DIAGNOSIS

IN VIVO TESTING:
SKIN-PRICK TESTING

SPTs with allergen extracts are an in vivo method to test for IgE-mediated sensitivity. The quality of extracts and test technique is important for reliable results. 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 (prick-prick testing), e.g. fruits, fish and shellfish. Results are influenced by certain medications like antihistamines, therefore patients will need to stop certain medications before skin prick testing. 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. Please see table below for a comparison of the advantages and disadvantages of SPT vs specific IgE (RAST):

<table>
<thead>
<tr>
<th>SPT</th>
<th>SPECIFIC IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inexpensive</td>
<td>• Not affected by concurrent drugs e.g. antihistamines</td>
</tr>
<tr>
<td>• Immediate results</td>
<td>• Not influenced by skin disease</td>
</tr>
<tr>
<td>• Extracts are difficult to standardise</td>
<td>• Completely safe</td>
</tr>
<tr>
<td>• Dependant on technique</td>
<td>• Tests for wider range of possible allergens</td>
</tr>
<tr>
<td>• Risk of systemic reactions / anaphylaxis</td>
<td>• Allergen component testing available</td>
</tr>
<tr>
<td></td>
<td>• Screening tests available, making it more cost-effective</td>
</tr>
<tr>
<td></td>
<td>• Quantitative reporting, reproducible</td>
</tr>
</tbody>
</table>

Skin prick testing and intradermal testing for drug allergies, including penicillin skin prick testing, can also be performed using a variety of different drugs.

PATCH TESTING:

Patch testing is used for the diagnosis of contact allergies and contact dermatitis. There are general screening panels available, e.g. the European baseline series (most common contact allergens), cosmetic series, sunscreen series, hairdressing series, etc. These tests measure delayed type hypersensitivity reactions on the skin of sensitised subjects. The patient’s skin is exposed to the occluded allergens for 48-72 hours and reactions are interpreted at 72 hours. This type of testing may sometimes be used for other allergens like food allergens (atopy patch test) in specialised settings.

DIAGNOSTIC TESTS OF UNPROVEN VALUE

Unfortunately there are many techniques available that have not been validated scientifically or that cannot identify allergy by means of a known immunological mechanism. These tests include the following:

- Neutralisation provocation (Miller) tests (based on multiple skin tests; environmental allergens include smoke, petrol, tobacco, etc.)
- Leukocytotoxic tests
- Hair analysis
- Vega testing (a ‘black box’ electrical test). The test is based on the addition of food 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 / ImmuPro allergy tests offered at some Pharmacies and Laboratories.
LOW SUSPICION OF ALLERGY

HISTORY

LOW SUSPICION OF ALLERGY

SCREENING TESTS TO EXCLUDE ALLERGY

Screen for IgE as well as non-IgE mediated allergy. May screen for IgE mediated first and if negative, proceed with non-IgE mediated testing

IgE mediated

Non IgE mediated

• Total IgE
• Phadiatop/Inhalant SPTs
• Food mix IgE/food SPTs

• Nasal eosinophils (rhinitis symptoms)
• CAST inhalant mix
• CAST food mix
• CAST colorants + preservatives

If positive, consider component testing:
• ISAC testing for complex allergies
• Specific IgE components on ImmunoCap®

If negative, consider other diseases

Correlation with clinical findings and history

TAKE A GOOD HISTORY:

• Decide whether you have a low or high suspicion of allergy
• Can you identify a specific allergen?
• What mechanism of allergy do you suspect?

HIGH SUSPICION OF ALLERGY

HISTORY

HIGH SUSPICION OF ALLERGY

Allergen specific screening tests or allergen targeted testing, e.g. foods, inhalants or both

DECIDE ON MECHANISM

IgE mediated

Non IgE mediated

• Phadiatop/specific inhalant IgE/inhalant SPTs AND/OR
• Food mix IgE/ specific food IgE/food SPTs

• Inhalant mix CAST/specific inhalant CASTs AND/OR
• Food mix CAST/specific food CAST/CAST colorants and preservatives

If positive, consider component testing:
• ISAC testing for complex allergies
• Specific IgE components on ImmunoCap®

Continue search if results are negative:
• Other allergen
• Other mechanism (consider T-cell mediated allergy testing)
• Other disease

Correlation with clinical findings and history
AN APPROACH TO INHALANT ALLERGY

CHAPTER 2
Inhalant allergies are allergies caused by airborne allergens, of which the most common are pollens, moulds, dust mites and animal danders. These allergens may cause respiratory allergy (asthma or rhinitis), conjunctivitis or even skin reactions (exacerbation of eczema / contact urticaria). Patient history is extremely important, with special attention given to the likelihood that the patient’s symptoms be attributed to allergy, seasonality of symptoms, environmental exposure to aeroallergens and geographical area where the patient lives.

Patients should be screened for allergies to aero-allergens by using a Phadiatop (ImmunoCap® IgE allergen mix for common aero-allergens) or a panel of aero-allergen skin prick tests (SPT). If a specific aero-allergen is suspected from the clinical history, testing to that specific allergen should be requested. An inhalant mix CAST can also be ordered when a non-IgE (basophil) mediated allergy is suspected.

If screening tests are used, it should specifically be requested that individual allergens be performed if the initial screen is positive, for the causative allergen(s) to be identified. This is essential for appropriate patient management, including avoidance and recommendation of appropriate allergen immunotherapy. Current recommendations from the Allergy Society of South Africa are that a positive Phadiatop inhalant screen should be followed by the following panel of allergen-specific IgE tests: Bermuda grass, Rye grass, Alternaria (mould), Cladosporium (mould), Aspergillus (mould), D. pteronyssinus (mite), B. tropicalis (mite), cat and dog.

In patients with asthma or rhinitis with exacerbation in spring, testing for tree pollens is recommended. The most sensible approach is by using tree pollen mixes, e.g. Tree mix 1 (olive, willow, pine, eucalyptus, acacia, maleleuca) or Tree mix 2 (Oak, elm, plane, willow, cottonwood). Individual tree pollen IgE testing can be requested separately should a specific culprit tree be suspected from the patient’s history. The most common allergenic tree pollens in South Africa are plane tree, oak, olive, cypress, eucalyptus, pine, acacia, willow, poplar, mulberry, elm, ash and elder. Some indigenous trees like stinkwood and karee are also thought to be allergenic, but allergy tests to these pollens are not currently available.

THE FOLLOWING ALLERGENS SHOULD BE CONSIDERED AND REQUESTED INDIVIDUALLY BASED ON THE PATIENT’S CLINICAL HISTORY AND GEOGRAPHICAL ENVIRONMENT:

| GAUTENG: Also consider tree pollens like plane, acacia, oak, cypress |
| WESTERN CAPE: Also consider German cockroach and epicoccum fungal spores. |
| HIGHVELD, FREESTATE AND NORTH WEST: Also consider maize pollen, Eucalyptus tree pollen (perennial symptoms) and weed pollens like cosmos and khakibos (weed mix IgE) |
| KWAZULU NATAL: Also consider cockroach |
| FARMING AREAS: Also consider maize and wheat pollen, storage mites, other animal danders (e.g. horse and cow), p.notatum (mould found in vineyards), pine and eucalyptus (plantations), etc. |
AN APPROACH TO INHALANT ALLERGY

POLLEN CROSS-REACTIVITY:

Please note that patients with pollen allergies are often sensitized to cross-reactive components that occur in pollens as well as foods of plant origin. The most common cross-reactive components are cross-reactive carbohydrate determinants (CCD), profilins, Proteinase-10 (PR-10) and lipid transfer proteins (LTP). The implication of this is that patients may test positive to multiple allergen-specific IgE tests, including other pollens and foods of plant origin. IgE to CCD, profilin, PR-10 and LTP should be requested in these patients to determine the likelihood that they have a relevant allergy or whether tests are positive due to cross-reactivity. This has important implications to advise on allergen avoidance and selecting patients for allergen immunotherapy. Immunotherapy is discussed in more detail in chapter 8.

**FIGURE 1: SAMPLE REQUEST FORM FOR INHALANT ALLERGIES**

<table>
<thead>
<tr>
<th>HISTORY</th>
<th>SUGGESTED PANEL</th>
</tr>
</thead>
</table>
| Asthma/Rhinitis  
(all year round) | • Phadiatop inhalant screen  
• Breakdown if positive:  
  Bermuda grass  
  Rye grass  
  Alternaria (mould)  
  Cladosporium (mould)  
  Aspergillus (mould)  
  D. pteronyssinus (mite)  
  B. tropicalis (mite)  
  Cat  
  Dog |
| Asthma/Rhinitis  
(with seasonal aggravation in Spring) | Add:  
• Tree mix 1  
  (olive, willow, pine, eucalyptus, acacia, maleleuca)  
• Tree mix 2  
  (oak, elm, plane, willow, cottonwood)  
• Other trees (specify) |
| Where does the patient live?  
- Western Cape  
- Highveld, Free state, Northwest  
- Kwazulu Natal | Consider:  
• Epicoccum (mould), Cockroach (German)  
• Weed mix (cosmos/ khakibos), Maize pollen,  
  Eucalyptus pollen  
• Cockroach (oriental) |
FIGURE 2: APPROACH TO THE DIAGNOSIS OF INHALANT ALLERGIES.

**HISTORY SUGGESTIVE OF INHALANT ALLERGY**

- Symptoms all year round
  - Phadiatop Inhalant Screen
    - Positive
      - Break down in ALLSA/NPG panel*
    - Negative

- Symptoms worse in Spring
  - Phadiatop Inhalant Screen
    - Positive
      - Break down in ALLSA/NPG panel*
    - Negative
      - Or SPT panel
        - Negative
        - if negative
          - ? OTHER MECHANISM
            - CAST inhalant mix **
              - Nasal eosinophils
            - Nasal eosinophils
            - Consider adding:
              - Epicoccum (mould)
              - Cockroach (German)
            - Consider adding:
              - Maize Pollen
              - Eucalyptus
              - Weed Mix (Cosmos, Kakhibos)

WHERE DOES THE PATIENT LIVE?

- Western Cape
  - Consider adding:
    - Epicoccum (mould)
    - Cockroach (German)

- KZN
  - Consider adding:
    - Cockroach (Oriental)

- Highveld, Free State, Northwest
  - Consider adding:
    - Maize Pollen
    - Eucalyptus
    - Weed Mix (Cosmos, Kakhibos)

* ALLSA/NPG panel: Bermuda grass, Rye grass, Alternaria (mould), Cladosporium (mould), Aspergillus (mould), D.pteronyssinus (mite), B.tropicalis (mite), cat, dog
** Request specific allergen breakdown if CAST inhalant mix is positive and phadiatop is negative.
CHAPTER 3
AN APPROACH TO
FOOD ALLERGY
Patients often assume that an adverse reaction to foods is due to an allergy, although non-immunologic reactions are more common than true food allergies.

The World Allergy Organization defines any adverse reaction to food as food hypersensitivity, and this can be divided into immunological and non-immunological mechanisms. Food allergies are immunological reactions and can be broadly categorized in IgE-mediated and non-IgE mediated mechanisms, with some disorders having characteristics of both mechanisms, such as atopic dermatitis or the eosinophilic gastrointestinal disorders.

IgE-mediated disorders are usually rapid in onset, within minutes to two hours and occur with each exposure. Reactions to the carbohydrate moieties of meat may present four to six hours later. Typical signs and symptoms involve the skin (pruritis, flushing, urticaria, angioedema), eyes (redness, pruritis, lacrimation, periorbital oedema), nose (sneezing, rhinorrhea, congestion), upper airway (oedema, metallic taste, hoarseness, stridor, sense of choking), lower airway (dyspnoea, tachypnoea, wheezing, dry and repetitive coughing, choking, difficulty in breathing), gastrointestinal (nausea, vomiting, crampy pain, diarrhoea), cardiovascular (hypotension, tachycardia or occasionally bradycardia, palpitations, lightheadedness, syncope), neurological (sense of impending doom).

Non-IgE mediated disorders may present immediately, but may be more subacute with/ or without chronic symptoms. The exclusive non-IgE-mediated food allergy disorders include food protein-induced enterocolitis syndrome, food protein-induced enteropathy, food protein-induced proctitis and proctocolitis (rectum and colon), coeliac disease and food-induced pulmonary haemosiderosis.

Basophil mediated reactions may be an immediate or a delayed response and may present like a classic IgE-mediated reaction. Symptoms include rhinitis/sinusitis, asthma, gastrointestinal symptoms and urticaria. The main allergens implicated are foods, colourants, preservatives and drugs. These reactions are often dose-dependant and cumulative.
### AN APPROACH TO FOOD ALLERGY

<table>
<thead>
<tr>
<th>TYPE OF REACTION</th>
<th>IgE-MEDIATED DISORDERS</th>
<th>MIXED IgE AND NON IgE MEDIATED REACTIONS</th>
<th>NON-IgE MEDIATED DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basophil mediated reactions</td>
<td>Food protein induced enterocolitis syndrome</td>
<td>Food protein-induced enteropathy</td>
</tr>
<tr>
<td></td>
<td>Basophil mediated response to allergenic proteins</td>
<td>May be mediated by T cells and other immune cells</td>
<td>Food protein-induced proctitis and proctocolitis</td>
</tr>
<tr>
<td></td>
<td>IgE antibodies directed to allergenic proteins</td>
<td></td>
<td>Food-induced pulmonary haemosiderosis</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Heterogenous group of disorders, characterized by eosinophilic inflammation of gastrointestinal tract</td>
<td></td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Onset</td>
<td>Any age</td>
<td>Any age</td>
<td>Any age</td>
</tr>
<tr>
<td>Symptom</td>
<td>Skin: pruritis, urticaria, angioedema</td>
<td>Any age</td>
<td>Any age</td>
</tr>
<tr>
<td></td>
<td>Eyes: pruritis, periorbital oedema</td>
<td></td>
<td>Infants</td>
</tr>
<tr>
<td></td>
<td>Nose: hay fever</td>
<td></td>
<td>By 6 months</td>
</tr>
<tr>
<td></td>
<td>Upper airway: hoarseness, sense of choking</td>
<td></td>
<td>Infants</td>
</tr>
<tr>
<td></td>
<td>Lower airway: dyspnoea, tachypnoea, wheezing, coughing, difficulty in breathing</td>
<td></td>
<td>Any age</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal: nausea, vomiting, diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular: hypotension, tachycardia or palpitations, lightheadedness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurological: sense of impending doom</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allergic eosinophilic esophagitis/gastroenteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate or a delayed response. Rhinitis, sinusitis, asthma, gastrointestinal symptoms, urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe vomiting and diarrhoea within 2-4 hours of ingestion of offending allergen, may cause profound dehydration, shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malabsorption, failure to thrive, anaemia, diarrhoea, vomiting, hypoprotein-aemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bloody-streaked, mucousy, loose stools, occasional diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrent pneumonia with pulmonary infiltrates, haemosiderosis, iron deficiency anaemia, failure to thrive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

...continued...
<table>
<thead>
<tr>
<th>TYPE OF REACTION</th>
<th>IgE-MEDIATED DISORDERS</th>
<th>MIXED IgE AND NON IgE MEDIATED REACTIONS</th>
<th>NON-IgE MEDIATED DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMON TRIGGERS</td>
<td>Cow's milk protein, Egg, wheat, soy, peanuts and tree nuts, seafood</td>
<td>Cow's milk protein, soy, wheat</td>
<td>Cow's milk protein, soy, rice, oats and wheat, shellfish in adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cow's milk protein, egg, wheat, soy, peanuts and tree nuts, seafood, colorants and preservatives</td>
<td>Cow's milk protein, occasionally rice</td>
</tr>
<tr>
<td>AVAILABLE TESTS</td>
<td>SPT Food mix IgE ImmunoCap® IgE tests to specific allergens Component testing</td>
<td>MELISA to above allergens occasionally positive; SPT IgE to above allergens</td>
<td>CAST testing to above and components</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No specific tests, usually responds to exclusion</td>
</tr>
</tbody>
</table>

**TABLE 1. FOOD ALLERGY: PATHOGENESIS, SYMPTOMS AND TESTING**

- HLA DQ2/DQ8
- If total IgA IgA<0.2 g/L: Do TTG IgG, Endomysial IgG and deamidated Gliadin IgG
- TTG IgA
- Deamidated gliadin IgA
- Endomysial IgA
- Intestinal biopsy
Food intolerance comprises most of the adverse reactions to foods and may be due to toxic contaminants in food (i.e. histamine in scombroid fish poisoning, bacterial toxins), pharmacologic agents in food, including caffeine, theobromine in chocolate and tea, histamine-like compounds (fish, wine etc.), tryptamine (tomato, plum), tyramine (aged cheese, pickled fish), serotonin (banana, tomato), phenylethylamine (chocolate), glycosidal alkaloid solanine (potatoes) and alcohol. Other nonallergic food reactions include lactose intolerance, fructose intolerance, gastroesophageal reflux, anatomic and neurologic abnormalities, enzyme deficiencies, metabolic disorders, gastrointestinal infections and food additive intolerance.

When a patient has a confirmed allergy to one food, evaluation of related foods may be indicated to determine if these foods are also problematic. It should always be kept in mind that a “positive” allergy test to a related food may simply represent immunologic cross-reactivity due to the presence of a homologous protein that does not have clinical significance. This is more common than true clinical cross-reactivity. A patient with a peanut allergy can therefore have “positive” serum immunoglobulin E (IgE) tests or skin prick tests to multiple legumes that are clinically tolerated. It is often difficult to decide what is clinically relevant.

Tree nuts, fish, and shellfish are more commonly clinically cross-reactive. Caution and possible allergy testing (including oral food challenges) are warranted if ingestion of related foods is being considered. Grains, fruits, vegetables, and legumes are clinically less cross-reactive and elimination diets/challenges with food diaries are generally recommended to expand the diet. Component testing is also valuable, for knowledge of certain components may predict the clinical relevance of the reaction. Please refer to table 2 on cross-reactive pollen and plant food components.

ORAL ALLERGY SYNDROME

The oral allergy syndrome (OAS), also known as the food-pollen syndrome, describes an IgE-mediated reaction, usually limited to the oropharynx, which occurs upon ingestion of certain fresh fruits and nuts or vegetables in pollen-sensitized individuals. The cross reactive components typically involved in the OAS include CCD, profilin, PR-10, and LTP. The symptoms result from contact allergy of the oropharynx. OAS is caused by ubiquitous plant allergens present in fruit, vegetables, nuts and pollen. Symptoms are usually confined to the mouth, but in rare circumstances, systemic reactions can occur. The responsible allergens are usually destroyed by cooking/peeling of food, but rarely, symptoms do occur in a small proportion of patients, with cooked food as well.
<table>
<thead>
<tr>
<th>STABILITY TO HEAT AND DIGESTION</th>
<th>CCD (CROSS-REACTIVE CARBOHYDRATE DETERMINANTS)</th>
<th>PROFILIN</th>
<th>PR-10</th>
<th>LTP</th>
<th>STORAGE PROTEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable, but usually not clinically relevant</td>
<td>Sensitive to heat and proteases.</td>
<td>Sensitive to heat and proteases.</td>
<td>Proteins stable to heat and digestion.</td>
<td>Proteins very stable to heat and digestion.</td>
<td></td>
</tr>
<tr>
<td>LOCALISATION OF ALLERGEN</td>
<td>Present throughout fruit.</td>
<td>Primarily localized to the pulp of the fruit.</td>
<td>LTP is primarily localized to the peel of fruit. Patients may be able to eat peeled fruit.</td>
<td>Localized in the seed/nut/kernel.</td>
<td></td>
</tr>
<tr>
<td>SEVERITY OF REACTION</td>
<td>Usually doesn’t cause symptoms.</td>
<td>Usually mild, may be severe.</td>
<td>Often associated with systemic and more severe reactions.</td>
<td>Sensitization is regarded as an important risk marker for severe systemic reactions.</td>
<td></td>
</tr>
<tr>
<td>COMMON SYMPTOMS</td>
<td>Usually none.</td>
<td>Usually no symptoms or oral allergy syndrome (OAS): symptoms are usually restricted to the oral cavity and include oral pruritus, swelling of the lips, tongue and throat, hoarseness, pharyngitis, and laryngeal oedema.</td>
<td>Often associated with local symptoms like OAS, but may also experience systemic symptoms.</td>
<td>May cause systemic reactions such as urticaria/angioedema, asthma and anaphylaxis.</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2: POLLEN - FOOD CROSS REACTIVITY AND PANALLERGENS**
AN APPROACH TO FOOD ALLERGY

FOOD ALLERGY DIAGNOSIS:

Patients should be screened for allergies to food allergens by using a food mix IgE (RAST) for common food allergens or a panel of food allergen skin prick tests (SPT). If a specific food allergen is suspected from the clinical history, testing to that specific allergen should be requested. If an allergy to food colourants and preservatives is suspected, CAST tests for colourants and preservatives can be requested. A food mix CAST can also be ordered when a non-IgE (basophil) mediated allergy is suspected.

Some foods commonly provoke allergic reactions; they include cow’s milk, egg, soya and peanut in infants and young children, and fish, shellfish, peanuts, tree nuts, wheat, fruit and food additives like colourants and preservatives in older children and adults.

COMPONENT TESTING FOR ALL THE MAJOR FOOD ALLERGENS IS AVAILABLE AND HAS THE FOLLOWING ADVANTAGES:

- Knowledge of protein structure and stability: gives information on allergenicity after heating, processing and digestion, e.g. Lipid Transfer Protein (LTP) vs profilin, casein vs alpha-lactalbumin
- Knowledge of severity of reactions based on protein families, e.g. Ara h 2 sensitization is associated with severe peanut allergy.
- Identify primary sensitizers for avoidance or allergen immunotherapy. This solves “cross-reactive puzzles” in allergy test results and prevents unnecessary avoidance measures

Up to 30% of patients suffering from pollinosis are simultaneously sensitized to fruits, vegetables, wheat, legumes and nuts. This may either be due to cross-reactivity or true co-sensitization. In patients with a pollen allergy who are also sensitized to the above mentioned foods (especially the combination of wheat, soy and peanut sensitisation), markers for cross-reactivity are indicated, which includes IgE to CCD, profilin, PR-10 and LTP.

THE FOLLOWING DIAGNOSTIC TOOLS ARE VALUABLE IN THE ASSESSMENT OF A POSSIBLE FOOD ALLERGY:

- Proper history and examination
- Skin prick testing or blood tests (ImmunoCap® IgE tests) for IgE-mediated food allergies
- Basophil activation testing (CAST tests) – for basophil mediated reactions
- MELISA testing – for delayed T cell-mediated reactions
- Gastroenterologic tests (including biopsies)
- Food diaries
- Elimination diets
- Food challenges
Cow’s Milk Allergy:

Cow’s milk allergy (CMA) is one of the most common food allergies and is generally the first allergen to be introduced into the infant’s diet. Most children will outgrow a milk allergy by the age of 8 years and 80% by the age of 16 years.

The major allergens in milk are casein (Bos d 8) and whey protein, consisting of alpha-lactalbumin (Bos d 4), beta-lactoglobulin (Bos d 5) and other minor proteins like bovine serum albumin (BSA)(Bos d 6) and lactoferrin (Bos d lactoferrin). It is important to identify which proteins (casein or whey) the patient is sensitized to, as it will greatly impact on dietary advice.

Casein is the most important and abundant allergen in milk and hard cheese and is heat stable. Patients with high levels of IgE to casein are at risk for severe reactions and are less likely to outgrow their milk allergy. Please note that there is a high homology between casein of different species and patients with casein reactivity have a high risk of reacting to the milk of other animal species. Whey proteins (alpha-lactalbumin and beta-lactoglobulin) are heat labile and patients reacting to these proteins may often tolerate heated or fermented milk products like yoghurt. Please note that different infant formulas may contain different milk proteins (e.g. casein or whey) and parents of allergic infants should be advised on appropriate, safe formulas. Partially hydrolysed infant formulas are only suitable for prevention of sensitization to milk in infants at risk of developing milk allergy, but not for infants already allergic to milk.

BSA is a serum albumin which is a main protein in mammalian blood and is an important allergen involved in milk, meat and epithelia allergy. Sensitised patients may react to different meats (beef, lamb and pork), epithelia (cat and dog) and cow’s milk.
### AN APPROACH TO FOOD ALLERGY

#### COW’S MILK ALLERGY:

<table>
<thead>
<tr>
<th>PATHOGENESIS</th>
<th>IgE MEDITED CMA</th>
<th>BASOPHIL MEDITED CMA</th>
<th>OTHER CELLULAR MEDITED CMA</th>
<th>EOSINOPHILIC CMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE antibodies directed to allergenic proteins, e.g. casein or whey</td>
<td>Basophil mediated response to allergenic proteins, e.g. casein or whey. May be IgE or non-IgE mediated.</td>
<td>Cell-mediated (other than basophils, eosinophils). May be mediated by T-cells and other immune cells</td>
<td>A heterogenous group of conditions characterized by eosinophilic inflammation of the gastrointestinal tract.</td>
<td></td>
</tr>
</tbody>
</table>

#### SYMPTOMS

- Immediate, often urticaria, angioedema or even anaphylaxis. Patients may also have eczema flare-ups, which may include T-cell and IgE mediated mechanisms
- Immediate or delayed symptoms. May present similar to IgE mediated reactions.
- Cow’s milk protein (CMP) induced proctocolitis:
  - Presents at <2 months in a thriving baby
  - Colic and fresh blood in stool
  - Usually resolves by 12 months, benign condition.
- Food protein induced enterocolitis syndrome (FPIES):
  - Severe, protracted diarrhea and vomiting 1-3 hours after ingestion.
  - Pallor, hypotonia, hypovolemic shock/sepsis-like picture
- Allergic dysmotility:
  - Vomiting, colic, treatment-resistant gastro-esophageal reflux and constipation.
- Eosinophilic enterocolitis:
  - Presents with gastro-oesophageal reflux or dysphagia
  - Vomiting, malabsorption, diarrhoea, abdominal pain.

#### AVAILABLE TESTS

- **Milk Skin Prick Test**
  - Milk IgE
- **Milk CAST**
  - Allergen components:
    - Casein: Most allergenic, is heat stable, leads to more severe reactions and predicts persistent allergy.
    - Alpha lactalbumin:
      - Whey protein, heat labile
    - Beta lactoglobulin:
      - Whey protein, heat labile
    - Bovine serum albumin:
      - Cross-reacts with beef and meat / epithelia of other mammals. May cause severe allergy e.g. anaphylaxis if eating meat and reactions to cats and dogs.
    - Lactoferrin:
      - Minor whey protein, used as a natural preservative.
  - Test if IgE mediated tests are negative with a suggestive patient history.
- **Milk CAST**
  - Allergen components:
    - Casein: Most allergenic, is heat stable, leads to more severe reactions and predicts persistent allergy.
    - Alpha lactalbumin:
      - Whey protein, heat labile
    - Beta lactoglobulin:
      - Whey protein, heat labile
- No specific tests, usually responds to exclusion.
- T-cell mediated tests (MELISA) to milk may be positive. Biopsy with staining for eosinophils.
EGG ALLERGY:

Egg allergy is common in infancy and childhood. However, most children will outgrow their egg allergy by the time they go to school. The most common symptoms are atopic dermatitis / eczema, which may present very early on in infants exposed to egg proteins through breast milk. Non-breastfed or older infants typically present at the age of first dietary exposure to egg. In addition to atopic dermatitis, gastro-intestinal, respiratory or even anaphylactic reactions may also occur. Some patients may also experience a delayed exacerbation of atopic dermatitis, which is thought to be T-cell mediated.

Egg white is most allergenic and the main allergens are ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin/conalbumin (Gal d 3) and lysozyme (Gal d 4). Although ovomucoid comprises of only 10% of the total egg white protein, it has been shown to be the dominant allergen and is allergenic in minute amounts. This protein is very stable to heat and digestion, therefore allergic patients cannot tolerate egg in baked products. High levels of IgE to ovomucoid are also associated with persistent egg allergy. On the contrary, absence or low levels of IgE antibodies to ovomucoid are associated with an increased probability of tolerance to ingestion of cooked egg and patients can be challenged with cooked / baked egg.

Egg livetin / serum albumin (Gal d 5) is the main egg allergen in egg yolk. This allergen also occurs in chickens as chicken serum albumin and may cause “bird-egg syndrome”, where patients may react to egg yolk, chicken meat and feathers. There is a lot of concern regarding the safety of certain vaccines in egg allergy sufferers. The only common vaccines that are manufactured using eggs are Influenza, Yellow Fever and some Rabies vaccines. Measles-Mumps-Rubella (MMR) vaccine is produced in fibroblast cell lines and doesn’t contain egg. It is therefore safe to administer in egg-allergic patients.

WHEAT ALLERGY:

Wheat is a grass and is one of the most common causes of food allergy in children. Immediate wheat allergy is mainly seen in children and is commonly outgrown by school age, but persists in some patients and may cause severe reactions. Occupational exposure (e.g. bakers) may lead to adult onset wheat allergy. Patients may present with a wide range of IgE-mediated, non IgE-mediated and mixed reactions. IgE-mediated reactions may occur within minutes to two hours of ingestion and may range from mild to life-threatening anaphylaxis. In teenagers and adults, anaphylaxis may also result from ingestion of wheat in conjunction with exercise or other triggers (including severe stress, alcohol consumption, concomitant NSAID intake) and this is called wheat dependant, exercise induced anaphylaxis (WDEIA). In addition to the IgE-mediated immediate reactions, it may also cause mixed reactions, including atopic dermatitis (third most common food allergen implicated in childhood eczema after egg and milk), allergic eosinophilic gastrointestinal disorders and non IgE-mediated reactions including food protein-induced enterocolitis syndrome. There are also other hypersensitivity reactions caused by wheat e.g. Coeliac disease and irritable bowel syndrome.

A positive result to wheat-flour extract does not always correlate with clinical symptoms, as cross-reactivity with grass pollen is common. This is a particular problem in South Africa, where incorrect diagnosis of wheat allergy occurs frequently in patients with actual grass allergy. The wheat component Tri α 19 omega-5 gliadin is associated with true wheat allergy and is an important risk marker for immediate reactions to wheat in children and for exercise-induced anaphylaxis after wheat ingestion in adults. The LTP α 14 lacks cross-reactivity to grass pollen allergens and is also a marker for clinical reactions. Patients with wheat allergy may react to other cereals such as rye and barley due to cross-reactivity between gluten proteins (gliadins and glutenins).

Baking products are the leading cause of occupational asthma in Western countries. IgE to the Alpha-amylase / Trypsin inhibitor component in wheat is associated with baker’s asthma or problems with inhalation of wheat flour. Coeliac disease is an immune-mediated enteropathy caused by gluten sensitivity in a genetically susceptible individual. In infants and young children this disorder classically presents as diarrhea, anorexia, abdominal distension and pain, failure to thrive or weight loss and occasionally vomiting. In older children and adults the symptoms are often much milder and also include steatorrhea, weight loss and signs of nutrient deficiencies due to malabsorption.
AN APPROACH TO FOOD ALLERGY

APPROACH TO THE DIAGNOSIS OF SUSPECTED WHEAT ALLERGY

WHEAT HYPERSENSITIVITY

WHEAT lgE

IF POSITIVE

GLIADIN
- Contains β, α, Y and ω gliadins
- Risk marker for systemic reactions
- Marker for wheat allergy persistence
- Supports diagnosis of wheat dependant exercise induced anaphylaxis

Tri a 14
- Lipid transfer protein (LTP)
- Risk for clinical reactions

IF NEGATIVE ADD:
- Grass pollen lgE
- CCD lgE
- Profilin lgE
- PR-10 lgE
- LTP lgE

Tri a 19
- Ω-5-Gliadin.
- Risk marker for systemic reactions.
- Marker for wheat allergy persistence.
- Supports diagnosis of wheat dependant exercise induced anaphylaxis.

alpha amylase lgE
(available on ISAC)

ADULT ONSET ASTHMA
+++ Contact with flour /baker

IF NEGATIVE

SYMPTOMS SUGGESTIVE OF WHEAT ALLERGY

SYMPTOMS AND SIGNS SUGGESTIVE OF COELIACS DISEASE

IgA
- Endomysial IgA
- TTG IgA
- DGP IgA
- HLA DQ2 and DQ 8

? OTHER MECHANISM
- Wheat CAST
- Wheat MELISA

? OTHER DISEASE
- Consider Coeliac disease:
  - IgA
  - Endomysial IgA
  - TTG IgA
  - DGP IgA
  - HLA DQ2 and DQ 8
- Consider irritable bowel syndrome
NUT AND SEED ALLERGY:

Peanut, tree nuts and seed allergies are amongst the most prominent food allergies in children and adults, may cause severe reactions and tends to persist. Reactions are mostly IgE-mediated with symptoms ranging from mild to severe, life-threatening anaphylaxis. Peanut, tree nut and seed allergies are amongst the most common causes of food-induced anaphylaxis. Peanuts are also implicated in non-IgE mediated and mixed IgE and non-IgE mediated disorders (atopic dermatitis and eosinophilic gastroenteritis). Peanut ingestion has also been shown to exacerbate atopic dermatitis in individuals with peanut allergy.

Peanut contains 32 known proteins, of which 18 have been identified as potential allergens. Five of these are currently offered as components on ImmunoCap® testing (Ara h 1, 2, 3, 8 and 9) and six on the ISAC (Ara h 1, 2, 3, 6, 8 and 9). Many individuals sensitized to peanut may be clinically tolerant to peanut. In children, approximately 10% are considered peanut sensitized, but only 1-2% are truly allergic. This may often be seen due to sensitization to cross-reactive components, e.g. CCD, profilin, PR-10 or LTP. Ara h 1, 2 and 3 are all major allergens, are associated with primary sensitisation to peanut and are all seed storage proteins. Patients with “true” peanut allergy often have antibodies to Ara h 2. In rare cases sensitization to only Ara h 1 and/or Ara h 3 can occur. Ara h 8 is a PR-10 protein and if a patient is symptomatic due to IgE to Ara h 8, symptoms are most commonly limited to oral allergy syndrome (OAS). Ara h 9 is an LTP and is often associated with systemic and more severe reactions in addition to OAS, although many patients with Ara h 9 sensitisation may be asymptomatic.

Storage proteins are the dominant allergens in nuts, seeds, fruit stones and kernels. The main storage proteins are designated according to molecular weight and are grouped in 7/8 S and 11S globulins and 2S albumins. These proteins are very stable to heat and digestion, therefore patients also react to cooked and processed foods. Sensitisation to storage proteins is regarded as an important risk factor for severe systemic reactions, particularly if sensitisation to more than one storage protein in a particular allergenic source is identified. The 2S albumin seems to be the dominant allergen with the highest risk for severe systemic reactions in tree nut, seed and peanut allergies. 30% to 50% of patients with peanut allergy have co-allergy to tree nuts, and about 50% of tree nut-allergic patients are sensitive to more than one nut. Cross-sensitization (i.e. positive specific IgE/SPT) is often observed with other legumes (soy, peas, green beans) in patients with a peanut allergy, but with the exception of lupine beans, these are rarely (<5 to 10%) clinically cross-reactive.

<table>
<thead>
<tr>
<th>FOOD ALLERGEN</th>
<th>2S ALBUMIN</th>
<th>7/8S GLOBULIN</th>
<th>11S GLOBULIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazelnut</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Almond</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Brazil Nut</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Cashew nut</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Pistachio nut</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Chick pea</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Garden pea</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Lentil</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Peanut</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Soybean</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Sesame seed</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Sunflower seed</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Pecan nut</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Walnut</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Buckwheat</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
AN APPROACH TO FOOD ALLERGY

SOY ALLERGY:

Soy protein is an important protein source worldwide. Soybean is another member of the legume family that may provoke a significant number of hypersensitivity reactions. Cutaneous and gastrointestinal symptoms are the most common symptoms of soy allergy, but severe and systemic reactions may also occur. Soy can be a hidden allergen in a wide variety of processed foods such as meat products, sausages, bread, baked goods, chocolate or breakfast cereals. Twenty-eight potential soy allergens have been identified, but only a few are recognized as major allergens. IgE-mediated soy allergy may be the result of primary sensitization, but may also be the result of cross-reactivity to pollens and a variety of legumes.

The main soy allergens are Gly m 5 and Gly m 6, seed storage proteins. These allergens indicate primary sensitization to soy and are also high-risk markers for severe allergic reactions to soy. Soy allergic patients with IgE antibodies to Gly m 5 and/or Gly m 6 may also react to similar storage proteins, such as the peanut components Ara h 1 and Ara h 3. Pollen-sensitised individuals may also react to Gly m 4, the PR-10 in soy. These patients may have severe OAS or even systemic reactions. Most commercial soy extracts contain low levels of Gly m 4, therefore pollen sensitized patients with a suspicion of soy allergy should be tested separately to Gly m 4.

FISH AND SHELLFISH ALLERGY:

The diagnosis of fish and shellfish allergy can often be challenging, as there is a lot of confusion regarding allergen groupings, common names for local fish species and distinguishing between allergy, intolerance and adverse reactions. There are also some myths, e.g. that patients that are allergic to fish are actually allergic to iodine, which may cause even more confusion. Ingredients like preservatives, spices and hidden allergens may also contribute to the patient’s symptoms.

Reactions to seafood can broadly be classified as IgE mediated allergy, non-IgE mediated allergy and adverse/toxic reactions to seafood. Seafood allergens can be categorized in fish and shellfish, the latter which consists of crustacea and molluscs. Please note that patients may also suffer from an IgE mediated reaction to a fish parasite Anisakis, which is found mainly in the gut of fish, but sometimes also in squid and crustaceans. Patients sensitized to Anisakis may present with true allergy symptoms after consuming fish, but have negative blood tests to the common fish allergens. It is therefore important that IgE to Anisakis also be requested in patients with symptoms of fish allergy.

Allergen components are very valuable in the diagnosis of fish and shellfish allergy. Cod (sea fish) and Carp (freshwater fish) parvalbumins are markers of fish sensitisation in general. Parvalbumin is also a useful marker when an ImmunoCap® IgE is not available for the specific fish species that the patient reacted to. There is a high degree of cross-reactivity between parvalbumins from different fish species, therefore clinically sensitized patients are often recommended to avoid all fish species. However, the difference in parvalbumin content in some species may explain tolerance in parvalbumin sensitized individuals to some species, e.g. tuna, mackerel or swordfish. Parvalbumin is a very stable protein, which may explain reactions to cooked fish as well as cooking vapour.

Tropomyosin is a muscle protein found in crustaceans (shrimp, lobster, crab), arachnids (house dust mite), insects (cockroach) and molluscs (squid). This protein is very heat stable and cross-reacts with other tropomyosins. This is a good indicator of shellfish allergy and should be requested specifically in patients where shellfish allergy is suspected. This is particularly useful if the specific shellfish species has not been identified or where the specific ImmunoCap® IgE is not available.
### SEAFOOD ALLERGY:

<table>
<thead>
<tr>
<th>PATHOGENESIS</th>
<th>IgE MEDIATED ALLERGY</th>
<th>NON-IGE MEDIATED ALLERGY</th>
<th>ADVERSE REACTIONS</th>
</tr>
</thead>
</table>
| **Scromboid toxins** – fish | Produced in improperly refrigerated fish with meat with a high histidine content (histidine converted to histamine), e.g. tuna, bonito, mackerel, yellowtail, snoek, herring and anchovy. | Basophil-mediated reaction, histamine and leukotrine release | Scromboid toxins:  
- Flushing, urticaria, vomiting, diarrhoea  
- Blooms of toxic algae (seen in August in the Cape) are taken up by filter feeders like mussels and oysters. |
| **Marine algae toxins** – shellfish (red tide) | Blooms of toxic algae (seen in August in the Cape) are taken up by filter feeders like mussels and oysters. | Marine algae toxins (red tide):  
- Paralytic shellfish poisoning (PSP): gastrointestinal symptoms, parasthesias, paralysis  
- Diarrhoeic shellfish poisoning (DSP): diarrhea, nausea, vomiting, abdominal pain  
- Ciguatera fish poisoning: Neurologic (temperature control, blurry vision) cardiovascular (tabile blood pressure, heart block) |

| SYMPTOMS | | |  
| Immediate symptoms, typical allergy symptoms, especially rhinitis and asthma. Patients may also react to cooking vapours.  
Molluscs:  
- Symptoms may be delayed up to 8 hours  
- Gastrointestinal symptoms common  
Crustaceans:  
- Often oral allergy syndrome, urticaria and anaphylaxis. | May present with immediate symptoms similar to IgE mediated allergy or may present with delayed symptoms. |  
| Scromboid toxins:  
- Flushing, urticaria, vomiting, diarrhoea  
- Blooms of toxic algae (seen in August in the Cape) are taken up by filter feeders like mussels and oysters.  
| Marine algae toxins (red tide):  
- Paralytic shellfish poisoning (PSP): gastrointestinal symptoms, parasthesias, paralysis  
- Diarrhoeic shellfish poisoning (DSP): diarrhea, nausea, vomiting, abdominal pain  
- Ciguatera fish poisoning: Neurologic (temperature control, blurry vision) cardiovascular (tabile blood pressure, heart block) |

| ALLERGENS | | |  
| Whole allergen extracts of fish and shellfish.  
Allergen components:  
- Parvalbumin: Cod (sea fish) and Carp (freshwater fish) - markers for fish sensitisation in general.  
- Tropomyosin: Found in crustaceans (shrimp, lobster, crab), arachnids (house dust mite), insects (cockroach) and molluscs (squid)-shellfish cross-reactivity and dominant allergen. | Whole allergen extracts of fish and shellfish | N/A |

| AVAILABLE TESTS | | |  
| Please see list of recommended allergens for ImmunoCap® IgE testing (table 2).  
Consider adding Anisakis IgE (fish parasite), testing for parvalbumin IgE to indicate general fish sensitisation or tropomyosin IgE for general shellfish sensitization.  
Skin prick tests to a limited variety of seafood allergens are commercially available.  
Prick-prick testing to fresh seafood available at Ampath Allergy Clinics in Pretoria by appointment. | Test if IgE mediated tests are negative with a suggestive patient history.  
CAST tests to:  
- Codfish  
- Shrimp  
- Squid  
- Crab  
- Oyster | No specific tests available. Diagnosis made on history and exclusion of allergy. |
### TABLE 2: LIST OF RECOMMENDED ALLERGENS FOR ImmunoCap® IGE TESTING TO SOUTH AFRICAN FISH AND SHELLFISH SPECIES

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>SOUTH AFRICAN SPECIES</th>
<th>BEST ImmunoCap® IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>COASTAL / ESTUARY FISH</td>
<td>Cape Salmon&lt;br&gt;Redeye / Herring&lt;br&gt;Sardine / Pilchard&lt;br&gt;Cape Anchovy&lt;br&gt;East/West Coast Sole&lt;br&gt;Other flat fishes:</td>
<td>Salmon&lt;br&gt;Herring&lt;br&gt;Sardine&lt;br&gt;Anchovy&lt;br&gt;Sole&lt;br&gt;Sole&lt;br&gt;Anisakis (fish parasite)&lt;br&gt;Cod parvalbumin (cross-reactive protein)</td>
</tr>
<tr>
<td>BOTTOM FEEDERS</td>
<td>Cape Hake&lt;br&gt;Kingklip&lt;br&gt;Other bottom feeders:</td>
<td>Hake&lt;br&gt;Cod&lt;br&gt;Cod&lt;br&gt;Anisakis (fish parasite)&lt;br&gt;Cod parvalbumin (cross-reactive protein)</td>
</tr>
<tr>
<td>OPEN OCEAN FISH</td>
<td>Cape horse Mackerel&lt;br&gt;Chub Mackerel&lt;br&gt;Elf&lt;br&gt;Yellowtail&lt;br&gt;Kabeljou&lt;br&gt;Tuna/Bigeye&lt;br&gt;Blue Marlin&lt;br&gt;Snoek and other open ocean fish</td>
<td>Mackerel&lt;br&gt;Mackerel&lt;br&gt;Mackerel&lt;br&gt;Tuna&lt;br&gt;Cod, Anisakis (fish parasite)&lt;br&gt;Cod parvalbumin (cross-reactive protein)&lt;br&gt;Tuna,&lt;br&gt;Swordfish&lt;br&gt;Mackerel, Anisakis (fish parasite)&lt;br&gt;Cod parvalbumin (cross-reactive protein)</td>
</tr>
<tr>
<td>FRESHWATER FISH</td>
<td>Rainbow trout&lt;br&gt;Other species</td>
<td>Trout&lt;br&gt;Carp parvalbumin (cross-reactive protein)&lt;br&gt;Anisakis (fish parasite)</td>
</tr>
<tr>
<td>CRUSTACEA</td>
<td>Prawn / tiger prawn&lt;br&gt;Cape Rock Lobster, Transkei Rock Lobster, Natal Rock Lobster, Langoustine&lt;br&gt;Crayfish</td>
<td>Shrimp&lt;br&gt;Lobster (spiny)</td>
</tr>
<tr>
<td>MOLLUSCS</td>
<td>Calamari, White/Red Squid&lt;br&gt;Octopus&lt;br&gt;Mussel&lt;br&gt;Clam&lt;br&gt;Oyster&lt;br&gt;Snail&lt;br&gt;Abelone, Perlemoen</td>
<td>Squid&lt;br&gt;Octopus&lt;br&gt;Mussel (blue)&lt;br&gt;Clam&lt;br&gt;Oyster&lt;br&gt;Snail&lt;br&gt;Abelone</td>
</tr>
</tbody>
</table>
THE FOLLOWING DIAGNOSTIC TOOLS ARE KEY IN THE ASSESSMENT OF A POSSIBLE FOOD ALLERGY:

HISTORY SUGGESTIVE OF FOOD ALLERGY

Specific food allergens not implicated

Food allergen screen on ImmunoCap® or SPT food panel

Positive

Breakdown in
- Egg white
- Milk
- Wheat
- Soya
- Peanut
- Codfish

If food IgE is positive do component testing to indicate risk, severity and for dietary advice
- Egg: ovomucoid
- Milk: casein
- Wheat: 5 gliadin
- Soya: gly m 5, 6 storage proteins
- Peanut: Arah 1, 2, 3 storage proteins
- Codfish: parvalbumin

? Other allergen
- Other food IgE/SPT's

Clear history indicates a specific food

Food allergen IgE or SPT

Positive

Clear history indicates a specific food

Negative

? Other allergen
- Other food IgE/SPT's

? Other mechanism
CAST test
- Food mix
- Colourants
- Preservatives
MELISA/patch test

? Other disease, e.g.
Coeliac disease
- HLA-DQ2+8
- IgA
- TTG IgA
- Endomysial IgA
- Deamidated Gliadin IgA

? Other mechanism
CAST test
- Food mix
- Colourants
- Preservatives
MELISA/patch test

? Other disease, e.g.
Coeliac disease
- HLA-DQ2+8
- IgA
- TTG IgA
- Endomysial IgA
- Deamidated Gliadin IgA

? Non Immunological Mechanism
i.e. lactase deficiency
- H-breath test
- Stool reducing substances

NBI! If soy, wheat and peanuts are positive, consider food-pollen syndrome
Add:
- Grass mix IgE
- Prolin
- PR-10
- CCD
- LTP

? Other disease, e.g.
Coeliac disease
- HLA-DQ2+8
- IgA
- TTG IgA
- Endomysial IgA
- Deamidated Gliadin IgA

? Non Immunological Mechanism
i.e. lactase deficiency
- H-breath test
- Stool reducing substances
### THE MOST IMPORTANT ALLERGEN COMPONENTS:

#### EGG WHITE

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Highly Allergenic</th>
<th>Heat Stable</th>
<th>Severe and Persistent Allergy</th>
<th>Cross-reacts Between Mammals (e.g., Goat's Milk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovomucoid (Gal d 1)</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovalbumin (Gal d 2)</td>
<td>• Heat labile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conalbumin (Gal d 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lysozyme (Gal d 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### EGG YOLK

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Occurs in Egg Yolk, Chicken Meat and Feathers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg serum albumin (Gal d 5)</td>
<td></td>
</tr>
</tbody>
</table>

#### MILK

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Heat Stable</th>
<th>Most Important Allergen</th>
<th>Severe and Persistent Allergy</th>
<th>Cross-reacts Between Mammals (e.g., Goats Milk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein (Bos d 8)</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α Lactalbumin (Bos d 4)</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β Lactoglobin (Bos d 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine serum albumin (Bos d 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactoferrin (Bos d lactoferrin)</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### FISH

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Heat Stable</th>
<th>Broad Cross-reactivity, Marker for General Fish Sensitization</th>
<th>Parvalbumin Content of Different Fish Species May Vary, E.g., Lower Levels in Tuna</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod pavalbumin (Cyp c 1)</td>
<td>•</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carp parvalbumin (Gad c 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### SHELLFISH

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Heat Stable Muscle Protein</th>
<th>Found in Crustaceans, Molluscs, Insects and Mites with Clinical Cross-reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropomyosin (Pen a 1)</td>
<td>•</td>
<td></td>
</tr>
</tbody>
</table>
### Profilin
- Heat labile
- OAS

### LTP
- Heat labile
- OAS
- Mild to severe symptoms

### CCD
- Usually no clinical symptoms

### Storage Proteins

<table>
<thead>
<tr>
<th></th>
<th>Profilin</th>
<th>PR-10</th>
<th>LTP</th>
<th>CCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ara h 1</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ara h 2</td>
<td>Profilin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ara h 3</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ara h 6</td>
<td>Profilin</td>
<td></td>
<td></td>
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<tr>
<td>Ara h 5</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ara h 8</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ara h 9</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PEANUT
- Stable to heat and digestion
- Risk of anaphylaxis
- Cross-reactive with other nuts and seeds

### SOYA
- Associated with severe reactions
- Heat stable

### WHEAT
- Risk marker for systemic reactions
- Wheat allergy persistence
- Wheat dependent exercise induced anaphylaxis

- Marker of severe reactions
- Marker of wheat allergy persistence

### POLLEN CROSS REACTIVE

<table>
<thead>
<tr>
<th></th>
<th>Profilin</th>
<th>PR-10</th>
<th>LTP</th>
<th>CCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ø 5 Gliadin</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tri a 19</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>αBw1 Gliadins</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTP Tri a 14</td>
<td>Profilin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- May have severe reactions
- Wheat dependent exercise induced anaphylaxis.
CHAPTER 4
AN APPROACH TO
ECZEMA AND DERMATITIS
CLASSIFICATION OF ECZEMA

The World Allergy Organization (WAO) recommends that the umbrella term for local inflammation of skin should be dermatitis. The term eczema describes several skin diseases with clinical characteristics in common, involving a genetically determined skin barrier defect. When the underlying inflammation is dominated by an IgE-associated reaction the term AE can be applied. The diagnosis of AE cannot be reached without IgE-antibody determination or skin tests. Non-atopic eczema applies to patients who do not have associated elevated IgE-antibody levels.

PATHOGENESIS

Atopic eczema is a complex interplay between genetics and the environment. Several genes, including the filaggrin gene, have been implicated in patients with atopic eczema. Allergens are important, but non-allergic factors such as Staphylococcus aureus infections, rough clothing, exposure to microbes during infancy, excessive heat and exposure to irritants also play a role in triggering eczema flare-ups.

DIAGNOSTIC CRITERIA

The diagnosis of AE requires evidence of itchy skin (or parental report of scratching or rubbing) and 3 or more of the following:

- History of involvement of the skin creases (e.g. fronts of elbows, backs of knees, fronts of ankles and areas around the neck or eyes).
- History of asthma or hay fever (or history of atopic disease in a first degree relative if the child is under 4 years of age).
- History of generally dry skin in the past year.
- Onset in a child under 2 years of age (criteria not used if the child is under 4 years of age).
- Visible flexural dermatitis (including dermatitis affecting the cheeks or forehead and outer aspects of limbs in children under 4 years of age).

CLINICAL MANIFESTATIONS:

Almost all patients report a dry skin and AE is always characterized by pruritis with secondary changes in the skin due to chronic rubbing or scratching. There are 3 age groups stages of AE: infantile (from infancy to 2 years old), childhood (from 2 – 12 years old) and the adult stage (>12 years). Atopic eczema will clear in nearly 40% of patients by adulthood.

The infantile stage may present with pruritic, red scaly and crusted lesions on the cheeks, scalp or extensor surfaces. The diaper area is usually spared. Acute lesions may consist of vesicles with serous exudates and crusts.

The childhood stage often demonstrates plaques in the flexure areas, especially the antecubital and popliteal fossae, volar aspects of the wrists, ankles and neck, with less exudation. The presence of pustules within areas of dermatitis suggest secondary infection with S. aureus.
DIFFERENTIAL DIAGNOSIS:

The differential diagnosis includes other eczematous disorders such as contact dermatitis, seborrheic dermatitis and drug reactions. In infants the following should be considered: scabies, hyperimmunoglobulin E syndrome, Wiskott-Aldrich syndrome, nutritional deficiencies, acrodermatitis enteropathica and Netherton’s syndrome.

THE ROLE OF ALLERGY IN ATOPIC ECZEMA:

Patients with atopic eczema have higher rates of allergic diseases than the general population. One to two of three infants and young children with eczema have underlying allergy and may benefit from avoidance advice. Up to 80% of children with atopic eczema develop asthma and/or allergic rhinitis later in childhood. Earlier onset (<3 months of age) and more severe AE is associated with high milk, egg and/or peanut specific IgE. Patients that are allergic to dust mite, egg or peanuts are more likely to have persistent atopic eczema beyond 5 years of age. A high total serum IgE level is a strong risk factor for AE in children from birth to six years of age.

Infants and young children with atopic eczema are more commonly sensitized to foods (wheat and egg sensitization are most prevalent). Children over 5 years and adults are more commonly sensitized to aeroallergens (house dust mite sensitization is most prevalent).

INDIVIDUAL ALLERGENS ADD UP TO SYMPTOMS:

Identifying the obvious allergen is not always enough e.g., pollen during pollen season. Knowing all relevant allergens is a prerequisite for giving patients comprehensive allergen avoidance advice and thereby pushing the patient below the symptom threshold.

- Up to 80% of allergy patients are poly-sensitized, i.e., allergic to more than one allergen.
- The average primary care patient is sensitized to three, and often more, allergens.

**AN APPROACH TO ECZEMA AND DERMATITIS**

![Diagram of allergic sensitization and symptoms](image)
DIAGNOSIS

Elimination of food allergens in patients with AE and confirmed food allergy can lead to significant clinical improvement. Foods however should not be eliminated from the diet randomly without any clinical suspicion. Foods should only be excluded from the diet based upon positive skin or ImmunoCap® tests, backed up when necessary by an elimination challenge test or a double-blind placebo controlled food challenge.

DIAGNOSTIC TESTS

SKIN PRICKS TESTS
- Paediatric food panel including egg, milk, wheat, peanut and fish.
- If any of the above positive, consider component testing.
- Contact allergens including house dust mites, cats and dogs.
- In patients with allergic rhinitis and/or asthma, also test for the inhalant aeroallergens including pollens and moulds.

ImmunoCap® BLOOD TESTS
- Food mix, including egg, milk, wheat, peanut, fish.
- Other suspected foods.
- If any of the above positive, consider component testing (see chapter 3 on food allergy).
- Contact allergens including house dust mites, cats and dogs.
- In patients with allergic rhinitis and/or asthma, also test for the inhalant aeroallergens including pollens and moulds.

CAST TESTS

The flow-CAST uses flow cytometry to identify basophils, activated either directly or through specific IgE in the patient’s serum. These assays are useful for inhalant allergens, any suggestive food stuff, drug allergies, colourants and preservatives (an exacerbation of eczema can occur secondary to preservative intolerances e.g. sulphite or benzoate).

ATOPY PATCH TESTING

Atopy patch testing (APT) with food allergens and aeroallergens may be helpful, but is not routinely available. Atopy patch testing with common contact allergens can be useful for excluding a diagnosis of suspected allergic contact dermatitis.
**ORAL FOOD CHALLENGES**

If there is suggestive history and a strongly positive allergy test food challenge is not necessary. If there is a history of anaphylaxis after food ingestion, the particular food stuff should be avoided, regardless of the IgE levels. An oral challenge should be considered if the IgE levels are low or the history is unclear. This should be performed under medical supervision.

**ELIMINATION DIETS**

Elimination or exclusion diets can be used in patients with chronic symptoms or when there is a high index of suspicion of a food-related cause. An elimination diet should be tailored to the patient’s symptoms or the suspect foods and should usually only consist of a few foods being eliminated, commonly dairy or eggs. A dietician referral is recommended to assist with a nutritionally balanced elimination diet.

**ALLERGIC CONTACT DERMATITIS**

Contact dermatitis refers to inflammation of the dermis and epidermis upon contact with a substance. Contact dermatitis can be divided into two broad categories: irritant contact dermatitis, which is an immediate reaction and allergic contact dermatitis. Allergic contact dermatitis is a delayed reaction and requires recruitment of previously sensitized, antigen-specific T lymphocytes into the epidermis after absorption of antigen from the skin. The resulting localized dermatitis begins 12 to 24 hours after allergen exposure, peaks in three to five days and may last for up to a month.

Clinically, allergic contact dermatitis presents as a persistent, pruritic dermatitis, in an unusual pattern of distribution, mostly localized to the site of allergen contact. A more generalized dermatitis may develop a week or two later.

**DIAGNOSIS OF ALLERGIC CONTACT DERMATITIS**

**PATCH TESTING**

After a thorough clinical history, tiny quantities of selected allergens are applied to the back in individual square chambers. These are kept in place with hypoallergenic adhesive tape for 48 hours. Bathing of the back or vigorous exercise should be avoided. After 48 hours and 72/96 hours, the patch test is read. The result for each test site is recorded as negative, irritant reaction, equivocal, weak positive (non-vesicular), strong positive (edematous or vesicular) or extreme reaction (ulcerative or bullous). A punch biopsy may be taken for equivocal reactions if deemed necessary.

Prior to testing any oral corticosteroids or other immunosuppressive medications should be discontinued for at least a week. Steroid inhalers or antihistamines are not a contra-indication. Sunburn or sunlight exposure on the back should be avoided for at least a week, as it may suppress a positive reaction. Patch testing panels available at Ampath Allergy Clinics include: European baseline series, hairdressing series, cosmetic series and sunscreen series.

**MELISA TESTING**

MELISA tests are available for various metals and other substances, including nickel, gold, platinum, aluminum, mercury, latex, etc.
ECZEMA

USUAL DISTRIBUTION
INFANT: Pruritic, red scaly and crusty lesions on cheeks, scalp and exterior surfaces
CHILDREN AND ADULTS: Plaques in the flexure areas, especially antecubital and popliteal fossea, volar aspects of wrists, ankles and neck

FOOD ALLERGENS
• SPT/ImmunoCap® food mix (milk, egg, wheat, peanuts, cod) +

CONTACT ALLERGENS
• Pet allergens
• House dust mite
• Latex IgE (if exposed)

IF HISTORY OF ASTHMA/ALLERGIC RHINITIS
Also consider skin prick testing or IgE testing to inhalants including pollens and moulds

IF NEGATIVE
• Consider food challenge
• Consider different mechanism: CAST
  - foods
  - contact aero-allergens (pets, house dust mite)
  - latex
  - colourants and preservatives
MELISA
  - Foods
  - contact aero-allergens
  - metals

Consider other eczematous disorders
- Seborrheic dermatitis
- drug reactions
- Scabies
- Hyper IgE syndrome
- Wiscott Aldrich
- Nutritional Deficiency

UNUSUAL DISTRIBUTION

PATCH TESTING
- European baseline, cosmetic, hairdressing or sunscreen series.
MELISA TESTING
- Metals (i.e. gold, nickel, platinum, mercury)
- Latex

• Pet allergens
• House dust mite
• Latex IgE (if exposed)
AN APPROACH TO
URTICARIA AND ANGIOEDEMA

CHAPTER 5
URTICARIA AND URTICARIAL VASCUITIS

Urticaria is not a diagnosis, but merely symptom and sign in the skin caused by mediator release from mast cells; histamine in particular.

Urticaria is classified as acute when it lasts for less than 6 weeks and chronic if it lasts longer than 6 weeks. Most urticaria is idiopathic with no trigger factors identifiable and occurs in genetically susceptible individuals with “unstable” mast cells. When a trigger factor can be identified, it is usually an infection or allergy causing acute urticaria. Chronic urticaria may be triggered by autoimmunity, infections, hypersensitivity or allergy, physical or psychological factors or a combination of factors.

THE FOLLOWING DIAGRAM EXPLAINS THE DIFFERENT TRIGGERS OF CHRONIC URTICARIA:
AN APPROACH TO URTICARIA AND ANGIOEDEMA

WHY DO LABORATORY TESTING IN PATIENTS WITH CHRONIC URTICARIA?

- To identify underlying treatable medical conditions
- To help advise on prognosis (probability of resolution of symptoms)
- To advise on trigger avoidance
- Assistance with choice of medication

HOW SHOULD I APPROACH THE WORKUP OF A PATIENT PRESENTING WITH URTICARIA?

Firstly, take a good history, which should include details of all possible trigger factors and significant aspects regarding the appearance of the lesions. Decide whether the patient suffers from acute (< 6 weeks) or chronic urticaria (> 6 weeks).

Urticarial lesions consist of multiple blanching papules / wheals surrounded by erythema. Wheals differ in shape and size and may range from small to confluent. Each individual lesion lasts from minutes to hours (less than 24 hours usually), with new wheals appearing in other places. Urticaria is itchy, but not painful. This is a description of classical urticaria with no unusual features.

Suspicious features that may point to urticarial vasculitis are painful lesions lasting longer than 24 hours in the same spot with bruising or scarring after resolution. These patients also don’t respond to high doses of antihistamines and may have systemic symptoms.

Physical urticarias include dermatographism, cold urticaria, cholinergic urticaria, delayed pressure urticaria, solar urticaria, aquagenic urticaria and vibrational urticaria. This is mainly diagnosed on the history and physical provocation tests. These are some features of the lesions that may also help with the diagnosis, e.g:

- DERMATOGRAPHISM:
  Wheal and flare occurs only on area where skin is stroked or scratched with light to moderate pressure. Often seen under belts / elastics.
- CHOLINERGIC URTICARIA:
  Small pin-point wheals which may become confluent and are intensely itchy. They are elicited by generalized heat or exercise.
- DELAYED PRESSURE URTICARIA:
  Swelling may occur 2-6 hours after sustained pressure like standing / manual labour. Patients may experience a burning sensation and it may last for 24-72 hours.
- AQUAGENIC URTICARIA:
  Small pin-point wheals which may become confluent and are intensely itchy. They are elicited by skin contact with water of any temperature.
- VIBRATIONAL URTICARIA:
  Lesions appear within minutes after vibration and disappear within an hour.
THE FOLLOWING FLOW-DIAGRAMS ASSISTS WITH AN APPROACH TO ACUTE AND CHRONIC URTICARIA:

**ACUTE URTICARIA FLOW-DIAGRAM:**

**ACUTE URTICARIA**

**OBVIOUS REACTION TO FOOD/FOOD ADDITIVE**

- **YES**
  - Positive
    - SPT/Specific IgE
    - CAST
    - Avoidance
    - Consider Challenge
  - Negative
    - Recent drug?
    - Recent acute infection?
    - Underlying disease?

- **NO**
  - Drug allergy testing
  - Symptomatic treatment
  - Investigate and treat disease

- **TREAT SYMPTOMATICALLY.**
- **IF NO RESOLUTION, INVESTIGATE AS FOR CHRONIC URTICARIA.**

**CHRONIC URTICARIA FLOW-DIAGRAM:**

**CHRONIC URTICARIA**

- **HISTORY**
- **APPEARANCE OF LESIONS**

**NO UNUSUAL FEATURES**

- LABORATORY INVESTIGATES TO IDENTIFY UNDERLYING / TREATABLE MEDICAL CONDITIONS

**URTICARIAL VASCUITIS**

- **SKIN BIOPSY (HISTOLOGY)**
- **INVESTIGATIONS TO DETERMINE CAUSE**

**PHYSICAL URTICARIA**

- **IDENTIFY BY CHALLENGE TESTING**
- **IF COLD URTICARIA, DO CRYOGLOBULINS**
AN APPROACH TO URTICARIA AND ANGIOEDEMA

LABORATORY INVESTIGATIONS RECOMMENDED FOR CHRONIC URTICARIA WITH NO UNUSUAL FEATURES:
(look for underlying/treatable medical conditions)

- FBC and ESR (Look for eosinophilia or signs of infections).
- LFT (If raised consider looking for viral hepatitis: chronic Hepatitis B, Hepatitis C, CMV, EBV).
- HIV.
- Autoantibodies:
  - Thyroid antibodies.
  - Antinuclear antibody (ANA) and extractable nuclear antibody (ENA) screen.
  - IgE receptor autoantibodies (Autologous serum skin test - can be done at Ampath Allergy clinics).
- H. Pylori Antibodies.
- IgG, IgA, IgM, protein electrophoresis (older patients).
- Allergy testing only if history consistent with allergy.
- CAST testing – colourants, preservatives, aspirin (in patients with a positive history).
- Stool for parasites.
- If prominent angioedema, do C3, C4.

LABORATORY INVESTIGATIONS RECOMMENDED FOR URTICARIAL VASCULITIS:

- Skin biopsy for histology
- FBC and ESR
- CRP
- C3, C4
- C1q antibodies
- Functional complement
- Urinalysis
- ANA, ENA
- ANCA
- Tests for any other suspected underlying medical condition.
ANGIOEDEMA

Angioedema is deep tissue swelling, which should be distinguished from urticaria. Isolated angioedema is rarely itchy, as histamine is not usually involved in the pathogenesis. However, angioedema may occur in combination with urticaria, where it usually responds well to antihistamines.

Angioedema is caused by activation of the kinin system with bradikynin production, leading to tissue oedema. Patients experience discomfort or even pain due to pressure or swelling of any part of the body (including the gut). Patients often experience a premonitory tingling before swelling occurs. The main causes of angioedema are the following:

- Idiopathic
- Hereditary angioedema
  - HAE type 1 (+/- 85% of cases)
    - Low levels of C1 inhibitor due to gene deletion
  - HAE type 2 (+/- 15% of cases)
    - Normal / increased levels of C1 inhibitor; function abnormal due to gene mutation
  - HAE type 3
    - Unknown abnormality; C1 inhibitor levels and function normal
- Drugs: ACE Inhibitors, NSAIDS, statins, PPIs
- Allergic (accompanied by urticaria, anaphylaxis)
- Acquired C1 esterase deficiency (autoimmune or lymphoma associated)
- Physical (pressure, vibration, water – often with urticaria)
- ACE deficiency (causing slow breakdown of naturally produced bradikynin)

HOW SHOULD I APPROACH THE WORKUP OF A PATIENT WITH ANGIOEDEMA?

Firstly, take a good history, which should include family history, medical history, symptoms of connective tissue disease, drugs, relation to physical stimuli and any other trigger factors. If urticaria is prominent, investigate as urticaria, not angioedema. Angioedema with urticaria is not HAE, therefore HAE should not be investigated in these patients.

RECOMMENDED INVESTIGATIONS FOR ISOLATED ANGIOEDEMA:

<table>
<thead>
<tr>
<th>FAMILY HISTORY OR ONSET AT A YOUNG AGE</th>
<th>NO FAMILY HISTORY, LATER ONSET</th>
</tr>
</thead>
<tbody>
<tr>
<td>• C1 Inhibitor</td>
<td>• FBC and diff, ESR</td>
</tr>
<tr>
<td>• C4</td>
<td>• ANA, dsDNA, ENA</td>
</tr>
<tr>
<td></td>
<td>• C1q antibodies</td>
</tr>
<tr>
<td></td>
<td>• IgG.A.M, protein elektor phoresis</td>
</tr>
<tr>
<td></td>
<td>• B2 microglobin</td>
</tr>
<tr>
<td></td>
<td>• Urinary Bence-Jones protein</td>
</tr>
<tr>
<td></td>
<td>• Consider chest/abdominal CT</td>
</tr>
</tbody>
</table>
## AN APPROACH TO URTICARIA AND ANGIOEDEMA

### TABLE 1: COMPARISON OF THE SYMPTOMS, CAUSES AND RECOMMENDED INVESTIGATIONS FOR ACUTE URTICARIA, CHRONIC URTICARIA, URTICARIAL VASCULITIS AND ANGIOEDEMA:

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>ACUTE URTICARIA</th>
<th>CHRONIC URTICARIA</th>
<th>URTICARIAL VASCULITIS</th>
<th>ANGIOEDEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms &lt; 6 weeks</td>
<td>Multiple blanching papules / wheals surrounded by erythema. Wheals differ in shape and size and may range from small to confluent. Each individual lesion lasts from minutes to hours (less than 24 hours usually), with new wheals appearing in other places. Urticaria is itchy, but not painful.</td>
<td>Multiple blanching papules / wheals surrounded by erythema. Wheals differ in shape and size and may range from small to confluent. Each individual lesion lasts from minutes to hours (less than 24 hours usually), with new wheals appearing in other places. Urticaria is itchy, but not painful.</td>
<td>Painful lesions lasting longer than 24 hours in the same spot. Heals with bruising or scarring. Unresponsive to antihistamines. May have systemic symptoms.</td>
<td>Discomfort or even pain due to pressure or swelling (any part of the body, including the gut). Often a premonitory tingling. Isolated angioedema is rarely itchy</td>
</tr>
</tbody>
</table>

### MOST COMMON CAUSES

| ACE | NSAIDS |
| PPIs | Statins |
| Hereditary Angioedema | ACE deficiency |
| Acquired C1 esterase deficiency | Autoimmune or lymphoma associated |
| Allergic | accompanied by urticaria, anaphylaxis |
| Physical | pressure, vibration, water – often with urticaria |

| Infections, especially viral | Allergic reactions, e.g. food, drugs, preservatives. |
| Auto-immune: | |
| IgE receptor antibodies | Connective tissue diseases |
| Thyroid antibodies | |
| Infections: | |
| HIV | Chronic infections |
| Blastocystis | H. Pylori |
| Other parasites | Fungal |
| Malignancies: | Especially lymphoproliferative diseases |
| Allergies: | Drugs, colourants and preservatives. rarely foods. |
| Physical stimuli: | Heat, cold, vibration, cholinergic, pressure |
| Psychological: | Stress |

| Autoimmune: | Connective tissue diseases |
| Autoantibodies to C1q |

| Drug reactions |
| Complement disorders |

| Malignancies | lymphoproliferative syndromes. |
### LABORATORY INVESTIGATIONS

-MAY INCLUDE THE FOLLOWING BASED ON HISTORY-

<table>
<thead>
<tr>
<th>ACUTE URTICARIA</th>
<th>CHRONIC URTICARIA</th>
<th>URTICARIAL VASCULITIS</th>
<th>ANGIOEDEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specific allergy testing, unless a prominent history of reactions within 2 hours of allergen exposure - test for the specific allergen.</td>
<td>FBC, diff and ESR</td>
<td>Skin biopsy</td>
<td>FBC, diff and ESR</td>
</tr>
<tr>
<td>If symptoms &gt; 6 weeks, test as for chronic urticaria.</td>
<td>LFT's (if raised do Hepatitis B and C, EBV and CMV antibodies)</td>
<td>FBC, diff and ESR</td>
<td>C4, C1q antibodies</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>CRP</td>
<td>C1 inhibitor</td>
</tr>
<tr>
<td></td>
<td>Thyroid antibodies</td>
<td></td>
<td>ANA, dsDNA, ENA</td>
</tr>
<tr>
<td></td>
<td>ANA, ENA</td>
<td></td>
<td>IgG, A, M, protein electrophoresis</td>
</tr>
<tr>
<td></td>
<td>H. Pylori Antibodies</td>
<td></td>
<td>B2 microglobulin</td>
</tr>
<tr>
<td></td>
<td>IgG, IgA, IgM, protein electrophoresis</td>
<td></td>
<td>Urinary Bence-Jones protein</td>
</tr>
<tr>
<td></td>
<td>IgE mediated allergy testing only if history consistent with allergy</td>
<td></td>
<td>Exclude lymphoma by examination and radiology</td>
</tr>
<tr>
<td></td>
<td>CAST testing – colourants, preservatives, aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If prominent angioedema do C3, C4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stool for parasites</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autologous serum skin test - can be done at Ampath Allergy clinics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Anaphylaxis is the most severe type of allergic reaction and is a medical emergency. Anaphylaxis is an unpredictable condition which may affect patients with known allergies who have one or more allergic reactions previously, or affect individuals that have never even been aware that they have an allergy. Even the first episode of anaphylaxis may be fatal.

The pathogenesis of anaphylaxis is based on a sudden, massive degranulation of mast cells which may be IgE mediated or non-IgE mediated (anaphylactoid reactions).

**SYMPTOMS:**

The most common symptoms of anaphylaxis are urticaria, angioedema, flushing, respiratory symptoms like tightness of the chest, wheezing or difficulty breathing, lightheadedness, dizziness, blurred vision, hypotension and loss of consciousness. Nausea, vomiting, abdominal cramps and diarrhoea are also often reported. Patients describe feelings of anxiety, confusion and a sense of impending doom.

**ANAPHYLAXIS TRIGGERS:**

Any substance may cause anaphylaxis, but the most common causes are as follows:

- **Venoms:**
  - Bee and wasp stings

- **Foods:**
  - Nuts, seeds and legumes (storage proteins)
  - Shellfish and fish
  - Egg
  - Milk
  - Any foods, including fruit, vegetables and additives

- **Drugs (any drug):**
  - Antibiotics, e.g. penicillin, cephalosporins, quinolones
  - Radiocontrast media
  - Analgesics
  - Anaesthetic agents, especially muscle relaxants

- **Biologicals:**
  - Antivenoms
  - Monoclonal antibodies
  - Peptide hormones

- **Allergen immunotherapy:** particularly to bee venom

- **Latex**
Excercise induced: either by itself, after food ingestion (especially wheat – Ω 5-gliadin or LTP allergy) or after ingestion of another co-factor (e.g. alcohol or NSAIDS)

- Airborne allergens, e.g. animal danders
- Mastocytosis
- Ideopathic anaphylaxis

TRIGGERS OF ANAPHYLACTOID REACTIONS:

- Direct mast-cell stimulation: drugs (opiates, vancomycin, radiocontrast media, anaesthetic agents, NSAIDS)
- Immune complex reactions with release of anaphylotoxins (C3a, C5a), e.g. reactions to blood products, antivenoms, etc.
- Massive histamine ingestion – spoiled fish (scromboid poisoning)
- Other immune mechanisms to allergens

DIAGNOSIS:

History is all important. The diagnosis of anaphylaxis is based on symptoms that occur within minutes to a few hours after exposure to a potential trigger, such as a food, medication or insect stings. Confirmation of anaphylaxis can be obtained by taking blood for mast-cell tryptase between 30 min and 4 hours after the reaction. Levels may still be raised up to 12 hours after the reaction. This is especially valuable for reactions under anaesthetics. Please remember to do a baseline tryptase after 24 hours to exclude mastocytosis (permanently raised tryptase levels). Tryptase is elevated in both anaphylactic and anaphylactoid reactions. Evidence should also be sought for the activation of complement (C3, C4).

Please note that the best time to investigate the specific trigger of anaphylaxis is 2-3 weeks after the event, as ImmunoCap® IgE may be false-negative in the acute phase due to consumption of IgE. CAST tests should also not be performed in the acute phase, as basophils usually have high background activation immediately after a severe allergic reaction.

TABLE FOR SUGGESTED TESTS FOR ANAPHYLAXIS:

<table>
<thead>
<tr>
<th>IMMEDIATE TESTS</th>
<th>LATER TESTS (AFTER 2-3 WEEKS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cell tryptase</td>
<td>Repeat baseline mast cell tryptase</td>
</tr>
<tr>
<td>C3, C4</td>
<td>Specific ImmunoCap® IgE / CAST tests for suspected allergens. (Risk for reactions, therefore SPT is not recommended)</td>
</tr>
<tr>
<td></td>
<td>- Food</td>
</tr>
<tr>
<td></td>
<td>- Drugs</td>
</tr>
<tr>
<td></td>
<td>- Venoms</td>
</tr>
<tr>
<td></td>
<td>- Latex</td>
</tr>
<tr>
<td></td>
<td>- ? Other allergens depending on history</td>
</tr>
</tbody>
</table>
ALGORITHM FOR THE TREATMENT OF SEVERE ANAPHYLACTIC REACTIONS

TREATMENT OF SEVERE ANAPHYLACTIC REACTIONS (ADULT AND CHILD)

ACUTE RESPIRATORY DIFFICULTY (Progressive Swelling, Stridor, wheeze, distress)
SIGNS OF SHOCK/HYPOTENSION (especially if skin changes are present)

ADRENALINE (1mg/ml 1:1000)
- > 12 yrs – 0.5 ml IM
- 6 -12 yrs – 0.3 ml IM
- < 6 yrs – 0.15 ml IM
Repeat every 5-15 minutes if no improvement

OXYGEN – MONITORS – IV ACCESS
- High flow oxygen
- Maintain patent airway (Intubate / Cricothyrotomy if necessary)
- BP, Sats, ECG monitoring
- High flow IV line

PROMETHAZINE (Antihistamine)
- > 12 yrs – 25 mg IM or slow IV
- 6-12 yrs – 12.5 mg IM or slow IV
- 2-6 yrs – 6.25 mg IM or slow IV
(Avoid if <2 yrs old)

CRYSTALLOID (e.g. Ringers lactate)
- Rapid infusion of 1-2 litres (20 ml/kg for children)
- if no response to adrenaline,
- Repeat IV infusion as necessary, as large amounts may be required
- Adrenaline infusion (0.1 – 1 ug/kg/min) ONLY if unresponsive to IM adrenaline and fluids

H₂ RECEPTOR ANTAGONIST (Ranitidine)
- Adult- 50mg IM or slow IV (diluted in 20 ml over 2 min)
- Child – 1mg/kg (max 50 mg)
OR CIMETIDINE
- Adult – 300 mg IM or slow IV (diluted in 20ml over 2 min)
- Child – 5 mg/kg (max 300 mg)

CRystalloid (e.g. Ringers lactate)
- Rapid infusion of 1-2 litres (20 ml/kg for children)
- if no response to adrenaline,
- Repeat IV infusion as necessary, as large amounts may be required
- Adrenaline infusion (0.1 – 1 ug/kg/min) ONLY if unresponsive to IM adrenaline and fluids

GLUCAGON
- Adult- 1-2 mg IM or slow IV every 5 min if unresponsive to adrenaline, and especially if on beta blockers.
- Child - 20μg/kg (max 1 mg) (watch out for vomiting and hyperglycaemia)

NEBULISED BRONCHODILATORS
(if severe bronchospasm, and especially if on beta blockers)
SALBUTAMOL
- > 6 yrs - 5 mg every 15-20 mins
- < 6 yrs - 2.5 mg every 15-20 mins
WITH IPRATROPIUM
- > 6 yrs - 0.5 mg every 15-20 mins
- < 6 yrs - 0.25 mg every 15-20 mins

HYDROCORTISONE (steroid)
- >12 yrs – 200 mg IM or slow IV
- 6-12 yrs – 100 mg IM or slow IV
- 1-6 yrs – 50mg IM or slow IV
- >1 yr - 25mg or slow IV

CRYSTALLOID (e.g. Ringers lactate)
- Rapid infusion of 1-2 litres (20 ml/kg for children)
- if no response to adrenaline,
- Repeat IV infusion as necessary, as large amounts may be required
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- Adult- 1-2 mg IM or slow IV every 5 min if unresponsive to adrenaline, and especially if on beta blockers.
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- >12 yrs – 200 mg IM or slow IV
- 6-12 yrs – 100 mg IM or slow IV
- 1-6 yrs – 50mg IM or slow IV
- >1 yr - 25mg or slow IV

Resuscitation Council of South Africa
Fig 1 - Current Allergy & Clinical Immunology, November 2011 vol 23, No. 4
Many patients experience adverse reactions to drugs, but most of these are predictable, dose dependant and don’t involve the immune system. These include side-effects, drug interactions and toxic effects due to overdosing. Some patients may also be very sensitive to the normal pharmacological effect of a drug or have a genetic or enzyme deficiency affecting the metabolism of certain drugs.

Drug allergy is an immunologically mediated reaction that is specific to a particular drug and reoccurs on subsequent exposure to that drug. Many different immunological mechanisms may be involved, including IgE, basophils, cytotoxic / complement mediated, immune complexes and T-cell mediated reactions. The World Allergy Organization (WAO) has recommended categorizing immunologic drug reactions upon the timing of the appearance of symptoms.

**IMMEDIATE REACTIONS:**
- IgE-mediated (Gell and Coombs type I) reactions, which account for many immediate reactions.
- May also be basophil-mediated reactions.
- On re-exposure; potential risk of life-threatening anaphylaxis.
- Classically symptoms begin within one hour of the first administered dose and may begin within minutes.
- Some IgE-mediated reactions may only appear after one hour:
  - Especially if administered orally, when taken with food or enterically coated drugs.
  - On first time allergic sensitization – initial symptoms may appear only later in the first course of treatment.
- Symptoms include: pruritus, flushing, urticaria, angioedema, wheezing, laryngeal oedema, abdominal distress with emesis or diarrhoea and hypotension.

**DELAYED TYPE REACTIONS:**
- Basophil-mediated reactions and may also present as delayed type hypersensitivity reactions.
- Delayed type reactions often appear after multiple doses of treatment, typically after days or weeks of administration.
- Cytotoxic, complement mediated reactions present as auto-immune haemolytic anemia, thrombocytopaenia and interstitial nephritis.
- Immune complex mediated reactions present as serum sickness or vasculitis.
- T-cell mediated reactions mainly present as maculopapular rashes or contact dermatitis.

**HOW DO I DIAGNOSE A DRUG ALLERGY?**

The starting point in the diagnosis of drug allergy is obtaining a detailed history of the event, including the onset of symptoms and signs and their timing in relation to drug exposure. When taking a history, try and answer the following questions:
- Is it a drug allergy or another type of adverse drug reaction?
- Is it an immediate or delayed reaction?
- What mechanism of allergy is probably involved?
- What is the eliciting drug? (important in patients taking multiple drugs – some drugs are more allergenic than others)

The aim is to establish or disprove a causal relationship between the drug and the patient’s reaction.

Please remember to correlate all results with your clinical history. If the diagnosis of drug allergy is confirmed, it is important to identify a safe alternative. If no alternative can be found and the patient needs the drug, in-patient drug desensitization can be done. There are many different protocols available for desensitization to different drug classes.
AN APPROACH TO DRUG ALLERGY DIAGNOSIS - MADE EASY WITH A FLOW DIAGRAM

HISTORY COMPATIBLE WITH DRUG ALLERGY

TIMING OF REACTION

IMMEDIATE
- ImmunoCap® CAST
  - NEG
  - POS
    - REFER TO SPECIALIST

- SPT DRUG INTRA-DERMAL TEST
  - NEG
  - POS
    - DRUG IMPORTANT? PROVOCATION POSSIBLE?
      - NO
        - DRUG PROVOCATION
          - NEG
            - NO AVOIDANCE
          - POS
            - NO AVOIDANCE
      - YES
        - DRUG PROVOCATION
          - POS
            - NO AVOIDANCE
          - NEG
            - NO AVOIDANCE

DELAYED
- CAST MELISA
  - NEG
  - POS
    - REFER TO SPECIALIST

- SPT DRUG PATCH TEST INTRA-DERMAL TEST
  - NEG
  - POS
    - DRUG IMPORTANT? PROVOCATION POSSIBLE?
      - NO
        - DRUG PROVOCATION
          - POS
            - NO AVOIDANCE
          - NEG
            - NO AVOIDANCE
      - YES
        - DRUG PROVOCATION
          - POS
            - NO AVOIDANCE
          - NEG
            - NO AVOIDANCE

DRUG ALLERGY CONFIRMED
- AVOID
- EDUCATE
- IDENTIFY SAFE ALTERNATIVE
ANTIBIOTIC ALLERGY IN A NUTSHELL:

1. PENICILLIN ALLERGY

Penicillin is the most commonly reported medication allergy. Although 5-10% of the general population self-report a penicillin allergy, approximately 85% of these patients are able to tolerate penicillin. The incidence of anaphylaxis after taking penicillin varies between one and four episodes per 10,000 administrations.

1.1 CROSS-REACTIVITY BETWEEN DIFFERENT PENICILLINS:

- Allergic reactions usually occur to the core ring structure that is common to all penicillins, or, much less commonly, to an epitope which includes the R-group side chains.
- Penicillins spontaneously degrade to reactive intermediates under physiologic conditions. 95% of penicillin degrades to the penicilloyl moiety, the “major antigenic determinant”. The remainder is degraded to Penicilloate and penilloate and are called “minor antigenic determinants.”
- Some patients may have side-chain specific reactions to aminopenicillins (amoxicillin and ampicillin), but be able to tolerate other penicillins.
- Patients who react to the combination of amoxicillin-clavulanate may be allergic to clavulanate and not the amoxicillin.
- When testing patients for a penicillin allergy, patients should be tested to the penicillin ring, major and minor determinants. When a reaction to aminopenicillins is suspected, the patient should also be tested to the amoxicillin / ampicillin side chain / clavulanate depending on the drug suspected of causing a reaction.
1.2 CROSS-REACTIVITY WITH OTHER BETA-LACTAMS:

- Approximately 2 – 5% of patients with proven sensitivity to penicillin can be expected to react to cephalosporins.
- A beta-lactam ring is also found in cephalosporins, carbapenems, and monobactams.
- The aminopenicillins amoxicillin and ampicillin each have R-group side chains that are identical to the side chains of certain cephalosporins. These R group side chains are believed to be most important in predicting cross-reactivity between aminopenicillins and cephalosporins.
- Carbapenems like imipenem, meropenem, doripenem and ertapenem share a common beta-lactam ring with penicillins, but 99% of patients with penicillin allergy will be able to tolerate carbapenems.
- There is no cross-reactivity between penicillin and monobactams like aztreonam.

<table>
<thead>
<tr>
<th>PRIMARY ALLERGY</th>
<th>SIMILAR SIDE-CHAIN WITH POTENTIAL CROSS-REACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pen G</td>
<td>Cefamandole, cefaloram, cephalotin, cephaloridine</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Cefaclor, cephaloxin, cephradine, lorbacef</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>Cephadroxil, Cefprozil, Cefatrizine</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Ceftazidime</td>
</tr>
</tbody>
</table>

2. SULFONAMIDE ALLERGY

Sulfonamide-containing antibiotics are the second most frequent cause of allergic drug reactions after the beta-lactams. The incidence of reactions to trimethoprim-sulfamethoxazole (TMP-SMX) is approximately 34 per 1000 patients exposed. Sulfonamides can be divided into two distinct groups based on chemical structure as well as clinical use – antimicrobial sulphonamides, which includes sulfamethoxazole (in TMP-SMX) and non-antimicrobial sulphonamides. There is minimal evidence of cross-reactivity between sulfonamide antimicrobials and non-antimicrobials, but information is based upon observational studies.

3. QUINOLONE ALLERGY

Quinolones are a group of broad-spectrum synthetic antibiotics with structural similarity suggesting frequent cross-reactivity. Some of the more frequently used quinolones are ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, gemifloxacin and norfloxacin. The prevalence of quinolone allergy is uncertain, but is reported to be approximately 4% of antibiotic allergy reactions. Strict avoidance of all quinolones is advisable in patients with quinolone allergy.

4. MACROLIDES

Macrolides are characterised by a basic structure made up of a lactonic cycle with 2 osidic chains. They are classified according to the number of carbon atoms in the cycle: 14-membered (erythromycin, roxithromycin, clarithromycin), 15-membered (azithromycin) and 16-membered (spiramycin). Macrolides are generally well tolerated and are considered to be the safest antibiotics in use from an allergy perspective. Adverse reactions are much more common than allergic reactions. Management is based on avoidance of the single causal macrolide, as cross-reactivity isn’t common. If doubt exists, we suggest that the patient be tested with the macrolide of choice before administering an alternative.
CHAPTER 8
AN APPROACH TO ALLERGEN IMMUNOTHERAPY
Allergen specific immunotherapy (SIT) is a process where a state of tolerance to a specific allergen is induced with the administration of gradually increasing doses of the allergen. This process is also known as allergy desensitization and represents a unique modality of treatment for allergies.

The benefits are twofold:
- SIT acts as symptomatic treatment
- SIT is unique in the sense that it acts as a biological response modifier and this changes profoundly and specifically the immunological response to allergens

**MECHANISM**

Immunotherapy induces T-regulatory (Treg) cells which in turn mediates T cell tolerance, opposing the Th2 T cell predominance observed in allergic disease. Induction of T-regulatory cells has the following effects (see figure 1), mainly effected by the cytokines TGF and IL-10:

**FIG 1: MECHANISM OF IMMUNOTHERAPY, MAINLY EFFECTED BY INDUCTION OF T REGULATORY CELL CYTOLINES, IL-10 AND IGF-B**

- B cells class switch to production of allergen specific IgG4 antibodies, which has a blocking effect. IgG4 is thought to capture the allergen before it reaches the effector cell-bound IgE. Increase in specific IgG4 levels accompany clinical improvement.
- Reduced production of allergen specific IgE antibodies.
- Direct and indirect suppressive action on the effector cells, including mast cells, basophils and eosinophils.
- Suppression of Th2 cell homing to tissue.
- Suppression of epithelial activation with less subsequent mucus production.
- Direct suppression of Th2 cells.
ADMINISTRATION ROUTES

There are currently two modes of administration, namely subcutaneous injection therapy and sublingual immunotherapy.

INJECTION IMMUNOTHERAPY

Injection immunotherapy involves the administration of subcutaneous injections of increasing doses (starting with a low dose) of the allergen extract. This is administered into the upper outer aspect of the arm in the subcutaneous tissues and not over the deltoid muscle. Initially the extracts are injected once a week until the maintenance dose level is achieved, usually after 13-14 weeks. Subsequently a maintenance dose is administered every four to six weeks for a period of three to five years (depending on the allergen). Allergen extracts have to be kept between 4 and 8°C in a refrigerator.

A number of precautions are advised for injection immunotherapy:

- Treatment should only be provided by a practitioner trained in the technique in a setting where emergency care can be provided.
- Be prepared to treat an anaphylactic reaction.
- Always have adrenaline drawn up.
- Check the patient’s name and double check the allergen.
- To ensure that injection is not administered directly into a blood vessel one should always draw back on the syringe.
- Do not give injection if the patient is wheezing, has a cold or is febrile.
- Record the patient’s pulse, blood pressure and peak flow before and after (at 30 min) giving the injection.
- The patient should avoid hot baths, exercise and alcohol for 6 hours after the injection.

REACTIONS TO INJECTED VACCINES

WARNING SIGNS

- Dizziness
- Sudden onset of nasal stuffiness
- Generalised itching
- Feeling of impending doom
- Itching of the throat, palms, soles
- Repeated clearing of throat
- Wheezing or coughing
- Sudden quietness in a normally lively child

REACTIONS SHOULD BE TREATED IMMEDIATELY

- Administer adrenalin.
- Be prepared to give antihistamine, bronchodilator, corticosteroids, oxygen and to set up an intravenous infusion.
AN APPROACH TO ALLERGEN IMMUNOTHERAPY

SUBLINGUAL IMMUNOTHERAPY

Sublingual immunotherapy has gained wide acceptance in many countries and has raised the interest in immunotherapy among generalists and allergists. This mode of administration has been proven to be an excellent alternative to subcutaneous immunotherapy, as published in the WAO position paper in 1998. Sublingual immunotherapy is administered by the patient at home and has been demonstrated to be very safe. Patients seldom experience side effects and then it is usually limited to the oral cavity, e.g. itching of the mouth. This form of immunotherapy represents a treatment modality that can be used beyond a specialised allergy centre.

Sublingual immunotherapy involves the daily administration of incremental amounts of a purified allergen. The drops are held under the tongue for two minutes and then swallowed. Doses are increased over a four week period to reach a maintenance dose and are then subsequently administered daily as a maintenance dose for a three year period. Sublingual immunotherapy is available as drops. This form of immunotherapy is not available for bee/wasp venom.

EFFECTICITY OF SPECIFIC IMMUNOTHERAPY

The efficacy of specific immunotherapy is most often evaluated by symptom scores and medication consumption.

EFFECTICITY ON RHINOCONJUNCTIVITIS:

Both sublingual and subcutaneous immunotherapy has been shown in large clinical trials to be effective on symptom and medication scores in patients with an inhalant allergy.

EFFECTICITY ON ALLERGIC ASTHMA:

A meta-analysis of 75 trials with subcutaneous SIT demonstrated efficacy on clinical symptoms, specific and non-specific bronchial hyper-responsiveness and medication consumption. Sublingual immunotherapy has been associated with reduced asthma symptoms, bronchial hyper-responsiveness, medication consumption reduction and FEV1 improvement. This efficacy persisted after 6 and 12 years in the treated group.

The risk of the later development of asthma in patients desensitized for allergic rhinitis has also been shown to be reduced.

The failure to produce allergen-specific IgG4 in an individual patient receiving immunotherapy does predict a lack of clinical response. It may therefore be of value to determine allergen specific IgE/IgG4 ratios prior to the start of SIT, with a repeat of these investigations one year later. If a change in this ratio cannot be demonstrated in a patient that does not appear to improve clinically, SIT should be discontinued.

INDICATIONS

The patient is only a candidate for SIT if it has been established that allergen sensitization, as demonstrated with SPT or serum specific IgE to a specific allergen is truly responsible for the patient’s symptoms. Patients with primary sensitization to allergen specific components have a better outcome of treatment as compared to patients sensitized only to cross-reactive components. SIT is not available for food allergens.
CLINICAL RELEVANCE IS ESTABLISHED BY THE PRESENCE OF BOTH OF THE FOLLOWING:

Symptoms upon natural exposure to the allergen
+
The presence of an IgE-mediated disease needs to be confirmed by a positive skin test and/or serum-specific IgE to the specific allergen

- Ideally component testing should be used to demonstrate that the patient is sensitized to the main vaccine components.

The indications for immunotherapy with aeroallergens:
- Seasonal +/- perennial allergic rhinitis/conjunctivitis
- Seasonal allergic asthma
- Allergic rhinitis + allergic asthma
- Patients with both asthma and allergic rhinitis derive particular benefit.
- Atopic dermatitis may respond to SIT if the patient is sensitized to inhalant allergens.
- Any patient with the above demonstrated may be a candidate for SIT, especially if they seek a long term solution for their allergic disease.
- Patients with an inadequate or partial response to environmental control and pharmacotherapy.
- Persistent symptoms on a seasonal and/or perennial basis.
- Side effects related to medication use.
- Cost burden associated with chronic medication use.
- Non-compliance with maintenance medication regimen.
- SIT can be administered to both adults and children and there are no defined age limits for its administration. It is preferable that children be able to understand regular injections for Subcutaneous Immunotherapy and mandatory that children can perform peak flow testing. Sublingual Immunotherapy can be started at a very young age, and it is actually more beneficial for the younger patient, as this may halt progression of allergic disease.

The following are contra-indications for SIT:
- Severe/uncontrolled asthma.
- Patients requiring beta-blockers.
- Patients with autoimmune disease or immunodeficiency.
- Starting immunotherapy with inhalant allergens during known pregnancy.
- Ischaemic heart disease, arrhythmias and other cardiac defects.
- Drugs, including immunosuppressants, beta-blockers.
- Psychiatric disease.
AN APPROACH TO ALLERGEN IMMUNOTHERAPY

MAKING AN ACCURATE DIAGNOSIS TO SELECT APPROPRIATE IMMUNOTHERAPY VACCINES

The success of allergen immunotherapy is dependent on appropriate patient and specific immunotherapy vaccine selection. It is therefore of the utmost importance to diagnose the patient’s allergy correctly. Some allergens are specific for the allergen source, whereas others are cross-reactive allergens of various unrelated allergen sources, therefore allergens need to be clearly identified. It is often difficult or even impossible to identify the disease-causing allergen in patients who are poly-sensitized. Demonstration of sensitisation to the actual component of the allergen that is present in the vaccine is essential for an accurate prescription of allergen-specific immunotherapy (SIT).

COMPONENT TESTING IS USEFUL TO DETERMINE THE PRIMARY SENSITIZER AND LIKELIHOOD OF SUCCESSFUL IMMUNOTHERAPY:

1. ANIMAL IMMUNOTHERAPY

Cross-reactions occur commonly between furry animals, therefore the primary sensitiser should be identified before choosing appropriate allergen immunotherapy. Cat uteroglobin (Fel d 1) is the major cat allergen component indicating primary sensitization to cat and can be used as a specific marker that cat allergen immunotherapy is likely to be of clinical value. Cat Fel d 2 (cat serum albumin) is likely to cross-react with most other mammalian albumins and Fel d 4, a lipocalin, with horse, dog and cow, therefore sensitization to these components should not be used as motivation for allergen immunotherapy. The dog allergens Can f 1 and Can f 2 are lipocalins and are associated with primary sensitization to dog. Can f 1 can be used as a specific marker indicating likelihood of successful allergen immunotherapy to dog. Can f 5, a prostatic allergen secreted by male dogs only, is also an indicator of primary sensitisation to male dogs, but is not represented in immunotherapy vaccines. Equ c 1, a horse lipocalin, is the major allergen in horse dander, but results should be interpreted in correlation with the clinical history, as there is some cross-reactivity with mouse and cat lipocalin.

2. POLLEN IMMUNOTHERAPY

Specific markers indicating the likelihood of success of grass pollen immunotherapy is Cyn d 1 or grass group 1 allergen for Bermuda grass allergy and Phi p 1 (grass group 1) and Phi p 5 (grass group 5) for Timothy grass allergy. There is a lot of similarity between the group 1 and group 5 grass pollen allergen components in other grass species, especially those belonging to the Pooidae subfamily, e.g. Rye grass. Patients sensitized to Phi p 1 only and not to any of the other allergen components in Timothy grass, is probably sensitized to Bermuda grass and/or Maize pollen and not to Timothy or Rye grass. This is relevant, as separate immunotherapy to maize pollen is recommended for patients sensitized to both grass and maize pollens.

3. HOUSE DUST MITE IMMUNOTHERAPY

Component testing can be used to diagnose a true single sensitization to pyroglyphidea mites (D. farinae, D. pteronyssinus) or Lepidoglyphus destructor/Blomia tropicalis as opposed to double sensitization. If true double sensitisation is present, immunotherapy to both is indicated, as Blomia tropicalis does not form part of house dust mite vaccines. If a positive skin prick test to mites is present, the determination of markers of specific sensitization to the different groups of mites is recommended.

4. BEE/WASP VENOM IMMUNOTHERAPY

Allergen components can be of value in selecting patients for bee venom immunotherapy. Patients frequently test positive to both bee and wasp venom. This may be due to CCD cross-reactivity or dual sensitization. Honeybee phospholipase A2 (Api m 1) can be used to indicate a true honeybee allergy and wasp phospholipase A1 (Ves v 1) and wasp antigen 5 (Ves v 5) to indicate true wasp allergy. This information can be used to select patients for bee venom immunotherapy, wasp immunotherapy, or both.
BEE VENOM IMMUNOTHERAPY (VIT)

Immunotherapy for venom allergy has been available for over 30 years. Bee stings can result in life-threatening anaphylaxis and the most severe reactions do not always respond to single or multiple doses of adrenaline. The risk of a systemic reaction to a subsequent sting is approximately 30 to 60 percent when VIT is not administered. This has been shown to be highly effective in adult patients with past systemic reactions and evidence of venom specific IgE.

Children (under 17 years of age) with symptoms limited to the skin (urticaria and/or angioedema) have about a 10 percent chance of a future systemic reaction. Most of these reactions will also be limited to the skin.

EFFECTIVENESS OF VENOM IMMUNOTHERAPY (VIT)

Venom immunotherapy is the most effective form of immunotherapy currently in use and protection from recurrent systemic allergic reactions appears to be established within a week of reaching maintenance doses and improves further with time. After completing a course of VIT, the risk of systemic reaction is reduced to 5 percent or lower. The few patients who do have recurrent systemic reactions, have much milder symptoms. VIT improves quality of life; it reduces anxiety and allows patients to participate in the outdoor activities that they prefer. Quality of life is not improved by avoidance and having self-administered adrenaline available.

INDICATIONS AND PATIENT SELECTION FOR VIT

- Reliable history of a systemic allergic reaction to an insect sting
- Elevated serum levels of venom-specific IgE

VACCINES AVAILABLE IN SOUTH AFRICA FOR IMMUNOTHERAPY

- ALK-Alutard.
- Stallergenes vaccines.
- Albey Bee Venom Vaccines.
- Vaccines are still not registered and permission must be obtained from the Medicines Control Council (MCC) on a named patient basis for each vaccine given to the patient. Assistance with MCC approval is given by the vaccine distributors in South Africa.
AN APPROACH TO
THE ALLERGIC PATIENT
<table>
<thead>
<tr>
<th>SYMPTOMS/HISTORY</th>
<th>CONSIDERATIONS</th>
<th>TESTING</th>
</tr>
</thead>
</table>
| **ASTHMA/RHINITIS/CONJUNCTIVITIS:**  
ASTHMA: Wheeze, tight chest, early morning cough.  
RHINO-CONJUNCTIVITIS: hayfever, postnasal drip, blocked nose, runny nose, itchy eyes, ears or throat. | • Seasonality of symptoms:  
- Perennial  
- Seasonal (aggravation in Spring) | All patients:  
• Phadiatop + breakdown if positive or  
- SPT: inhalant profile  
• Test for tree pollens (tree mixes or individual IgE) if seasonal symptoms |
|  | • Geographic: where does patient live? | Add the following:  
Western Cape: Epicoccum, Cockroach  
KZN: Cockroach  
FS, Highveld, NW: Maize pollen, eucalyptus. |
|  | • Consider other mechanism/disease  
- Basophil mediated  
- Vasomotor rhinitis  
- Eosinophilic Rhinitis | If negative, do:  
-CAST inhalant screen + breakdown if positive  
- Nasal mucus for eosinophils |
| **FOOD ALLERGY/GIT SYMPTOMS:**  
**ORAL ALLERGY SYNDROME (OAS):**  
Symptoms localised to oral cavity. Itching, tingling or swelling of the lips, tongue or mouth. |  |  |
| **GASTRO-INTESTINAL SYMPTOMS:** diarrhoea, bloating, abdominal discomfort, nausea, vomiting. | CONSIDER POLLEN-FOOD CROSS-REACTIVITY.  
Immediate Onset:  
• IgE/ basophil mediated  
Delayed onset:  
• Basophil mediated  
• T-cell mediated/ cellular  
• Eosinophilic  
• Other immunological disease, e.g. coeliac’s.  
• Enzymatic deficiencies | • Test for pollen allergy.  
• Test for pollen allergen cross-reactive components:  
- Profilin  
- PR-10  
- LTP  
- CCD  
• Food mix IgE with breakdown if positive  
• Specific Immuno Cap.  
If positive, do main allergen components.  
• Food mix CAST, CAST colourants + preservatives.  
• MELISA (foods)  
• Intestinal biopsy  
• TTG IgA, Endomysial IgA, deaminated gliadin IgA, total IgA, HLA DQ2/DQ8  
• Stool for reducing substances, H-breath test |
| **ECZEMA/ SKIN RASH:**  
ECZEMA: Itchy, dry skin and history of involvement of the skin creases. Flexural involvement in adults and involvement of cheeks, forehead and outer aspects of limbs in infants/young children.  
CONTACT DERMATITIS: Persistent, itchy rash in an unusual pattern of distribution, usually localised to the site of allergen contact. | • Patient has an intrinsic/genetic defect in skin barrier  
• In atopic patients, exposure to allergens (food allergens or contact with aeroallergens) cause symptom flares. | • Food allergen IgE screen.  
• Contact with aeroallergens, e.g. house dust mite, animal danders. Suggest Phadiatop inhalant screen + breakdown if positive if concomitant respiratory symptoms.  
• CAST (foods, inhalants, preservatives, drugs etc).  
• Patch test (e.g. European baseline, Cosmetic, hairdressing, sunscreen series).  
• MELISA tests (e.g. nickel, latex etc) |
# AN APPROACH TO THE ALLERGIC PATIENT

**SYMPTOMS/HISTORY**

<table>
<thead>
<tr>
<th>URTICARIA/ ANGIOEDEMA:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria: Multiple blanching papules/ wheals surrounded by erythema. Lesions are itchy and last &lt;24 hours on a single site.</td>
</tr>
</tbody>
</table>

**CONSIDERATIONS**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks (acute)</td>
<td>- Drug?</td>
</tr>
<tr>
<td>&gt;6 weeks (chronic)</td>
<td>- Food?</td>
</tr>
<tr>
<td>- ? Infection</td>
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</table>

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<tbody>
<tr>
<td>&gt;24 hours, heals with bruising or scarring.</td>
<td>Skin biopsy for histology, FBC and ESR, CRP, C3, C4, C1q antibodies, Functional complement, Urinalysis, ANA, ENA, dsDNA, ANCA. Tests for any other suspected underlying medical condition.</td>
</tr>
</tbody>
</table>

**URTICARIAL VASCULITIS:**

May have systemic symptoms like arthralgia, myalgia or fatigue. Doesn’t respond to high doses of antihistamines

**ANGIOEDEMA:**

Deep tissue swelling which often involves the eyes, tongue or lips, but which may involve any part of the body. Patients experience discomfort or pain, but no itching.

<table>
<thead>
<tr>
<th>ANAPHYLAXIS:</th>
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<tbody>
<tr>
<td>Dizziness, faintness, sense of impending doom, breathing difficulty, flushing, urticaria, angioedema, abdominal pain, nausea, vomiting, diarrhoea, hypotension, shock.</td>
</tr>
</tbody>
</table>

**ANACELLERICAL SYMPTOMS:**

If urticaria is prominent, investigate as urticaria, not angioedema

Angioedema with urticaria is not HAE

**DRUG ALLERGY:**

Gell + Coombs classification

| I: uticaria, bronchospasm, angioedema, anaphylaxis |
| II: haemolytic anaemia, thrombocytopenia |
| III: serum sickness, drug fever, cutaneous rashes, vasculitis |
| IV: contact dermatitis, maculopapular rashes, interstitial nephritis, hepatitis, Stevens – Johnson Syndrome (SJS) |

**CONSIDERATIONS**

| Is it an allergy / adverse reaction? |
| Immediate reaction (Gell + coombs I) or delayed (Gell + coombs II, III, IV)? |
| Which drug(s) are most likely to be involved? |

**TESTING**

| CAST test |
| SPT |
| Immediate reaction: |

**INSECT VENOM ALLERGY:**

Localised / diffuse swelling, urticaria, angioedema, difficulty breathing, anaphylaxis after insect sting.

**CONSIDERATIONS**

| Allergy to bee or wasp or both? |
| How long ago was the patient last stung? (IgE/ basophil reactivity may decrease over time) |
| Bee/ wasp venom is CCD cross-reactive. May be false positive in pollen allergic patients |

**TESTING**

| IgE and or CAST bee venom and / or wasp venom. |
| Components to identify primary sensitisation and cross-reactivity. |
| - Bee venom: Phospholipase A2 |
| - Wasp venom: Phospholipase A1, Ves V1, Ves V5 common wasp allergen |
| - CCD marker |