An approach to the Diagnosis of an Allergy

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AN APPROACH TO DRUG ALLERGY

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

YES

DRUG PROVOCATION

NEG

POS

NO AVOIDANCE

DELAYED

CAST
MELISA

POS

NEG

REFER TO SPECIALIST

SPT DRUG
PATCH TEST
INTRA-DERMAL TEST

POS

NEG

DRUG IMPORTANT?
PROVOCATION POSSIBLE?

YES

NO

DRUG PROVOCATION

NEG

POS

NO AVOIDANCE

• AVOID
• EDUCATE
• IDENTIFY SAFE ALTERNATIVE

• AVOID
• EDUCATE
• DOCUMENT

• AVOID
• EDUCATE
• DOCUMENT
AN APPROACH TO DRUG ALLERGY

When testing for penicillin allergy, patients should be tested to the penicillin ring, major and minor determinants and relevant side-chains.

A beta lactam ring is also found in cephalosporins (2-5% penicillin cross-reactivity), carbapenems (1% penicillin cross-reactivity) and monobactams (no cross-reactivity).

Quinolones frequently cause drug allergy and cross-reacts with other quinolones.

Macrolides don’t often cause allergies and cross-reactivity between macrolides is uncommon.

NSAID allergy is common. Aspirin, diclofenac and ibuprofen are the best indicators of NSAID allergy. Please distinguish between Aspirin allergy and Aspirin exacerbated respiratory disease, where cox-inhibition leads to greatly induced leukotrine production. This is not a true allergy and patients may present with nasal polyps and asthma.

Local anaesthetic allergy is common, but patients may tolerate 1/more alternate local anaesthetics.

Radiocontrast medium allergy is caused by an immunological reaction to quaternary iodine components. This does not cross-react with iodated table salt or seafood.

CLINICAL PEARLS
AN APPROACH TO ECZEMA AND DERMATITIS

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 fossae, 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 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

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

IF HISTORY OF ASTHMA/ALLERGIC RHINITIS
- European baseline, cosmetic, hairdressing or sunscreen series.

MELISA TESTING
- Metals (i.e. gold, nickel, platinum, mercury)
- Latex

PATCH TESTING
- European baseline, cosmetic, hairdressing or sunscreen series.

MELISA TESTING
- Metals (i.e. gold, nickel, platinum, mercury)
- Latex

• Consider other eczematous disorders
  - Seborrhoeic dermatitis
  - Drug reactions
  - Scabies
  - Hyper IgE syndrome
  - Wiscott Aldrich
  - Nutritional Deficiency
Patients with eczema have an intrinsic/impaired skin barrier defect, but allergen exposure causes flares in atopic patients.

Common allergens are food allergens or contact inhalant allergens like dust mite or animal danders.

Patients with very high IgE levels, as is commonly seen in atopic eczema, can lead to multiple positive allergy tests (cross-reactivity and non-specific binding). An ISAC test is not influenced by non-specific binding and can identify cross-reactivity, therefore is recommended in these patients.

Patients with an unusual distribution of their rash should be investigated for contact dermatitis (patch testing).
THE FOLLOWING FLOW-DIAGRAMS ASSISTS WITH AN APPROACH TO ACUTE AND CHRONIC URTICARIA:

**ACUTE URTICARIA**

**FLOW-DIAGRAM:**

- **YES**
  - OBVIOUS REACTION TO FOOD/FOOD ADDITIVE
    - SPT/Specific IgE
    - CAST
    - Positive: Avoidance
    - Negative: Consider Challenge
  - NO
    - Recent Drug?
    - Recent acute infection?
    - Underlying disease?
      - YES
        - Investigate and treat 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:**

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

- **NO UNUSUAL FEATURES**
  - LABORATORY INVESTIGATES TO IDENTIFY UNDERLYING/TREATABLE MEDICAL CONDITIONS

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

- **PHYSICAL URTICARIA**
  - IDENTIFY BY CHALLENGE TESTING
  - IF COLD URTICARIA DO CRYOGLOBULINS
Urticaria may be triggered by multiple factors in genetically susceptible individuals, e.g. infections, autoimmunity, malignancies, hypersensitivity and physical or psychological factors.

Allergy is rarely (5-10%) the cause of chronic urticaria.

The most common allergens implicated are drugs, foods, colourants and preservatives.

Urticaria is itchy, not painful. It may be associated with angioedema.

Suspicious features of urticarial vasculitis is painful or non-itchy lesions that last > 24 hours on the same spot and heal with bruising or scarring.

Physical urticarias include dermatographism, delayed pressure urticaria, cholinergic urticaria, aquagenic urticaria and vibrational urticaria and should be diagnosed from clinical history.
AN APPROACH TO ANGIOEDEMA

**HISTORY OF ONSET, FAMILY HISTORY**

- Positive family or history of onset at a young age
  - C1 inhibitor
  - C4 levels

- Associated urticaria
  - Investigate as chronic urticaria

- No family history/ later onset
  - FBC and Diff + ESR
  - ANA, ds DNA, ENA
  - C4
  - C1q
  - IgG, A, M
  - Protein electrophoresis
  - B2 microglobulin
  - Urinary Bence-Jones proteins
  - Examine for lymphadenopathy/splenomegaly
  - Consider chest/ abdominal CT

- Drugs
  - ? ACE inhibitors
  - ? Statins
  - ? NSAIDS
  - ? PPI

- Trial of substitution/ discontinuation of drug
AN APPROACH TO ANGIOEDEMA

• Angioedema is not itchy, but “tingly”, burning or painful.
• If urticaria/itch is prominent, investigate and manage as for urticaria.
• Hereditary angioedema (HAE) usually presents early or with a positive family history.
• Angioedema with urticaria is not HAE.
• The most common cause of angioedema in adults is ACE inhibitors or NSAIDS.
• Angioedema (without urticaria) is not an allergy and patients should be investigated for an underlying disease, e.g. autoimmunity or malignancy.
AN APPROACH TO THE DIAGNOSIS OF ANAPHYLAXIS

Immediate Tests
- Most cell tryptase (always do a baseline after 24 hours)
- C3, C4

Later tests (after 2 or 3 weeks)
- Repeat mast cell tryptase
- Specific ImmunoCap® IgE/CAST depending on history:
  - Venoms
    - Bee / Wasp
  - Foods
    - Nuts, seeds, legumes
    - Fish and shellfish
    - Egg
    - Milk
    - Any food, including fruit, vegetables and additives
  - Drugs
    - Antibiotics
    - Radiocontrast media
    - Analgesics
    - Anaesthetic agents, especially muscle relaxants
    - Biologicals
  - Latex

Immediate Tests
- C3, C4
• Mast cell tryptase is very important to diagnose anaphylaxis and is positive in anaphylactic (IgE mediated) and anaphylactoid (non-IgE mediated) reactions.
• Always do a baseline tryptase level at least 24 hours later.
• Do not investigate for the anaphylaxis trigger within 2-3 weeks of the reaction as basophils in CAST tests may have increased background activation and IgE may be negative due to increased consumption.
• Consider co-factor dependant anaphylaxis e.g. wheat induced – exercise – induced anaphylaxis (LTP/Ω-5–gladin), NSAID or alcohol co-factor anaphylaxis.

CLINICAL PEARLS
AN APPROACH TO INHALANT ALLERGY

HISTORY SUGGESTIVE OF INHALANT ALLERGY

Symptoms all year round

Phadiatop Inhalant Screen

Positive

Break down in ALLSA/NPG panel*

Negative

Symptoms worse in Spring

Or SPT panel

if negative

Phadiatop Inhalant Screen

Negative

Positive

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)

? OTHER MECHANISM
CAST inhalant mix **
Nasal eosinophils

Break down in ALLSA/NPG panel* AND allergy tree mix/individual trees

* 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.
AN APPROACH TO INHALANT ALLERGY

The majority of inhalant allergies are IgE mediated, therefore IgE mediated testing, e.g. Phadiatop/ skin prick tests are recommended as first line tests.

In patients with a history highly suggestive of inhalant allergies and negative IgE allergy tests, consider:

a) Another mechanism
   - Do CAST inhalant screen.
   - Do nasal mucus smear for eosinophils.

b) Another allergen
   - ?Tree pollen, animal, weed, occupational allergen.

The most allergenic tree pollens in South Africa are plane tree, oak, olive, cypress, eucalyptus, pine, acacia, willow, poplar, mulberry ash and elder.

Screening tests (Phadiatop) for inhalant allergies should always be broken down if positive, so individual allergens can be identified for avoidance or immunotherapy.

Patients are often sensitized to cross-reactive components that occur in pollens and foods of plant origin. Test for these components, nl. LTP, PR-10, Profilin and CCD in patients sensitized to pollens and foods of plant origin.
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
    - **Negative**
    - **Positive**
      - Breakdown in
        - Egg: ovomucoid
        - Milk: casein
        - Wheat: gliadin
        - Soya: storage protein
        - Peanut: storage protein
        - Codfish: parvalbumin
      - If food IgE is positive do dietary component testing to indicate risk, severity and for dietary advice
        - Add:
          - Grass mix IgE
          - Proflin
          - PR-10
          - CCD
          - LTP
      - NB! If soy, wheat and peanuts are positive, consider food-pollen syndrome
      - ? Other mechanism
        - CAST test
          - Food mix
          - Colourants
          - Preservatives
          - MELISA/patch test
    - ? Other disease, e.g.
      - Coeliacs disease
        - HLADQ2+8
        - IgA
        - TTG IgA
        - Endomysial IgA
        - Deamidated Gliadin IgA
    - ? Non Immunological Mechanism
      - i.e. lactase deficiency
      - H-breath test
      - Stool reducing substances

- **Clear history indicates a specific food**
  - Food allergen IgE or SPT
    - **Positive**
    - ? Other allergen
      - Other food IgE/SPT's
    - ? Other mechanism
      - CAST test
        - Food mix
        - Colourants
        - Preservatives
        - MELISA/patch test
    - ? Other disease, e.g.
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AN APPROACH TO FOOD ALLERGY

CLINICAL PEARLS

- It is important to distinguish between immediate (<2 hours) hypersensitivity reactions, which are usually IgE / basophil mediated and delayed reactions, which may include other immune mechanisms. Testing should be requested accordingly.
- Screening with a food mix (IgE or CAST) should always be broken down if positive.
- Consider allergy to food additives like colourants and preservatives in addition to the specific food allergens.
- In patients with symptoms suggestive of wheat hypersensitivity and negative allergy tests, please consider testing for Coeliac disease.
- Oral allergy syndrome (OAS) is usually caused by pollen-food cross-reactivity. Test for pollen allergy and cross-reactive pollen components: IgE to LTP, PR-10, profilin and CCD.
- Relevant components should be requested if food-specific IgE is positive to advise on risk, avoidance and prognosis.
- ISAC testing should be considered in patients with multiple food and inhalant allergies.
### THE MOST IMPORTANT ALLERGEN COMPONENTS:

#### EGG WHITE
- **Ovomucoid**
  - Gal d 1
  - Highly allergenic
  - Heat stable
  - Severe and persistent allergy

- **Ovalbumin**
  - Gal d 2

- **Conalbumin**
  - Gal d 3

- **Lysozyme**
  - Gal d 4

- **Egg serum albumin**
  - Gal d 5

- **Heat labile**
- May tolerate well-cooked egg

#### EGG YOLK
- **Egg serum albumin**
- Occurs in egg yolk, chicken meat and feathers

#### MILK
- **Casein**
- Bos d 8
- Heat stable
- Most important allergen
- Severe and persistent allergy
- Cross-reacts between mammals (e.g. goats milk)

- **α lactalbumin**
- Bos d 4
- Main whey proteins
- Heat labile
- May tolerate well-cooked milk, boiled/baked milk, long-life milk, hard cheese and yoghurt.

- **β lactoglobulin**
- Bos d 5
- Heat labile
- May tolerate well cooked milk and dairy.
- Cross-reaction with other mammals.

- **Bovine serum albumin**
- Bos d 6
- Occurs in milk and beef/red meat.
- Heat labile, may tolerate well cooked milk and dairy.

- **Lactoferrin**
- Bos d lactoferrin
- Heat labile.
- May be used as a preservative in beef and nasal sprays.

#### FISH
- **Cod parvalbumin**
- Cyp c 1
- Heat stable
- Broad cross-reactivity, marker for general fish sensitization.
- Parvalbumin content of different fish species may vary, e.g. lower levels in tuna.

- **Carp parvalbumin**
- Gad c 1

#### SHELLFISH
- **Tropomyosin**
- Pen a 1
- Heat stable muscle protein.
- Found in crustaceans, molluscs, insects and mites with clinical cross-reactivity.
### FOOD ALLERGEN COMPONENTS: POLLEN, PEANUT, SOYA, WHEAT

#### POLLEN CROSS REACTIVE

<table>
<thead>
<tr>
<th>Protein</th>
<th>Heat Labile</th>
<th>OAS</th>
<th>Mild to Severe Symptoms</th>
<th>Heat Stable</th>
<th>OAS</th>
<th>Severe Clinical Symptoms or Anaphylaxis</th>
<th>Usually No Clinical Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Profilin</td>
<td>● Heat labile</td>
<td>● OAS</td>
<td></td>
<td>● Heat labile</td>
<td>● OAS</td>
<td></td>
<td></td>
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<tr>
<td>PR-10</td>
<td>● Heat labile</td>
<td>● OAS</td>
<td></td>
<td>● Heat stable</td>
<td>● OAS</td>
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<tr>
<td>LTP</td>
<td></td>
<td></td>
<td></td>
<td>● Severe clinical symptoms or anaphylaxis</td>
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<tr>
<td>CCD</td>
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<td></td>
<td></td>
<td>● Usually no clinical symptoms</td>
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#### PEANUT

**Storage Proteins**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Heat Stable</th>
<th>Digestion</th>
<th>Risk of Anaphylaxis</th>
<th>Cross-reactive with other nuts and seeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ara h 1</td>
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<td>Ara h 9</td>
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</tbody>
</table>

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

#### SOYA

**Storage Proteins**

<table>
<thead>
<tr>
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<th>Heat Stable</th>
<th>Digestion</th>
<th>Risk of Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gly m 5</td>
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<tr>
<td>Gly m 6</td>
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</tbody>
</table>

- Associated with severe reactions
- Heat stable
- May have severe reactions

#### WHEAT

**Gluten Proteins**

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<th>Protein</th>
<th>Heat Stable</th>
<th>Digestion</th>
<th>Risk of Anaphylaxis</th>
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<tr>
<td>α 5 Gliadin</td>
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<td>Tri a 19</td>
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<td>αBSW Gliadins</td>
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</table>

- Risk marker for systemic reactions
- Wheat allergy persistence
- Wheat dependent exercise induced anaphylaxis
- Marker of severe reactions
- Marker of wheat allergy persistence
- Wheat dependent exercise induced anaphylaxis.