

# An overview of allergies and a diagnostic approach

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# Introduction

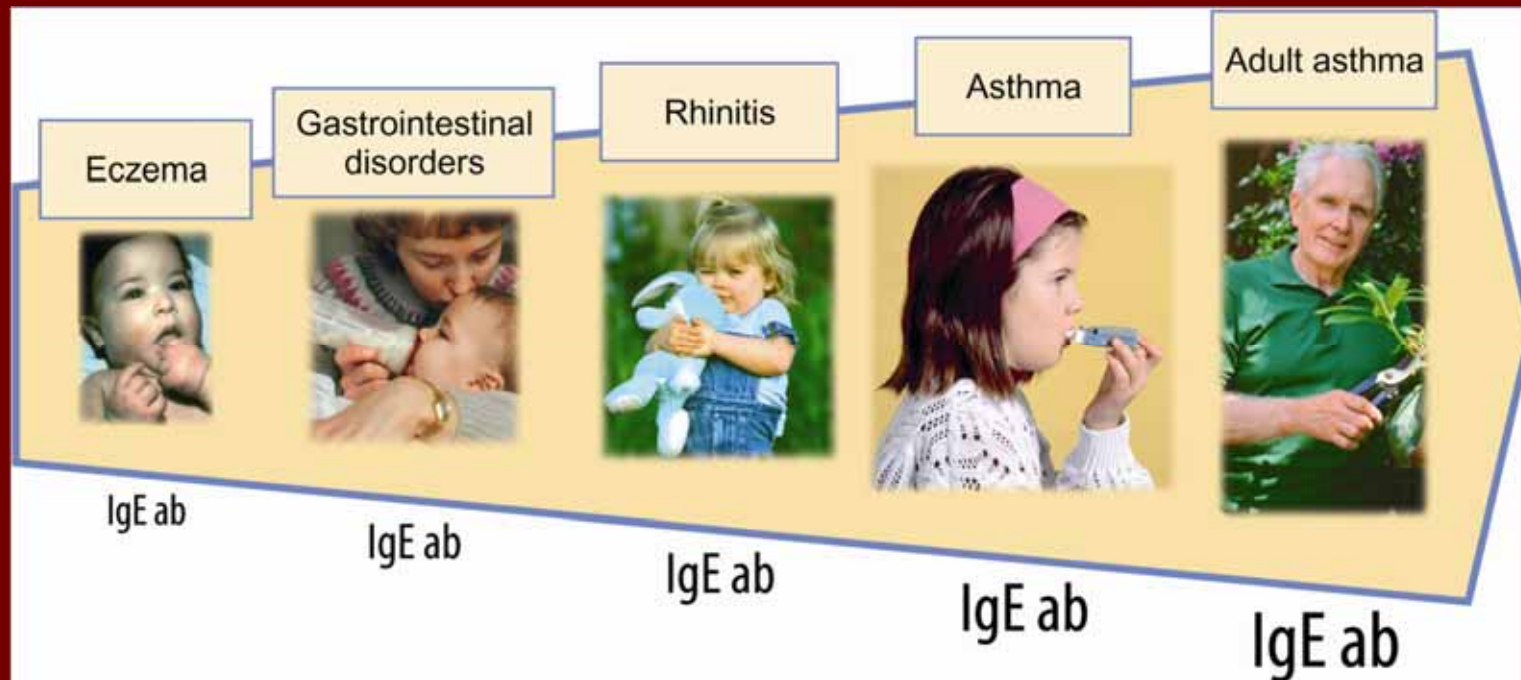
- Allergies are on the increase; approximately 25% of urban populations affected.
- Common problem in adult and paediatric practices.
- Diagnosis of specific allergy often challenging



# Why is allergy a growing disease?

- Allergy is a multifactorial disease
  - Genetic constitution
  - Allergen exposure
  - Environmental factors
  - Life-style differences
- As allergic disease is multifactorial, allergic children may have non-allergic parents.

# Allergy symptoms and progression



# Approach to the allergic patient

- A good history is the most important component of allergy diagnosis.
- There are several different mechanisms of allergy and a range of different tests to diagnose these different mechanisms.
- A negative test to one mechanism of allergy only excludes that specific mechanism, but not any other mechanism.
- All laboratory tests should be correlated with the clinical findings.
- Management consists of patient education, avoidance and pharmacological and or immunomodulatory therapy

# Allergy history

## ALLERGY CLINICAL HISTORY:

- |   |  |   |
|---|--|---|
| <input type="checkbox"/> ASTHMA         | <input type="checkbox"/> EXCESSIVE MUCUS | <input type="checkbox"/> ANGIO-OEDEMA   |
| <input type="checkbox"/> WHEEZE         | <input type="checkbox"/> HAY FEVER       | <input type="checkbox"/> URICARIA       |
| <input type="checkbox"/> COUGH          | <input type="checkbox"/> BLOCKED NOSE    | <input type="checkbox"/> ITCHING THROAT |
| <input type="checkbox"/> CROUP          | <input type="checkbox"/> NASAL DISCHARGE | <input type="checkbox"/> ITCHING EARS   |
| <input type="checkbox"/> RECURRENT URTI | <input type="checkbox"/> SINUSITIS       | <input type="checkbox"/> ITCHING EYES   |
| <input type="checkbox"/> RECURRENT LRTI | <input type="checkbox"/> POST NASAL DRIP | <input type="checkbox"/> CONJUNCTIVITIS |
| <input type="checkbox"/> GI UPSET       | <input type="checkbox"/> ECZEMA          | <input type="checkbox"/> INSECT STING   |
| <input type="checkbox"/> HEADACHE       | <input type="checkbox"/> SKIN RASH       | <input type="checkbox"/> OTHER          |

- KEY** URTI - UPPER RESPIRATORY TRACK INFECTION  
LRTI - LOWER RESPIRATORY TRACK INFECTION  
GI - GASTROINTESTINAL

## DETAILS OF ABOVE (INCLUDING DATE OF ONSET):

SEASONAL AGGRAVATION:  J  F  M  A  M  J  J  A  S  O  N  D

DAILY AGGRAVATION: WORSE  MORNING  DAYTIME  NIGHT

# Allergy history

## AGGRAVATING FACTORS:

- |                                     |                                   |  |  |
|-------------------------------------|-----------------------------------|--|--|
| <input type="checkbox"/> HUMIDITY   | <input type="checkbox"/> HEAT     | <input type="checkbox"/> POLLUTION     | <input type="checkbox"/> WEATHER CHANGES |
| <input type="checkbox"/> HOUSE DUST | <input type="checkbox"/> COLD     | <input type="checkbox"/> INLAND        | <input type="checkbox"/> STRESS          |
| <input type="checkbox"/> OUTDOORS   | <input type="checkbox"/> EXERCISE | <input type="checkbox"/> COASTAL AREAS | <input type="checkbox"/> ANIMALS         |
| <input type="checkbox"/> INDOORS    | <input type="checkbox"/> WATER    | <input type="checkbox"/> SUNSHINE      | <input type="checkbox"/> OTHER           |

OTHER / DETAILS OF ABOVE: .....

## HYPERSENSITIVITIES

KNOWN: .....

SUSPECTED: .....

FAMILY HISTORY OF ALLERGIES: .....

## ENVIRONMENT:

PETS: .....

PILLOWS: .....

CARPETS: .....

HOBBIES: .....

OCCUPATION: .....

EXPOSURES: .....

OTHER: .....

# Allergy history

PREVIOUS ALLERGY TESTS (PLEASE ATTACH A COPY OF PREVIOUS RESULTS):

TEST	RESULTS	DATE

## MEDICATION

CURRENT: .....

PREVIOUS: .....

WHICH MEDICATION HELPED: .....

DRUG ALLERGIES: .....

OTHER MEDICAL HISTORY: .....

## PHYSICAL EXAMINATION

### GENERAL:

"SHINERS"       NASAL CREASE       ADENOID FACIES

SYSTEMIC: .....

RESP: .....

ENT: .....

SKIN: .....

OTHER: .....





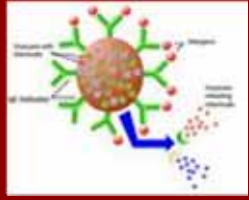
# Allergy diagnosis: Why test?

- Appropriate, effective therapy
- Avoid trigger allergens
- Specific immunotherapy for certain allergens
- Exclude allergy
  - Unnecessary pharmacotherapy
  - Unnecessary avoidance
    - Expensive, harmful (foods)
    - Upsetting (pets)



# Before we test....General considerations

- The term allergy is loosely applied to many different reactions. We need to distinguish between allergic reactions (mediated by the immune system), intolerance reactions (not mediated by the immune system) and other reactions, e.g. side-effects of certain drugs, etc.
- Allergy testing can only be done for immunologically mediated reactions.



# Mechanisms of allergy

- IgE mediated allergy
- Non-IgE mediated allergy
  - Basophil mediated allergy
  - T-Cell mediated allergy
  - Eosinophilic mediated reactions

# IgE mediated allergy

<u>Type of allergy</u>	<u>%IgE mediated</u>
■ Food allergy	40-60%
■ Atopic dermatitis	33-40%
■ Asthma	70-90%
■ Drug allergy	<5%

# IgE mediated allergy

- IgE mediated allergy refers to the production of specific IgE to an allergen.
- Immediate symptoms
- Symptoms, e.g. erythema, itch, skin rash, urticaria, angioedema, bronchospasm, coughing, hay fever, anaphylaxis, etc.
- Symptoms occur after each exposure, EXCEPT patients with low levels of food specific IgE and repeated exposure to food allergen. (Chronic, low-grade response)
- Specific IgE can be tested irrespective of age, medication, symptoms or disease severity.

# Basophil mediated allergy

- May be an immediate or a delayed response.
- May present like a classic IgE mediated reaction.
- Rhinitis/sinusitis, asthma, gastrointestinal symptoms and urticaria often prominent
- Foods, colourants, preservatives, drugs often allergens.
- Reactions are dose-dependant and cumulative.

# T-cell mediated allergy

- Delayed allergic reaction (longer than 3 days)
- Symptoms are frequently skin reactions (especially maculopapular rashes) or respiratory symptoms, but other symptoms also occur less frequently.
- Allergens are often drugs, foods or metals.



# Most common allergens

- Food allergens-children <3-4 years of age
  - Cow's milk
  - Egg white
  - Peanuts, soya, wheat, nuts, fish, etc.
  - Colourants and preservatives
- Inhalant allergens
  - Usually not a problem before 2 years
  - House dust mite
  - Cat, dog and other furry animals
  - Pollens, e.g. grass





# Most common allergens

- Children > 3-4 years of age - foods
  - Cow's milk
  - Egg white
  - Peanuts
  - Wheat, nuts, fish, etc.
  - Colourants and preservatives
- Inhalant allergens
  - Pollens (grass)
  - House dust mite
  - Cats, dogs and other furry animals



# Most common allergens

## ■ Adults-foods

- Peanuts and nuts, shellfish and other fish
- Wheat, cow's milk, egg, cheese, soya
- Citrus, tomato
- Colourants and preservatives

## ■ Adults-inhalants

- Pollens (grass)
- House dust mite
- Moulds
- Cats, dogs and other furry animals

# Diagnostic tests for allergies

- In vitro tests:
  - Total IgE
  - Allergen specific IgE (RAST tests) to individual or group allergens.
  - IgE allergen components (ISAC microarray chip)
  - Basophil activation tests (CAST tests) to individual or group allergens.
  - T-cell proliferation assays (MELISA tests)
  - Nasal eosinophils
  - Mast cell tryptase (Used to diagnose anaphylaxis)
  - ECP (Used for monitoring asthma therapy)

# Diagnostic tests for allergies

- In vivo tests
  - Skin prick tests
  - Intradermal tests
  - Patch tests
  - Provocation tests



# Total IgE

- Total IgE isn't a very sensitive or specific test, but does have some value as a screening test and an indicator of immune dysregulation.
- Pointers for interpretation:
  - Lower IgE values in children and the aged
  - Increased in parasitic infections, lymphoma, liver disease, vasculitis (Churg-Strauss), ABPA
  - May be normal – allergy in small target organ.
- Raised IgE may be valuable when specific IgE is negative – correct allergen not yet identified?

# Allergen specific IgE (RAST)

- Reliable for inhalant allergies, but not always in food and drug allergies.
- A variety of screening tests available, e.g. phadiatop for inhalant allergies.
- Allergen-specific IgE measures sensitisation, not necessarily clinically relevant allergy. Low levels should therefore be interpreted cautiously
- Cross-reactions may occur between certain allergens. Cross-reactive peptides may be clinically relevant, but CCD's (cross-reacting carbohydrate derivatives) are usually not clinically relevant

# RAST tests vs Skin prick tests

## RAST

- Highly reproducible
- Quantitative values
- Not influenced by medication
- Screening tests available
- Cross-reactions may occur
- Fruit allergens labile
- More expensive
- Allergen components

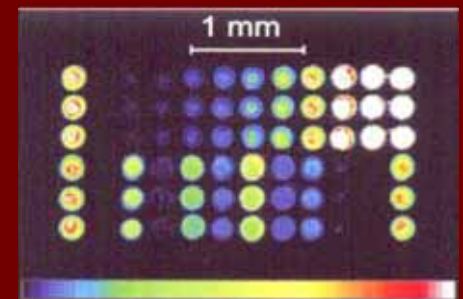
## SPT

- Results available immediately
- Cheaper than RAST tests
- Difficult to standardise
- Dependant on technique
- Results influenced by medication
- Cannot be performed – eczema / skin disease on site
- No screening tests
- Small risk of systemic reactions

# ISAC

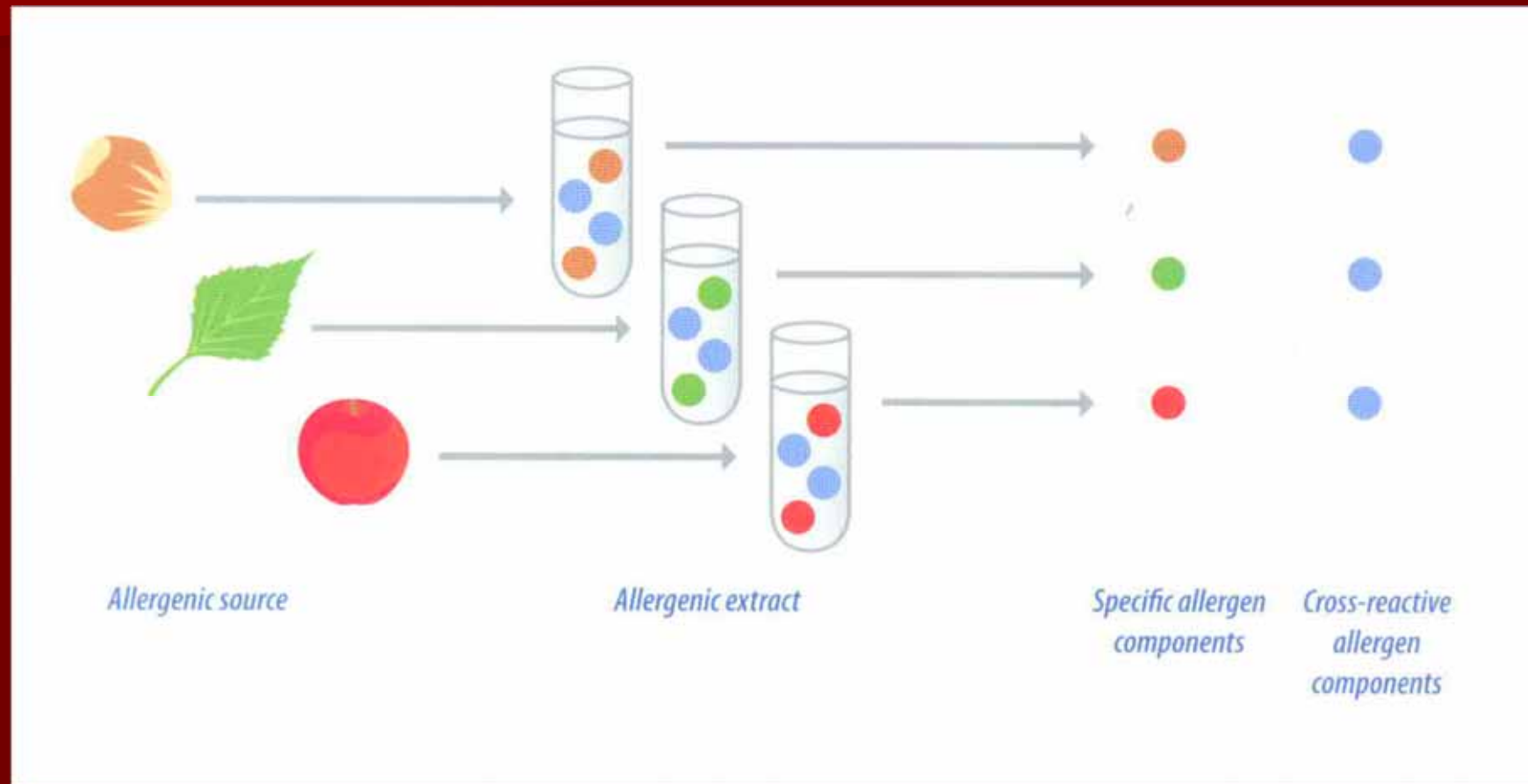
## Immuno Solid-phase Allergen Chip

- Multiplex IgE allergy assay with 103 recombinant allergens
- Additional diagnostic insight
  - Cross-reactivity: CCD, profilin, LTP, stor. Prot
  - Prediction of severity of allergy: rArah2
  - Heat lability of allergens
- Small amounts of serum needed – 20ul
- Specialised comments needed

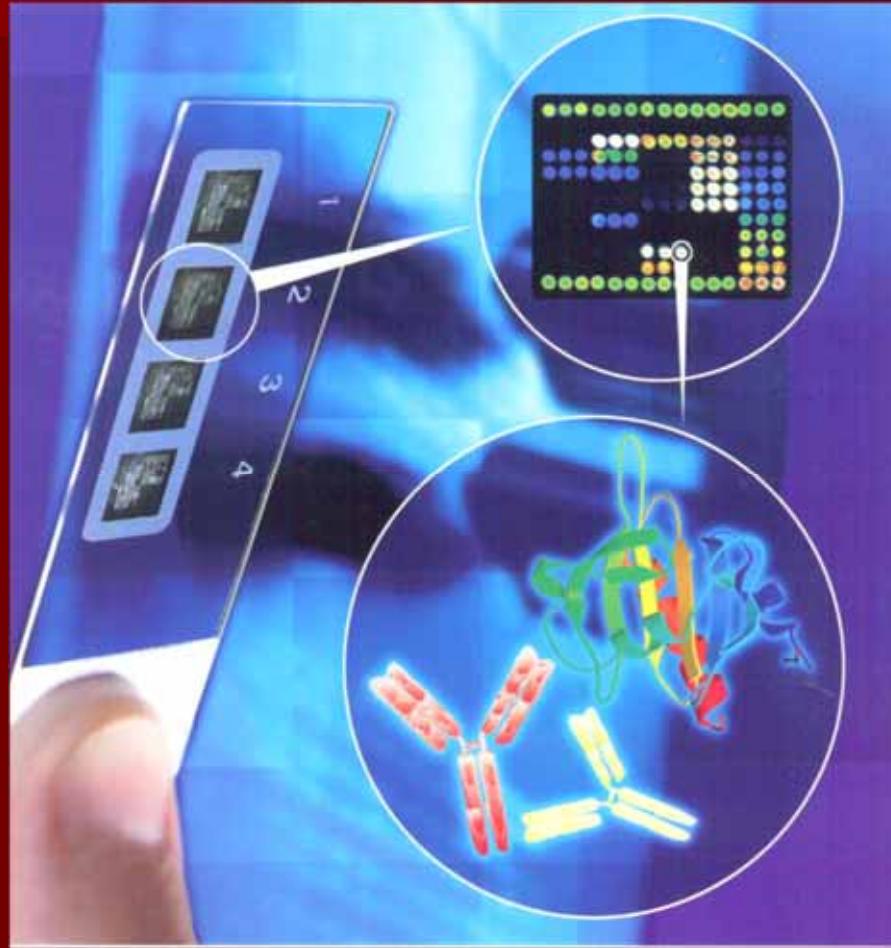




# Allergen components



# ISAC methodology



# Who will benefit from ISAC?

- Patients with multiple allergies
- Patients with combined food and inhalant allergies
- Patients with suspected allergen cross-reactivity
- Patients who require a more in-depth knowledge and interpretation of their allergies.

	ISU	Class
rBet v 1	78.4	■■■■■
rAin g 1	53.7	■■■■■
rCor a 1.0101	10.6	■■■■■
rCor a 1.0401	17.8	■■■■■
rMal d 1	13.4	■■■■■
rPru p 1	0	■■■■■
rGly m 4	16.6	■■■■■
rAra h 8	9.8	■■■■■
rApi g 1	3.1	■■■■■
rDau c 1	1.4	■■■■■

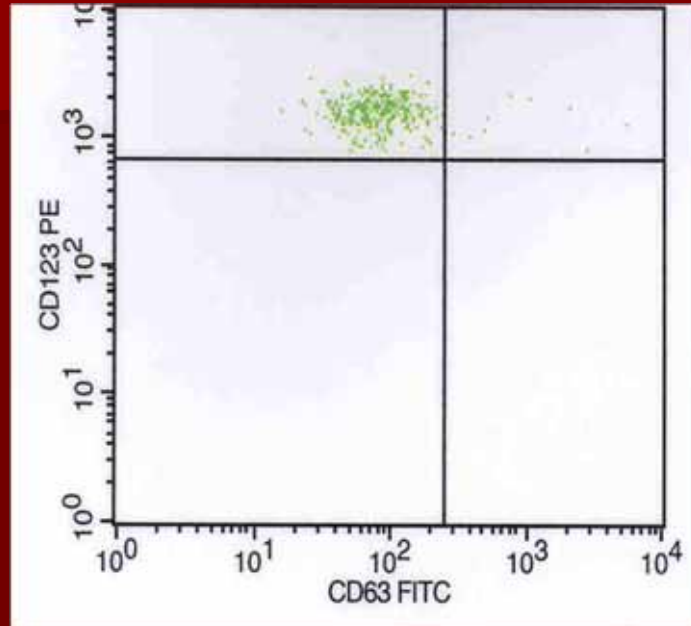
# CAST (Cellular Antigen Stimulation Tests)

- This test measures basophil activation after basophil stimulation with a specific allergen.
- A heparinised blood specimen is used and as live basophils are stimulated the specimen must reach the lab within 24 hours of collection.
- Basophil activation is measured by detecting basophil activation markers by flow-cytometry

# CAST test

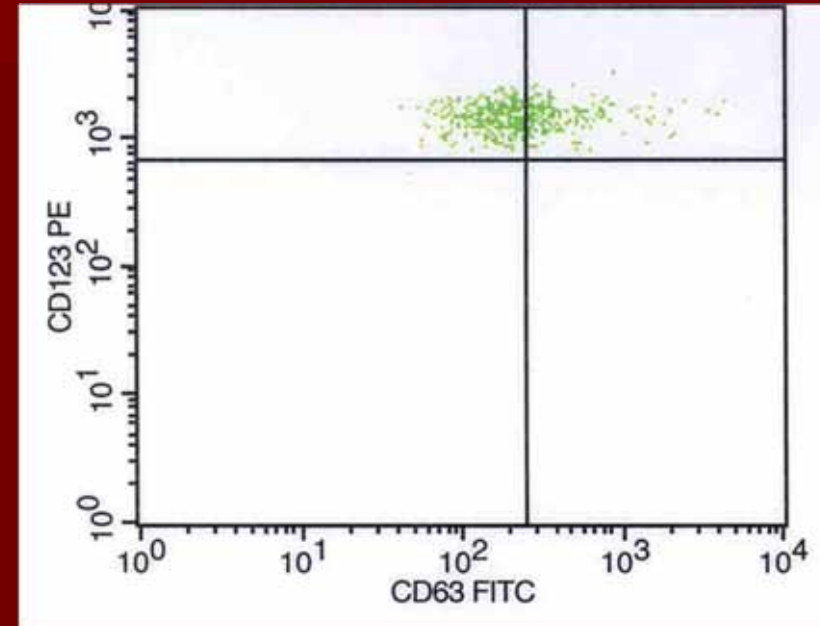
- IgE as well as non-IgE mediated reactions can be measured (Basophils have IgE receptors on their surfaces)
- Indicated in food allergies, reactions to colourants and preservatives and drug allergies. (Small molecular weight)
- Screening tests are available
- Sensitivity estimated at 80% depending on allergen tested.

# BASOPHIL ACTIVATION TESTS (CAST)



Quad	Events	% Gated
UL	300	96.15
UR	12	3.85
LL	0	0.00
LR	0	0.00

**Negative Control**



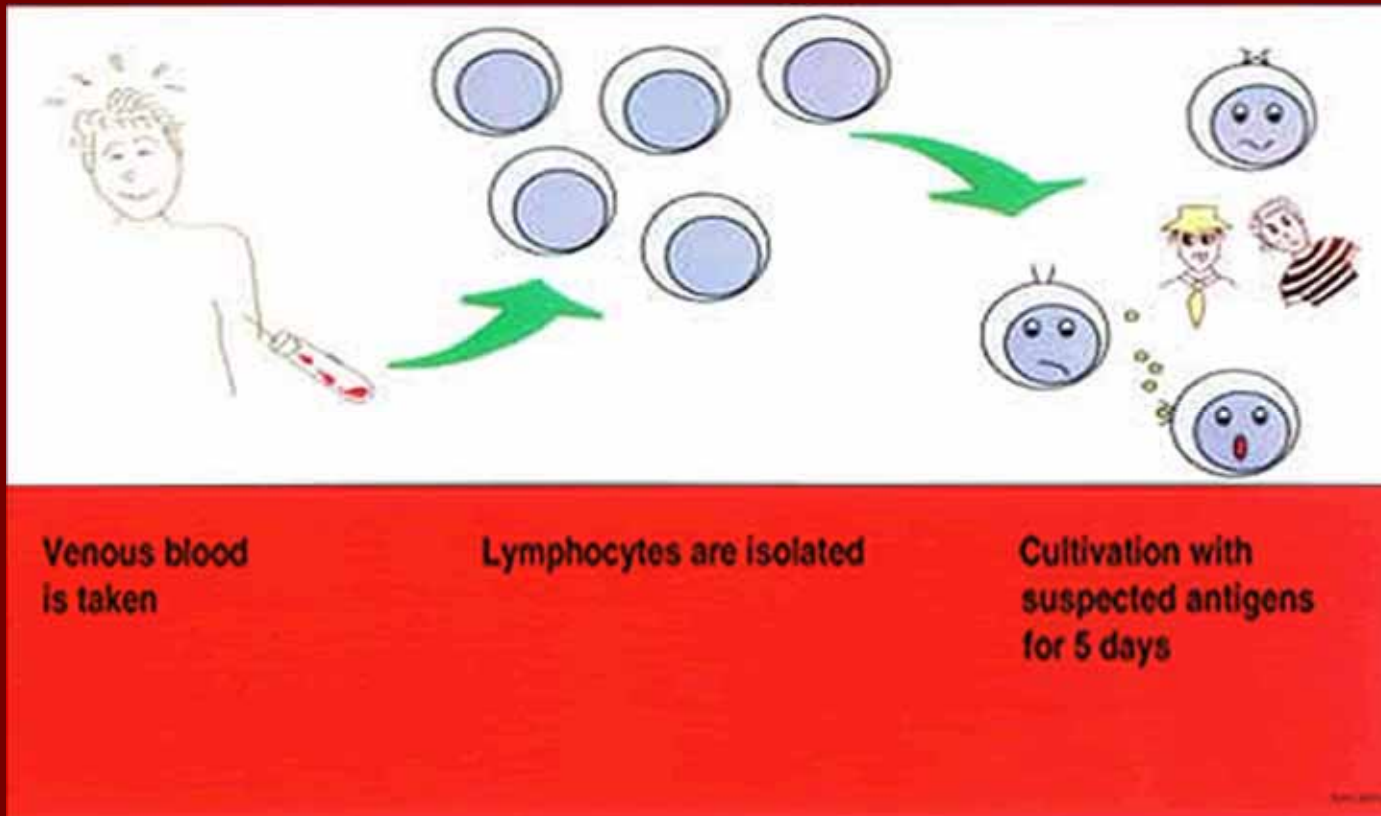
Quad	Events	% Gated
UL	284	61.34
UR	179	38.66
LL	0	0.00
LR	0	0.00

**Lidocaine**

# MELISA (Memory lymphocyte immunostimulation assay)

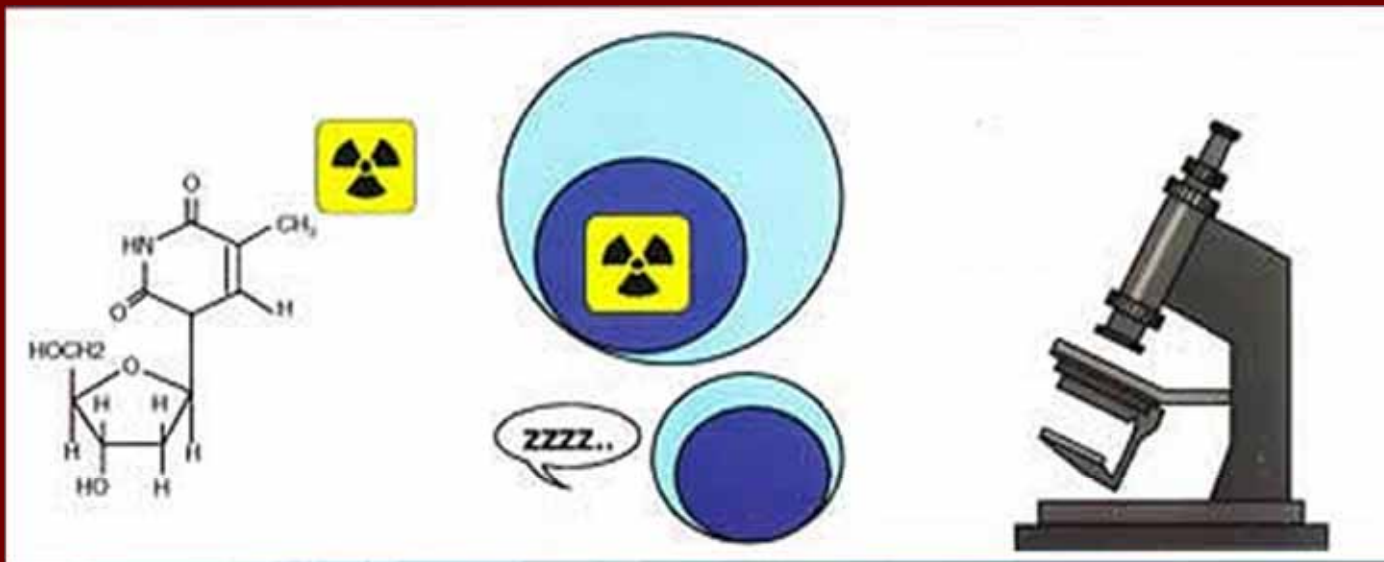
- This assay measures T-lymphocyte proliferation after stimulation with allergens for 5 -6 days.
- Clinically patients usually have a delayed reaction to allergens.
- This test is especially well suited to the diagnosis of drug allergy, metal allergy and some cases of food allergy.
- Specimens must reach the lab within 24 hours.

# Method of MELISA assay





# Method of MELISA assay



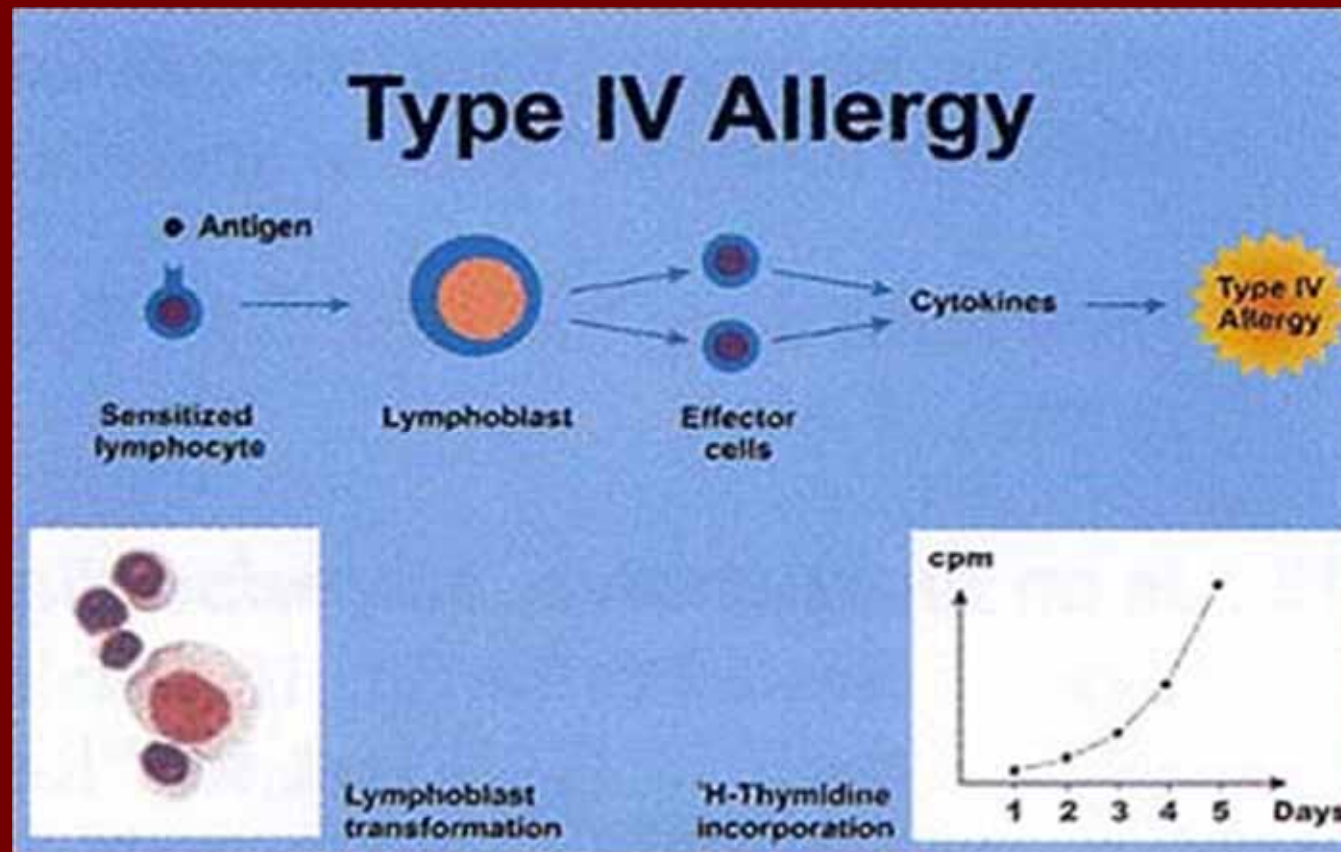
After 5 days in culture the cells are pulsed with  $^3\text{H}$ -thymidine and the radioactivity in DNA is measured after 4 hours

Cultures with stimulated memory cells have higher radioactivity than unstimulated

Presence of stimulated lymphocytes is also checked by microscopy

# Method of MELISA assay

"Type IV Allergy" is a delayed allergic response, which appears after approximately 2 days following exposure to the allergen

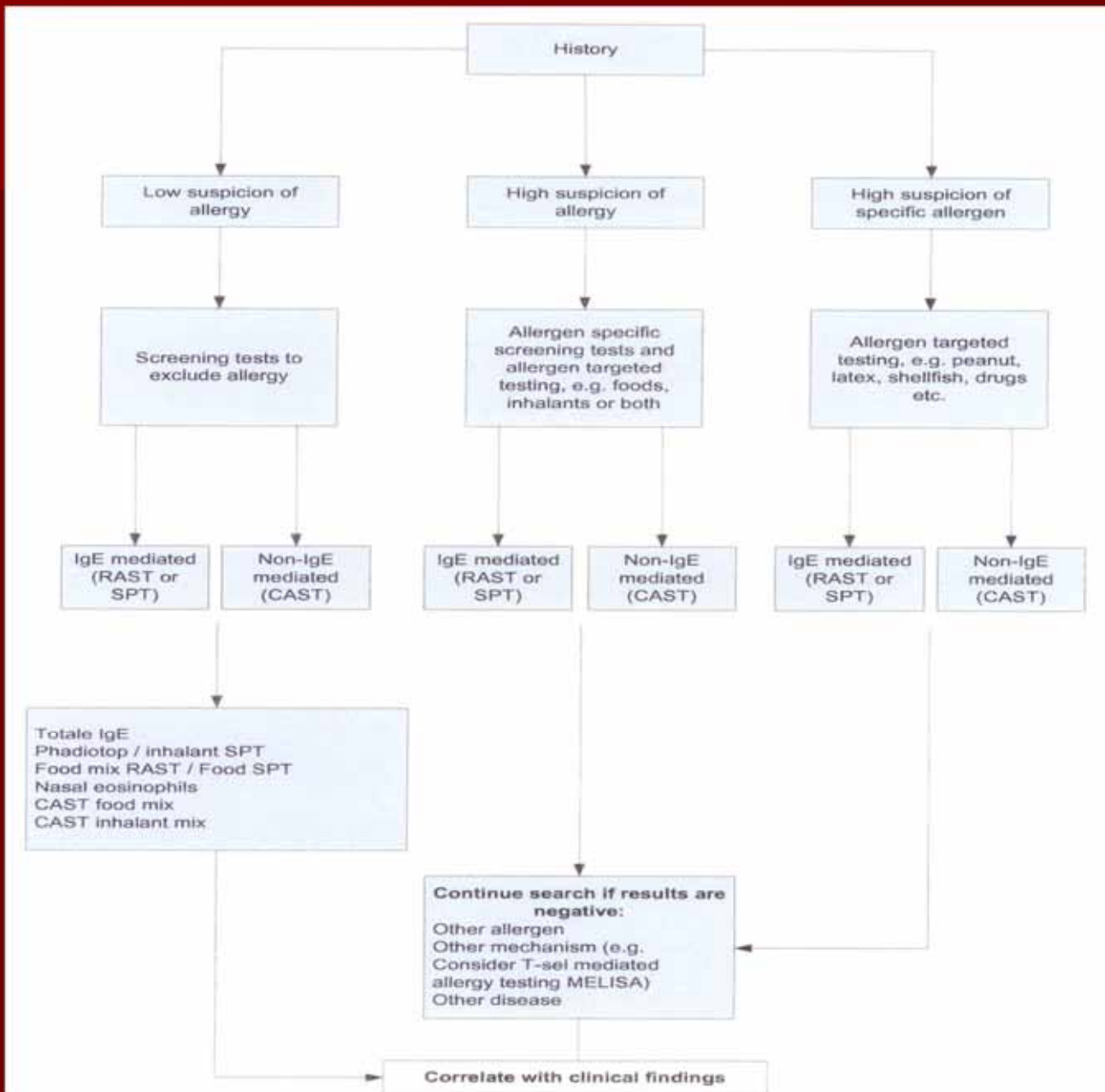




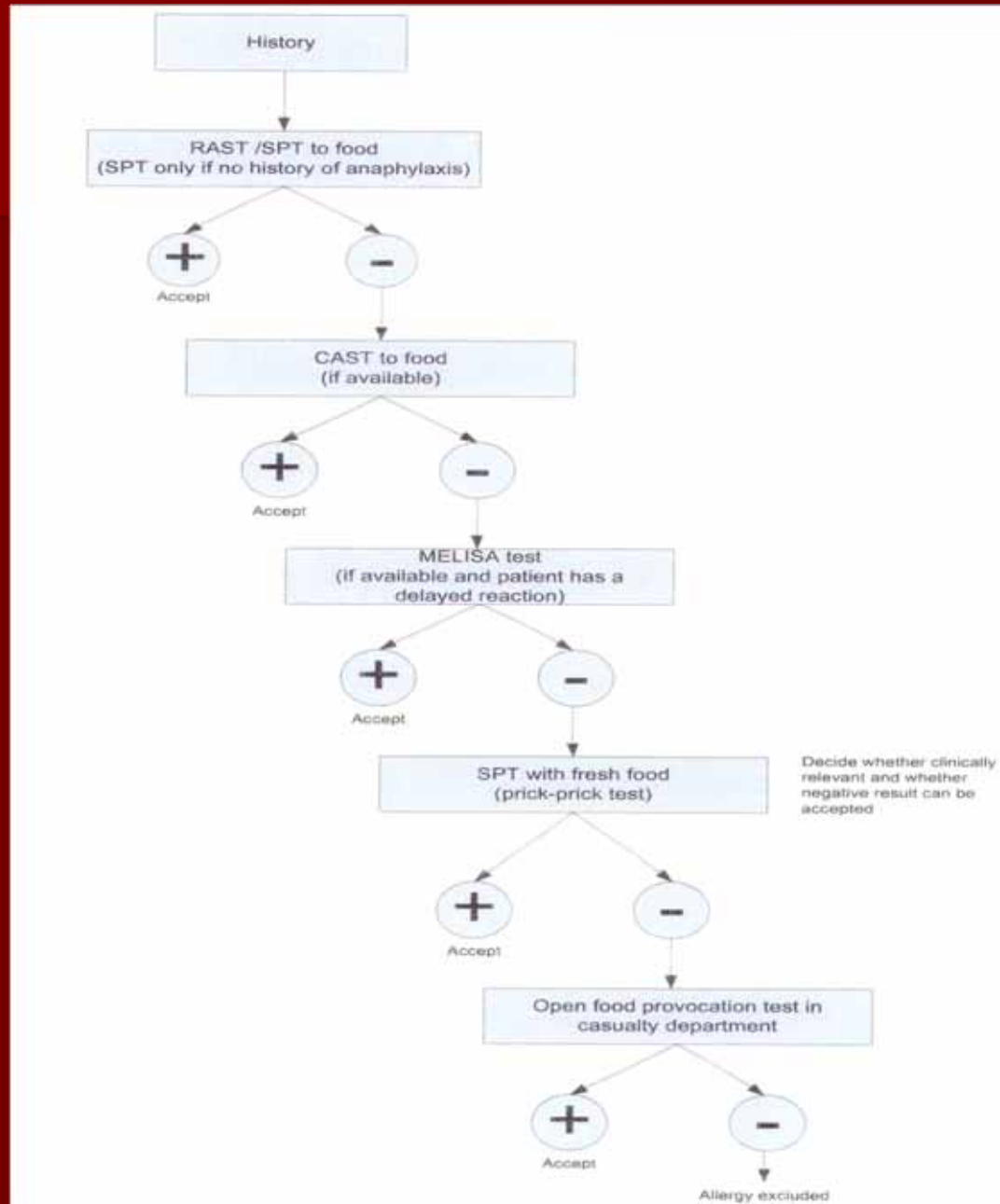
## Other diagnostic tests

- Nasal smears for eosinophils to distinguish between allergic and vasomotor rhinitis
- Mast cell tryptase to diagnose an anaphylactic reaction
- Skin prick tests and intradermal tests for drug allergy
- Atopy Patch tests
- Provocation tests (open or double-blind placebo controlled)

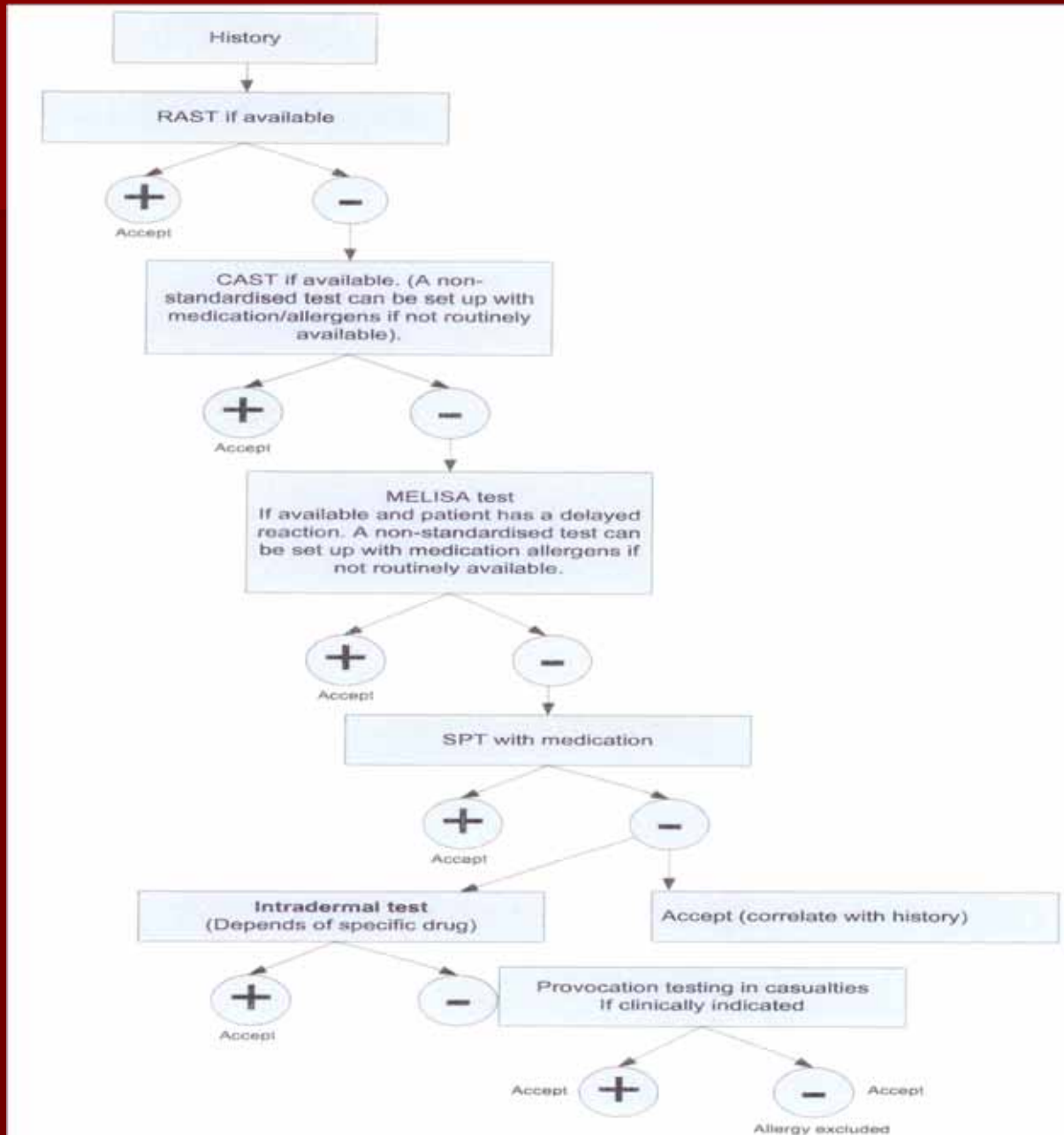
# Approach to allergy diagnosis



# Suspicion of food allergy



# Drug allergy





# Management of allergies

- Patient education
- Avoidance measures
- Pharmacotherapy
- Immunomodulatory therapy

# Management of allergies

## ■ Patient education

- Basics of pathogenesis
  - Dose-dependent and cumulative symptoms
  - Urticaria, eczema
- Allergen avoidance
- Pharmacotherapy
  - Appropriate use and chronic compliance
- Emergency plan for anaphylaxis
  - When and how to use medication
  - Written plan for schools / caregivers
  - Medic-alert
- Immunotherapy do's and don'ts





# Why allergen avoidance?

- Can prevent allergy symptoms, e.g. seafood allergy.
- Can reduce or control symptoms:
  - Patients may be sensitised, but asymptomatic (tolerance up to a certain threshold). Exposure above this threshold may lead to symptoms
  - Individuals with multiple sensitisations may experience worse symptoms when exposed to multiple allergens, e.g. allergies complicate other allergies.



# Management of allergies

## ■ Avoidance measures

### – Foods:

- Identify and avoid offending foodstuff
- If doubt about clinical relevance vs sensitisation exists – elimination diet + challenge
- Components can help
  - Nut allergy: storage proteins higher risk – stricter avoidance
  - Dairy: casein, alpha lactalbumin, beta lactoglobulin, lactoferrin, bovine serum albumin
  - Egg: ovomucoid – cannot tolerate cooked egg
  - OAS due to pollen crossreactivity: PR-10 and profilin is heat-labile
- Dietician can help: nutritional, challenges, salicylates, etc.



# Avoidance measures

## ■ Drug allergy

- Avoid offending drug
- Allergy is often class-dependant, therefore class should be avoided if individual testing cannot be done
- Cross-reactions between different classes of drugs which may have common structures, e.g. penicillin, cephalosporins and carbapenems, sulphonamides and COX-2 inhibitors
- Always try and identify safe alternatives beforehand.



# Avoidance measures

## ■ Environmental control

- Patient information leaflets, internet resources, e.g. [www.allergysa.org](http://www.allergysa.org)
- House dust mite avoidance
  - Mattress protector, pillow and duvet protectors, carpets, vacuums, soft toys, bedding
- Mould avoidance
  - Ventilation, dehumidifiers, indoor plants, tumble driers, damp fabrics, washing surfaces with bleach, compost heaps, etc.
- Pet allergen avoidance
  - Saliva vs dander, regular washing, pets outdoors



# Management of allergies

## ■ Pharmacological

- Antihistamines (non-sedating and first generation, topical and systemic, H1 and H2)
- steroids (topical and systemic)
- leukotrine antagonists
- mast cell stabilisers (ketotifen)
- topical calcineurin inhibitors
- other immunomodulatory and anti-inflammatory drugs
- biologicals (anti-IgE omalizumab), etc.



# Management of allergies

- Immunomodulatory (desensitisation)
  - Drug desensitisation
    - Patients with severe allergy to a drug and where there is no other alternative available
    - Usually antibiotic allergies, in hospital setting, works only for duration of therapy, protocols available
    - Aspirin desensitisation: Samter's triad (therapeutic and longterm), cardiac patients
  - Allergen Immunotherapy



# Allergen immunotherapy

- Allergen immunotherapy is the administration of gradually increasing quantities of an allergen vaccine to an allergic patient, reaching and maintaining a dose where exposure to an allergen no longer results in clinical reactions in most cases or markedly reduced symptoms in some.



# Allergen immunotherapy

- Immunotherapy is the only disease-modifying treatment for allergies and can “cure” a specific allergy.
- Consists of an up-dosing phase and a maintenance phase for 3-5 years.
- Success rate of 80-90%, dependant on the allergen used
- Only available for inhalant allergies and bee and wasp venom. (Not for food allergy) Sublingual immunotherapy for latex is available.





# Allergen immunotherapy

- Subcutaneous immunotherapy is the gold standard and the most effective, but sublingual immunotherapy can also be used for inhalant allergies (not for insect sting allergies). New developments – tablets, intranasal, etc.
- Latest data shows that allergen immunotherapy to pollens can also address oral allergy syndrome (food allergy) to cross-reactive allergen components.



# Allergen immunotherapy

## ■ Practical aspects

- Ensure compliance, good patient information
- Exclude contra-indications
- Pre-medication with antihistamines – bee venom IT. Identification of high-risk patients.
- Monitoring: BP, pulse, peak-flow before as well as after. Monitor for skin / systemic reactions. At least 30 min after IT
- Full emergency / resuscitation facilities and protocols for adverse reactions.
- Knowledge of allergen components helpful

# Thank you!

- Questions?

