Classification, pathogenesis and diagnostics of allergic diseases

Dr. med Anna Gschwend, PhD

Division Allergology,
Inselspital,
University of Bern,
CH 3010 Bern
Switzerland
Of all the body's organs, the immune system may be the most challenging to coordinate. The system is collection of individual immune cells, immune cell aggregates, immune tissues, and immune organs.
• Billions of immune cells communicate with each other.

• Functional integration of the immune system is accomplished mainly by cell-to-cell communication.

• Every immune system cell is equipped with different surface molecules and is able to synthesize and release a variety of small molecules that travel to other cells and stimulate those cells to become either more active or less active.
**Allergy:** immune reaction to a non replicating (harmless) substance (protein, chemical, drug, metal), which leads to clinical symptoms like.

In contrast to infections: symptoms are caused almost exclusively by the immune reaction, not by the „bug“ (virus, bacteria, etc.)
Allergens

• Non-reproducing foreign substances
• Mostly Proteines/Glykoproteines
  – Of animal or vegetable origin
  – Drugs/Chemicals
Examples of allergens:
- Pollen
- House dust mite
- Hymenoptera venom
- Food
- Drugs

Some allergens appear to have structural features able to activate the innate immunity (enzymes like papain, Der p2, some pollen grains).

**Allergens = 2% of proteins**

*Radauer et al. J Allergy Clin Immunol 2008*
The allergy is not directed to pollen, but to proteins within pollen!

Pollen = carrier (grain) + allergen (surface) + lipids
Betula verrucosa 1
Bet v 1
Major Allergen
House dust mites allergens are a common cause of asthma and allergic symptoms worldwide

• *D. pteronyssinus* (European)
• *D. farinae* (American)
• feed on organic detritus, such as flakes of shed human skin

The mite's gut contains potent digestive enzymes (proteases) that persist in their feces

Der p 1
Major Allergen
## Allergic to your Pet?

**Hilger C, Zahradnik E. Allergologie 2015;38:83-90**

### Can f 1 saliva

### Fel d 1 saliva and skin

### Table: Allergens in Cat and Dog Saliva and Skin

<table>
<thead>
<tr>
<th>species</th>
<th>Allergen</th>
<th>Proteinfamilie</th>
<th>UniProtKB accession No</th>
<th>Apparentes MG in kDa</th>
<th>Allergenquelle</th>
<th>Sensibilisierungsrate in %</th>
<th>In-vitro-Diagnostik verfügbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katze</td>
<td>Fel d 1</td>
<td>Sekretoglobin</td>
<td>P30438; P30440</td>
<td>18</td>
<td>Speicheldrüse, Haut</td>
<td>60 – 100</td>
<td>ja</td>
</tr>
<tr>
<td></td>
<td>Fel d 2</td>
<td>Serumalbumin</td>
<td>P49064</td>
<td>69</td>
<td>Leber</td>
<td>14 – 23</td>
<td>ja</td>
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<tr>
<td></td>
<td>Fel d 3</td>
<td>Cystatin</td>
<td>Q5WNR9</td>
<td>11</td>
<td>Haut</td>
<td>10</td>
<td>nein</td>
</tr>
<tr>
<td></td>
<td>Fel d 4</td>
<td>Lipokalin</td>
<td>Q5VFH6</td>
<td>22</td>
<td>Speicheldrüse</td>
<td>63</td>
<td>ja</td>
</tr>
<tr>
<td></td>
<td>Fel d 5</td>
<td>IgA</td>
<td>–</td>
<td>400</td>
<td>Speichel, Serum</td>
<td>38</td>
<td>ja</td>
</tr>
<tr>
<td></td>
<td>Fel d 6</td>
<td>IgM</td>
<td>–</td>
<td>800 – 1000</td>
<td>Serum</td>
<td>–</td>
<td>nein</td>
</tr>
<tr>
<td></td>
<td>Fel d 7</td>
<td>Lipokalin</td>
<td>E5D2Z5</td>
<td>17,5</td>
<td>Zunge</td>
<td>38</td>
<td>nein</td>
</tr>
<tr>
<td></td>
<td>Fel d 8</td>
<td>Latherin</td>
<td>F6KOR4</td>
<td>24</td>
<td>Speicheldrüse</td>
<td>19</td>
<td>nein</td>
</tr>
<tr>
<td>Hund</td>
<td>Can f 1</td>
<td>Lipokalin</td>
<td>O18873</td>
<td>23 – 25</td>
<td>Zunge</td>
<td>50 – 75</td>
<td>ja</td>
</tr>
<tr>
<td></td>
<td>Can f 2</td>
<td>Lipokalin</td>
<td>O18874</td>
<td>19</td>
<td>Zunge, Speicheldrüse</td>
<td>22 – 30</td>
<td>ja</td>
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<tr>
<td></td>
<td>Can f 3</td>
<td>Serumalbumin</td>
<td>P49822</td>
<td>69</td>
<td>Leber</td>
<td>25 – 35</td>
<td>ja</td>
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<tr>
<td></td>
<td>Can f 4</td>
<td>Lipokalin</td>
<td>D7PBH4</td>
<td>18</td>
<td>Zunge</td>
<td>35</td>
<td>nein</td>
</tr>
<tr>
<td></td>
<td>Can f 5</td>
<td>Kallikrein</td>
<td>P09582</td>
<td>28</td>
<td>Urin</td>
<td>70</td>
<td>ja</td>
</tr>
<tr>
<td></td>
<td>Can f 6</td>
<td>Lipokalin</td>
<td>H2B3G5</td>
<td>27 – 29</td>
<td>Speicheldrüse</td>
<td>61</td>
<td>nein</td>
</tr>
</tbody>
</table>
Bee / Wasp Allergy
Peanut allergy
The immune system is highly specific and needs danger signals to become activated.

How can a harmless/innocuous substance like a pollen potentially induce an IgE mediated immune reaction?
Ability of „innocuous“ proteins to activate immune system

1. House dust mite allergen Der p1: cysteine protease cleaves tight junction protein occludin → Increased epithelial permeability and facilitating its entry into the tissue

2. House dust mite allergen Der p2: structural and functional homology with MD-2, LPS-binding component of TLR 4 signaling complex → facilitates signaling through direct interactions with the TLR4 complex

3. Pollen-associated lipid mediators (PALMs): When pollen grains are hydrated on the respiratory epithelia, they release allergens and eicosanoid lipids → so-called pollen-associated lipid mediators (PALMs) → act as stimulators of DC
Airway immune response

Air pollutants

Bacteria

Allergen

Antigen

Virus

DC modulating factors

TSLP

PGE2

TGF-β

IL-10

GM-CSF

Recruitment by chemokines

Inflammatory cytokines

Lymph node

Treg cells

Th1 cells

Th2 cells

Th17 cells

Naïve Th cells

dc

J. van Tongeren et al. Allergy 2008: 63: 1124–1135
TH2 polarisation is critical for the IgE production
**Sensitization Phase**

- Allergen
- Epithelial barrier
- DC
- T cell (naiv)
- Clonal expansion
- TH2
- TH2
- IL-4, IL-5, IL-13
- B cell
- Ig Switch
- TH2
- TH2
- TH2
- IL-4, IL-5, IL-13, IL-31
- B cell
- Ig Switch
- Production of allergen-specific IgE
- Plasma cell
- Lymph node
- Early phase
- Epithelial barrier
- Late phase
- Tissue cells
<table>
<thead>
<tr>
<th>IgM pentamer</th>
<th>IgG monomer</th>
<th>Secretory IgA dimer</th>
<th>IgE monomer</th>
<th>IgD monomer</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="IgM pentamer diagram" /></td>
<td><img src="image2" alt="IgG monomer diagram" /></td>
<td><img src="image3" alt="Secretory IgA dimer diagram" /></td>
<td><img src="image4" alt="IgE monomer diagram" /></td>
<td><img src="image5" alt="IgD monomer diagram" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heavy chains</th>
<th>μ</th>
<th>γ</th>
<th>α</th>
<th>ε</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of antigen binding sites</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Molecular weight (Daltons)</td>
<td>900,000</td>
<td>150,000</td>
<td>385,000</td>
<td>200,000</td>
<td>180,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of total antibody in serum</th>
<th>6%</th>
<th>80%</th>
<th>13%</th>
<th>0.002%</th>
<th>1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosses placenta</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Fixes complement</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Fc binds to</td>
<td></td>
<td>phagocytes</td>
<td>mast cells and basophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor</td>
<td>Main blood antibody of secondary responses, neutralizes toxins, opsonization</td>
<td>Secreted into mucus, tears, saliva, colostrum</td>
<td>Antibody of allergy and antiparasitic activity</td>
<td>B cell receptor</td>
</tr>
</tbody>
</table>
Type-I (immediate hypersensitivity)

IgE Antikörper

Mastzelle

FcεRI
Lawren C. Wu and Ali A. Zarrin et al. Nature Immunology Review 2014
Plasma cell (produces IgE antibody)

Mast cell (releases mediators)

IgE cross linking by antibody

Activation

Symptoms

Histamine and other mediators
Cross linking of 2 Fc-IgE-RI
Is required for mast cell activation

Mediator release

LTD4, PGD2, CCL19, histamin, etc.
Mast cell

Nature Reviews | Immunology
Activated mast cell (or basophil)

- Biogenic amines (e.g., histamines)
- Lipid mediators (e.g., PAF, PGD₂, LTC₄)
- Cytokines (e.g., TNF)
  - Lipid mediators (e.g., PAF, PGD₂, LTC₄)
- Enzymes (e.g., tryptase)

- Vascular leak
- Bronchoconstriction
- Intestinal hypermotility
- Inflammation
- Tissue damage
Symptoms of IgE mediated (immediate) reaction

Eyes: Conjunctivitis
Nose: Rhinitis
Lungs: Asthma
Skin: Urticaria Angioedema
Airway immune response

TH2 polarisation is critical for the IgE production

- Air pollutants
- Bacteria
- Allergen
- Antigen
- Virus
- DC modulating factors
- TSLP
- PGE2
- TGF-b
- IL-10
- GM-CSF
- Recruitment by chemokines
- Inflammatory cytokines

J. van Tongeren et al. Allergy 2008: 63: 1124–1135
What drives Th2 polarisation?

- antigen dose,
- nature of the antigen,
- direct cell-to-cell interaction with APCs
- the cytokine receptors available on the naive cell
- Genetic predisposition
- enviromental factors
- gastrointerstinal Flora
Hygien-Hypothesis

«Western» Lifestyle → Traditional Lifestyle

Th2
IL-4, IL-5

Allergy-Epidemic → Allergy-Prevention
Protective effect of the farm environment

Protective effect by parasite infection

Response starts in utero

Microbial exposure boosts Th1 response

Microbial exposure alters Th2 response

Gern et al. Nature Reviews 2002
Too much hygiene is harmful for horses !!!!

- Clean stables increase allergic diseases in horses.
- In Switzerland every 10th horse has Asthma to Hay-/stables

Prof. Vinzenz Gerber, Head of Clinics for Horses, University of Bern, 2009
Prevalence of Allergic diseases and Autoimmune diseases has increased from 1900 to 2000.

Prevalence of Infectious diseases has decreased from 1900 to 2000.
Clinical Manifestations of IgE-mediated (immediate type) allergic reactions
<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Time Before Clinical Signs</th>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Anaphylactic)</td>
<td>&lt;30 min</td>
<td>IgE binds to mast cells or basophils; causes degranulation of mast cell or basophil and release of reactive substances such as histamine</td>
<td>Anaphylactic shock from drug injections and insect venom; common allergic conditions, such as hay fever, asthma</td>
</tr>
<tr>
<td>Type II (Cytotoxic)</td>
<td>5–12 hours</td>
<td>Antigen causes formation of IgM and IgG antibodies that bind to target cell; when combined with action of complement, destroys target cell</td>
<td>Transfusion reactions, Rh incompatibility; hemolytic anemia, thrombocytopenia, granulocytopenia</td>
</tr>
<tr>
<td>Type III (Immune Complex)</td>
<td>3–8 hours</td>
<td>Antibodies and antigens form complexes that cause damaging inflammation</td>
<td>Arthus reactions, serum sickness</td>
</tr>
<tr>
<td>Type IV (Delayed Cell-Mediated, or Delayed Hypersensitivity)</td>
<td>24–48 hours</td>
<td>Antigens activate T(_C) that kill target cell</td>
<td>Rejection of transplanted tissues; contact dermatitis, such as poison ivy; certain chronic diseases, such as tuberculosis</td>
</tr>
</tbody>
</table>
Classification of allergic reactions according to Mueller
Anaphylaxis

= potentially life threatening situation; rapid onset

Massive mediator release

different organs are involved (skin, respiratory, cardiovascular system)

most frequent cause in Switzerland: hymenoptera venom allergy, drug allergy, food allergy
Is anaphylaxis always IgE mediated???

No, Anaphylaxis may involve other mechanisms than IgE, e.g.:

- Complement activation
- IgG and IgM immune complexes
- Non-immunologic mechanisms
- Pseudo allergies (radio contrast media)
- Toxic effects of insect venom
- Non-steroidal anti-inflammatory drugs
Food Allergy
Adverse reaction Food

1. Toxic

2. Nontoxic
   A) Immune mediated
      - IgE mediated
      - Non-IgE mediated
   
   B) Non immune mediated (food intolerance)
      - enzymatic (e.g. lactase deficiency)
      - pharmacological (abnormal reactivity to substances e.g. amines)
      - undefined (e.g. food additive intolerance)
Prevalence

- 6-8% of children have food allergy during the first 3 years of life

- Up to 85% outgrow the food allergy in the first 5-10 years of life

- Adults: USA 4% have food allergy (real allergy?)

Symptoms

- Gastrointestinal tract, skin, airways, anaphylaxis

- Co-factors: alcohol, exercise, medications
2 Groups of food allergy

Food sensitization develops as a consequence of sensitization to airborne allergens

- Mostly adults, cross reactivity

Food sensitization occurs by gastrointestinal tract (often stable proteins)

- Mostly in children, "real food allergy"
Oral allergy syndrome

Sensitization to heat/pepsine labile plant-derived proteins in patients with pollen allergy

Cross reactivity between homologous plant derived proteins and pollen proteins

Bet v1 → nuts, apple, kiwi

heated normally well tolerated

Allergen cross reactivity seems to be due to IgE antibodies that recognize structurally similar epitopes on different proteins that are phylogenetically closely related or present evolutionarily conserved structures
<table>
<thead>
<tr>
<th><strong>Birch</strong></th>
<th><strong>Apiaceae</strong></th>
<th><strong>Cantaloupe Honeydew Watermelon Zucchini Cucumber Cucurbitaceae</strong></th>
<th><strong>Banana Musaceae</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ragweed</strong></td>
<td><strong>Apiaceae</strong></td>
<td><strong>Celery Carrot Parsley Caraway Fennel Coriander Aniseed</strong></td>
<td><strong>Bell pepper Solanaceae Black pepper Piperaceae</strong></td>
</tr>
<tr>
<td><strong>Mugwort</strong></td>
<td><strong>Brassicaceae</strong></td>
<td><strong>Mustard Cauliflower Cabbage Broccoli Garlic Onion Peach Rosaceae</strong></td>
<td><strong>Ragweed Cucurbitaceae</strong></td>
</tr>
<tr>
<td><strong>Orchard</strong></td>
<td><strong>Amaranthaceae</strong></td>
<td><strong>Swiss chard</strong></td>
<td><strong>Orange Rutaceae</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Peanut Fabaceae (old Leguminosae)</strong></td>
<td><strong>White potato Solanaceae</strong></td>
</tr>
</tbody>
</table>
Food allergy - crossreactivity

celery-birch-mugwort-spices syndrome

shellfish and dust mite allergy
Food allergy - crossreaktivity

Latex-fruit syndrome

Cat-pork syndrome

Fel d 2

Pig serum albumine
2 Groups of food allergy

Food sensitization develops as a consequence of sensitization to airborne allergens

Mostly adults, cross reactivity

Food sensitization occurs by gastrointestinal tract (often stable proteins)

Mostly in children “real food allergy”
Lipid transfer proteins

Role in defence against fungi and bacteria

Heat stable, begin to unfold above 95°, protein refold on cooling

More severe allergic reactions
Triggers of food allergy - age groups
Exercise-induced anaphylaxis (EIA\text{An})

- Non-food-dependent (EIA\text{An})
  - Food-specific
  - Non-food-specific
- Food-dependent (FDEIA\text{An})
  - Food-specific
  - Non-food-specific

Tri a 19
Bee / Wasp Allergy

- Bee: Api m 1, Api m 3, Api m 4, Api m 10
  - Phospholipase A₂
  - Saure Phosphatase
  - Mellitin
  - Icarapin

- Wasp: Phospholipase A₁, Antigen 5
  - Ves v 1
  - Ves v 5

- Api m 2: Hyaluronidasen (Ves v 2)
- Api m 5: Dipeptidylpeptidase (Ves v 3)
- Api m 12: Vitellogenine (Ves v 6)
Hymenoptera venom allergy

- The prevalence of an allergy systemic reaction after a Hymenoptera sting is estimated between 1 and 7% in Europe.

- Mortality: 200 cases per year in Europe.

- One of the most frequent causes of Anaphylaxis in the adult population.

- Bee sting 50 μg (30-140 mg) of venom proteins, after a wasp sting 3–5 μg of venom proteins are introduced to the body of the victim.

- Toxic reaction > 50-100 stings (in adults); > 10 stings (in children)
Mortality due to bee/wasp sting in Switzerland 1961 – 2012
Erwin K. Wüest, EDI BFS
Local reactions after hymenoptera stings

Large local reaction=
Swelling exceeding 10 cm

Not an Allergy!
Classification of allergic reactions according to Mueller
Drug allergy
**IgE mediated drug allergies**
**(immediate reactions)**

<table>
<thead>
<tr>
<th><strong>Anaphylactic IgE-mediated reactions</strong></th>
<th><strong>Antibiotics</strong></th>
<th><strong>Chemotherapy drugs</strong></th>
<th><strong>Monoclonal antibodies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing, pruritus, urticaria, angioedema, laryngeal edema, rhinorrhea, conjunctivitis, shortness of breath, wheezing, bronchospasm, nausea, vomiting, diarrhea, hypotension</td>
<td><strong>Beta-lactams</strong></td>
<td><strong>Platins</strong></td>
<td><strong>Rituximab, trastuzumab</strong></td>
</tr>
<tr>
<td></td>
<td>Penicillins, cephalosporins, amino-penicillins</td>
<td>Carboplatin, cisplatin, oxaliplatin</td>
<td>Chronic inflammatory diseases, cancers (leukemias, breast, ovarian )</td>
</tr>
<tr>
<td></td>
<td><strong>Fluroquinolones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin, levofloxacin</td>
<td>Primary and recurrent metastatic cancers (breast, ovarian, colon)</td>
<td></td>
</tr>
</tbody>
</table>

**Desensitization often possible!!!**
Non-IgE mediated drug allergies (immediate reactions)

<table>
<thead>
<tr>
<th>Anaphylactoid</th>
<th>Aspirin/NSAIDs</th>
<th>Cardiac protection, asthma w/ nasal polyposis, chronic inflammatory diseases (RA, Crohn's)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct mast cell/basophil, complement, and leukotriene metabolism reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing, pruritus, urticaria, angioedema, throat tightness, shortness of breath, nausea, vomiting, diarrhea, hypotension, hypertension, back and/or abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>MRSA</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy drugs</td>
<td>Primary and recurrent metastatic cancers (breast, ovarian, colon)</td>
</tr>
<tr>
<td></td>
<td>Taxenes</td>
<td>Paclitaxel, docetaxel</td>
</tr>
</tbody>
</table>
Chemical structure of drug molecule

No protein drugs, small molecules
1-2 kDa, haptens

Protein drugs
Large molecules >20 kDa
Haptens

Small molecules alone are not immunogenic!
Haptens = reactive proteins binding to a larger protein → hapten-carrier complex
→ resistant to intracellular processing
→ danger signal (activation of innate immunity e.g. DC’s)
→ forms neo-antigenic determinants able to induce both a T-cell and B-cell immune response.

Not immunogenic

hapten + carrier protein = hapten-carrier complex

Not immunogenic  Not immunogenic  Immunogenic
Hapten

p-i (TCR)

p-i (HLA)

Immune reaction

Pharmacological interaction
p-i concept:

a) the drug binds first to the TCR (by non covalent bonds; not restricted to a HLA-allele)

or

b) the drug binds first to the HLA molecule, and the HLA-peptide-drug complex is then recognized by the TCR (HLA-class I restricted, CD8)
IgG mediated drug hypersensitivity (Typ II)

Haemolytic anaemia

Drug binds on Cell surface

Alters antigen on red blood cell Hapten

Recognition By antibodies

Culprit drugs: e.g. penicillins, cephalosporins
Symptoms: cytopenia (anemia, thrombocytopenia)
IgG mediated drug hypersensitivity (Typ III)

Immune complexes may deposit preferentially in joints → triggers an inflammatory response.

Clinic: vasculitis, skin, serum sickness, lungs, joints, fever
Symptoms of T cell mediated drug allergy

- Makulo-papular Exanthem
- bullous Exanthem
- Acute generalized exanthematous Pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS) toxic-epidermal Necrolysis (TEN)
- DRESS, Hepatitis, interstitial Nephritis, Pneumonitis
Contact Dermatitis
Contact Dermatitis

non-infectious reaction of the skin to external substances

**Allergic contact dermatitis**
T-Zell mediated immune response to contact allergens like:
- Nickel, lanolin, Peru balsam or potassium dichromate
- Jewellery, medication cosmetics, dyes impregnating agents

**Irritative contact dermatitis**
Non immune mediated response to physical, chemical irritants and physical influences
- Rubbing, pressure, heat and cold or UV rays
- Water, soap, disinfectants,
Allergic Contact Dermatitis

- The reaction usually occurs 24–48 hours after contact with the allergenic substance.
- The skin is inflamed and reddened, it may swell up and blisters or papules may appear.
- These symptoms are often combined with severe itching.
- The skin reaction appears at the site of the body where the skin came into contact with the irritant, but may also spread to nearby or remote regions of the skin.
Allergic Contact Dermatitis

Allergic Contact Dermatitis from a Henna Tattoo
Diagnostics of allergic diseases
Diagnostics of allergic diseases

- Medical history
- Symptoms
- Tests
Diagnostics of allergic diseases

Typ I Hypersensitivity

Skin prick test

Prick-to-prick Test
Diagnostics of allergic diseases

In-Vito Test and molecular allergy diagnostics

Type I Hypersensitivity

Serum IgE
In-Vito Test and molecular allergy diagnostics
Diagnostics of allergic diseases
Basophil activation Test
Conjunctival provocation tests (CPT, allergen solution)

No standardization of CPT; no grading of ocular reactions

Digital image analysis possesses the potential of being an objective evaluation method compared to the wide-spread subjective

Dogan et al. Int Arch Allergy Immunol 2014;163:59–68
Oral provocation tests

Food challenge Tests
Patch Tests
Type IV Hypersensitivity
Therapy principles
Therapy principles

1. Symptomatic therapy
   - antihistamines
   - corticosteroids
   - leukotriene antagonists
   - antiasthmatics (inhaled medication)
   - biologics (Omalizumab, anti-IgE), (Mepolizumab anti-IL5)

Inhibition of inflammatory mediators released during effector phase:

- anti histamines
- mast cell stabilizers
- leukotriene antagonists
- anti IL-4, IL-5
- anti IgE
- Glucocorticoids
Anti IgE therapy (omalizumab)

Binding of omalizumab to the ce3 domain of IgE.

Adapted from Francés et al. 2014 Actas Dermosifiliogr. 2014;105:45-52. - Vol. 105 Num.01
Therapy principles

Allergen-specific Immunotherapy alters course of disease
Bee keepers

Systemic reactions in 45% of beekeepers with <15 bee sting / year

No/less systemic reactions in Beekeepers with > 200 bee sting / year

Why???
Milestones in Specific Immunotherapy

• 1911–1914 subcutaneous desensitization with pollen extracts
  Noon L: Prophylactic inoculation against hay fever. Lancet 1911;I:1572–3
  Freeman J: Further observations on the treatment of hay fever by Hypodermic inoculations of pollen vaccine. Lancet 1911;II:8141
  Freeman J: Further observations on the treatment of hay fever. Lancet 1914;II:1178

• 1930 Introduction of rush desensitization

• 1954 first double blind placebo controlled SIT study

• 1959 first study with semi-depot extracts

• 1969 first sublingual immunotherapy for foods and 1970 for inhalant allergens
Allergen-specific Immunotherapy

Reduktion allergischer Symptome
Calderon et al. JACI 2011;127:30-8
Radulovic et al. Allergy 2011;66:740-52

Asthma prevention
Jacobsen et al. Allergy 2007;62:943-8
Möller et al. JACI 2002; 109: 251-256
Schmitt J et al. JACI 2015;136:1511-6
Subcutane Immuntherapie (SCIT)

Präseasonal

- Kurzzeit
- 4-8 Injektionen
- Später Start
  - 2 Monate vor der Saison

Allergovit®, ALK 7®, PolVac®

Perennial

- ca. 45 Injektionen pro Jahr

ALK Alutard®, Novo-Helisen Depot®, Alyostal®
Sublingual Immunotherapy SLIT
Passalacqua et al. JACI 2007;119:881-91
Mechanisms of SIT

A

Early desensitization:
decrease in mast cell and
basophil activity for
degranulation
and systemic anaphylaxis

T cell tolerance
induction of $T_{Reg}$ cells
suppression of Th2-Th1 cells

Late desensitization:
decrease in tissue mast cells
and eosinophils
and release of their mediators

B

Type I skin test reactivity
Specific IgE
Specific IgG4

Burks et al. J
Allergy Clin Immunol 2013;131:1288-96.
Summary
Definitions

**Atopy:** genetic determined readiness to react by IgE formation to substances taken up via aerogenous or gastro-intestinal routes

**Sensitization:** immune reaction to a foreign substance (proven in skin tests, serology, cellular tests...)
**Allergy:** immune reaction to a non replicating (harmless) substance (protein, chemical, drug, metal), which leads to clinical symptoms like.

Sensisitation and Atopy  =  Allergy
Type 1 hypersensitivity

Key Players:

- IgE
- Allergen
- Eosinophils
- B cells
- TH2
- Cytokines (IL-4, IL-5, IL-13)
- APC
- Chemokines
- Mast cells