Classification, pathogenesis and diagnostics of allergic diseases

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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.
„know that I know nothing“  
Socrates
### Prävalenzen von Allergien

<table>
<thead>
<tr>
<th></th>
<th>Welt</th>
<th>Europa</th>
<th>Schweiz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allerg. Rhinitis</td>
<td>&gt; 500 Mio.</td>
<td>90 Mio.</td>
<td>2 Mio.</td>
</tr>
<tr>
<td>Asthma</td>
<td>300 Mio.</td>
<td>25 Mio.</td>
<td>0,6 Mio.</td>
</tr>
<tr>
<td>Nahrungsmittelallergie</td>
<td>250 Mio.</td>
<td>17 Mio.</td>
<td></td>
</tr>
<tr>
<td>Medikamentenallergie</td>
<td></td>
<td>5% hospitalisierter Patienten</td>
<td></td>
</tr>
</tbody>
</table>
Overview

• Definitions (Allergy/Atopy and Allergens)
• Types of allergic reactions
• Immuncells and Mechanism involved in development of allergic reactions
• Diagnostic
• Treatment
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.

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 Proteins/Glykoproteins
  - Of animal or vegetable origin
  - Drugs/Chemicals
Allergens

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).

Pflanzen: > 3500 Arten Schweiz
Pilze: ~ 10‘000 Arten Schweiz
Tiere: ~ 1,5 Millionen Welt
Hymenopteren: ~ 100‘000 Welt
Berufsstoffe: > 400 beschrieben
Arzneimittel: ~ 7000 Swissmedic

Allergens = 2% of proteins

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
Pollen
Early and late blooming flowers

www.pollenundallergie.ch / www.meteoschweiz.ch
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>
<thead>
<tr>
<th>Spezies</th>
<th>Allergen</th>
<th>Proteinfamilie</th>
<th>UniProtKB accessions 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>
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<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>Q6WNR9</td>
<td>11</td>
<td>Haut</td>
<td>10</td>
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<tr>
<td></td>
<td>Fel d 4</td>
<td>Lipokalin</td>
<td>Q5VFH6</td>
<td>22</td>
<td>Speicheldrüse</td>
<td>63</td>
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<tr>
<td></td>
<td>Fel d 5</td>
<td>IgA</td>
<td></td>
<td>400</td>
<td>Speichel, Serum</td>
<td>38</td>
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<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>
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<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>
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<tr>
<td></td>
<td>Fel d 8</td>
<td>Latherin</td>
<td>F6K0R4</td>
<td>24</td>
<td>Speicheldrüse</td>
<td>19</td>
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<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>
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<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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<td>Can f 3</td>
<td>Serumalbumin</td>
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<td>Leber</td>
<td>25 – 35</td>
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<td>Can f 4</td>
<td>Lipokalin</td>
<td>D7PBH4</td>
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<td>Zunge</td>
<td>35</td>
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<td></td>
<td>Can f 5</td>
<td>Kallikrein</td>
<td>P09582</td>
<td>28</td>
<td>Urin</td>
<td>70</td>
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<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>
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</table>
Bee / Wasp Allergy

<table>
<thead>
<tr>
<th>Api m 1</th>
<th>Phospholipase A(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Api m 3</td>
<td>Saure Phosphatase</td>
</tr>
<tr>
<td>Api m 4</td>
<td>Mellitin</td>
</tr>
<tr>
<td>Api m 10</td>
<td>Icarapin</td>
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</table>

<table>
<thead>
<tr>
<th>Ves v 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ves v 5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Ves v 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ves v 3</td>
</tr>
<tr>
<td>Ves v 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Api m 2</th>
<th>Hyaluronidasen</th>
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</thead>
<tbody>
<tr>
<td>Api m 5</td>
<td>Dipeptidylpeptidasen</td>
</tr>
<tr>
<td>Api m 12</td>
<td>Vitellogenine</td>
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</table>

<table>
<thead>
<tr>
<th>Phospholipase A(_1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ves v 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ves v 3</td>
</tr>
<tr>
<td>Ves v 6</td>
</tr>
</tbody>
</table>
Peanut allergy

[Diagram showing various peanut proteins and their allergenic properties]
Classification according to mechanisms

IgE mediated immune reactions:
  e.g. rhinitis & conjunctivitis, asthma, urticaria, anaphylaxis

IgG mediated reactions:
  vasculitis, immune hemolytic anemia, thrombocytopenia and granulocytopenia, Arthus reaction

T-cell reactions:
  contact dermatitis, drug allergies, atopic dermatitis, asthma
<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>Immediate type Reaktion &lt; 1h</td>
<td></td>
<td></td>
<td></td>
</tr>
<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</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>
<tr>
<td></td>
<td>IgM pentamer</td>
<td>IgG monomer</td>
<td>Secretory IgA dimer</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Heavy chains</strong></td>
<td>μ</td>
<td>γ</td>
<td>α</td>
</tr>
<tr>
<td><strong>Number of antigen binding sites</strong></td>
<td>10</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Molecular weight (Daltons)</strong></td>
<td>900,000</td>
<td>150,000</td>
<td>385,000</td>
</tr>
<tr>
<td><strong>Percentage of total antibody in serum</strong></td>
<td>6%</td>
<td>80%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Crosses placenta</strong></td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Fixes complement</strong></td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Fc binds to</strong></td>
<td></td>
<td>phagocytes</td>
<td>mast cells and basophils</td>
</tr>
<tr>
<td><strong>Function</strong></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>
</tr>
</tbody>
</table>
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 $\rightarrow$ 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 $\rightarrow$ 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 $\rightarrow$ so-called pollen-associated lipid mediators (PALMs) $\rightarrow$ act as stimulators of DC
Airway immune response

Air pollutants

Bacteria

Allergen

Virus

Antigen

DC modulating factors

TSLP

PGE2

TGF-β

IL-10

GM-CSF

Inflammatory cytokines

Recruitment by chemokines

Lymph node

Treg cells

Th1 cells

Th2 cells

Th17 cells

Naïve Th cells

Airway immune response

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

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
- environmental factors
- gastrointestinal Flora
What drives Th2 polarisation?

- **IL-2** proliferation and clonal expansion of T cells
- **IL-4** An autocrine of Th2 cells during their maturation
- **IL-6** is secreted by T cells and macrophages
- **IL-31** activated CD4+ T lymphocytes, in particular activated TH2 helper cells, mast cells, macrophages, and dendritic cells. IL-31 is believed to play a role in atopic dermatitis and eczema.
- **IL-33** is expressed by a wide variety of cell types, including fibroblasts, mast cells, dendritic cells, macrophages, osteoblasts, endothelial cells, and epithelial cells
- **TSLP** is produced mainly by non-hematopoietic cells such as fibroblasts, epithelial cells and different types of stromal or stromal-like cells
Hygien-Hypothesis

«Western» Lifestyle

Traditional Lifestyle

Th2
IL-4, IL-5

Allergy-Epidemic

Allergy-Prevention
Microbial exposure boosts Th1 response

Microbial exposure alters Th2 response

Response starts in utero

Protective effect of the farm environment

Protective effect by parasite infection

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

- Clean stables increase allergic diseases in horses.
- in Switzerland every 10\textsuperscript{th} horse have Asthma to Hay-/stables

Prof. Vinzenz Gerber, Head of Clinics for Horses University of Bern, 2009
Sensitization Phase

- DC
- T cell (naïve)
- Clonal expansion
- IL-4, IL-5, IL-13
- B cell
- Ig switch
- Production of allergen-specific IgE

Effector Phase

- Mast cell
- Basophil
- Histamine
- Prostaglandin
- TNF-α
- Early phase
- Late phase
- T cells
- TH2
- TH17
- TH1
- Epithelial barrier
- Lymph node
Plasma cell (produces IgE antibody)

Mast cell (releases mediators)

IgE cross linking by antibody

Histamine and other mediators

Activation

Symptoms
Cross linking of 2 Fc-IgE-RI is required for mast cell activation

Mediator release
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
Mast cell

Resting

Degranulated

Nature Reviews | Immunology
symptoms of immediate reaction

Eyes: Conjunctivitis

Nose: Rhinitis

Lungs: Asthma

Skin: Urticaria Angioedema
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
Symptoms of IgE induced late reaction

**chronic**
- Swelling
- Infiltration by inflammatory cells
- Damage to epithelia
- Thickening of basal membrane, restructuring of lung tissue
- Mucus production

(LT, cytokine, PG, PAF, ECP, EPO, EDN,... IL-13, TNFa)
- blocked nose
- bronchial hyper reactivity
- reduced lung function
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)
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
Allergen cross reactivity
structurally similar epitopes on different proteins

Crystallographic structures of Pru a1 and Bet v1
Food allergy - crossreaktivity

**celery-birch-mugwort-spices** syndrome

shellfish and dust mite allergy
Food allergy - crossreactivity

- Latex-fruit syndrome
  - Kiwi
  - Banana
  - Chestnut
  - Orange
  - Potato

- Cat-pork syndrome
  - Cat
  - Pig
  - Pig serum albumine

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
Peanut allergy
Triggers of food allergy - age groups

Exercise-induced anaphylaxis (EIAn)

- Non-food-dependent (EIAn)
- Food-dependent (FDEIAn)
  - Food-specific
  - Non-food-specific

Tri a 19
Bee / Wasp Allergy

- Api m 1: Phospholipase A₂
- Api m 3: Saure Phosphatase
- Api m 4: Mellitin
- Api m 10: Icarapin
- Ves v 1: Phospholipase A₁
- Ves v 5: Antigen 5
- Ves v 2: Hyaluronidasen
- Ves v 3: Dipeptidylpeptidasen
- Ves v 6: Vitellogenine
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 hymenoptera allergic reactions

Classification according to Mueller
Drug allergy
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.

\[ \text{hapten} + \text{carrier protein} \rightarrow \text{hapten-carrier complex} \]

Not immunogenic  Not immunogenic  Immunogenic
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)
IgE mediated drug allergies (immediate reactions)

<table>
<thead>
<tr>
<th>Anaphylactic IgE-mediated reactions</th>
<th>Antibiotics</th>
<th>Chemotherapy drugs</th>
<th>Monoclonal antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing, pruritus, urticaria,</td>
<td>Beta-lactams</td>
<td>Platins</td>
<td>Monoclonal antibodies</td>
</tr>
<tr>
<td>angioedema, laryngeal edema,</td>
<td>Penicillins, cephalosporins,</td>
<td>Carboplatin, cisplatin, oxaliplatin</td>
<td>Rituximab, trastuzumab</td>
</tr>
<tr>
<td>rhinorrhea, conjunctivitis,</td>
<td>amino-penicillins Fluroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>shortness of breath, wheezing,</td>
<td>Ciprofloxacin, levofloxacin</td>
<td>Primary and recurrent metastatic cancers (breast, ovarian, colon)</td>
<td>Chronic inflammatory diseases, cancers (leukemias, breast, ovarian )</td>
</tr>
<tr>
<td>bronchospasm, nausea, vomiting,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhea, hypotension</td>
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<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>Pseudo-allergic reactions radio contrast media: direct membrane effects related to the osmolarity of contrast media solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct mast cell/basophil, complement, and leukotriene metabolism reactions</td>
<td>Cardiac protection, asthma w/nasal polyposis, chronic inflammatory diseases (RA, Crohn's)</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>MRSA</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Chemotherapy drugs Taxenes Paclitaxel, docetaxel</td>
<td>Primary and recurrent metastatic cancers (breast, ovarian, colon)</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Immune Reactant</th>
<th>Antigen</th>
<th>Effector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Soluble antigen, Cell- or matrix-associated antigen, Soluble antigen, Antigen presented by cells or direct T cell stimulation, Cell-associated antigen or direct T cell stimulation, Soluble antigen presented by cells or direct T cell stimulation</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>Cell- or matrix-associated antigen, Soluble antigen, Antigen presented by cells or direct T cell stimulation, Cell-associated antigen or direct T cell stimulation, Soluble antigen presented by cells or direct T cell stimulation</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>Soluble antigen, Antigen presented by cells or direct T cell stimulation, Cell-associated antigen or direct T cell stimulation, Soluble antigen presented by cells or direct T cell stimulation</td>
<td></td>
</tr>
<tr>
<td>Type IVa</td>
<td>IFNγ, TNFα (T_H1 cells), IL-5, IL-4/IL-13 (T_H2 cells), Perforin/granzymeB (CTL)</td>
<td></td>
</tr>
<tr>
<td>Type IVb</td>
<td>IL-5, IL-4/IL-13 (T_H2 cells), Perforin/granzymeB (CTL)</td>
<td></td>
</tr>
<tr>
<td>Type IVc</td>
<td>Perforin/granzymeB (CTL), CXCL-8, IL-17 GM-CSF (T cells)</td>
<td></td>
</tr>
<tr>
<td>Type IVd</td>
<td>CXCL-8, IL-17 GM-CSF (T cells)</td>
<td></td>
</tr>
</tbody>
</table>

**Example of hypersensitivity reaction**

- **Type I**
  - Allergic rhinitis, asthma, systemic anaphylaxis
  - Hemolytic anemia, thrombocytopenia (e.g., penicillin)
  - Serum sickness, Arthus reaction
  - Tuberculin reaction, contact dermatitis (with IVc)
  - Chronic asthma, chronic allergic rhinitis
  - Maculopapular exanthema with eosinophilia
  - Contact dermatitis
  - Maculopapular and bullous exanthema
  - Hepatitis

- **Type II**
  - Anaphylaxis
  - Allergic reaction
  - Drug hypersensitivity

- **Type III**
  - Immediate-type reaction
  - Cross-reactive hypersensitivity

- **Type IVa**
  - Delayed-type reaction
  - Cell-mediated hypersensitivity

- **Type IVb**
  - Immediate-type reaction
  - Cell-mediated hypersensitivity

- **Type IVc**
  - Immediate-type reaction
  - Cell-mediated hypersensitivity

- **Type IVd**
  - Immediate-type reaction
  - Cell-mediated hypersensitivity

**Antibody (I–III) and T cell-orchestrated hypersensitivity reactions (IVa–d)**
Contact Dermatitis

non-infectious reaction of the skin to external substances

Allergic contact dermatitis
T- Zell mediated immune response to contactallergens 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.
• 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
Allergy diagnosis

Allergy = sensitization + clinical symptoms

Skin prick test

Serum IgE
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
Diagnosis of food allergy

Prick-to-prick Test

Detection of specific IgE Antibodies

Bet v 1 versus Pru p 3

Food challenge Tests
Peanut allergy
Patch Tests
Therapy principles

1. Symptomatic therapy
   • antihistamines
   • corticosteroids
   • leukotriene antagonists
   • antiasthmatics (inhalative 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
Binding of omalizumab to the cε3 domain of IgE.

Adapted from Francés et al. 2014 Actas Dermosifiliogr. 2014;105:45-52. - Vol. 105 Num.01
2. Specific /causal therapy

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???
Allergen-specific Immunotherapy

The only causal therapy of allergic Diseases

1998 WHO accepts the therapy


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
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.
Efficacy of different Interventions in seasonal allergic Rhinitis (1. year)
Side effects of SCIT

Severity of side effects: Mild symptoms to life-threatening anaphylaxis and even death

Table 2. Systemic Reactions (SRs) per 10,000 Injection Visits\textsuperscript{a} between July 2008 and 2010

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Any type of SR</td>
<td>10.2</td>
<td>9.7</td>
</tr>
<tr>
<td>Grade 1 (mild SRs)</td>
<td>7.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Grade 2 (moderate SRs)</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Grade 3 (severe SRs)</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy—year 2


SLIT has a better safety profile than SCIT (home administration possible)
Summary

Allergy?

specific immune reaction to harmless foreign substances with clinical symptoms

Sensitisation and Atopy $\neq$ Allergy
Type 1 hypersensitivity

Key Players:

- Allergen-specific IgE
- Allergen
- B cells
- TH2
- APC
- Eosinophils
- Cytokines (IL-4, IL-5, IL-13)
- Tissue Mast cells
- Chemokines
Are IgE antibodies needed for Mast cell activation?

Yes
No
<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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</table>

Is allergen needed to induce anaphylaxis?
Which antibody is blocked by omalizumab (Xolair)?

IgE  IgM  IgG  IgA
What is the only causal therapy for allergic diseases?

Corticostroids?  
Xolair?

Antihistamines?

Allergen-specific immunotherapy?