Diagnosing drug allergy
Session IV – T-cell mediated allergic diseases

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Prevalence of Adverse Drug reactions (ADR)

- Considerable morbidity
  - ADR are frequent
  - In 10 to 20% of hospitalized patients
  - In 7% of the general population

- Considerable mortality:
  - 0.32% of hospitalized patients in the US*
  - 106,000 deaths in the 1994 year
  - The fourth most frequent cause of death

- Mortality due to
  - Anaphylaxis
  - SJS (10% mortality) and TEN (30%)
  - Multisystem organ hypersensitivity
  - Organ-specific involvement (hepatitis, etc.)

*Lazarou et al. JAMA 279, 1200, 1998
several difficulties

- innumerable drugs
- heterogeneous signs/symptoms
- diverse mechanisms
- limited testing procedures
- considerable knowledge deficits
- several differentials
## Skin Manifestations in Drug Allergy

<table>
<thead>
<tr>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria, angioedema</td>
</tr>
<tr>
<td>Exanthems</td>
</tr>
<tr>
<td>- macular</td>
</tr>
<tr>
<td>- papular</td>
</tr>
<tr>
<td>- vesicular</td>
</tr>
<tr>
<td>- pustular</td>
</tr>
<tr>
<td>- bullous</td>
</tr>
<tr>
<td>- fixed drug exantheme</td>
</tr>
<tr>
<td>- hemorrhagic-necrotic</td>
</tr>
<tr>
<td>- lichenoid</td>
</tr>
<tr>
<td>- psoriasiform</td>
</tr>
<tr>
<td>- exfoliative</td>
</tr>
<tr>
<td>- erythroderma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucous membranes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- erosions, aphthous lesions, ulcers</td>
</tr>
<tr>
<td>- stomatitis</td>
</tr>
<tr>
<td>- genital lesions</td>
</tr>
<tr>
<td>- conjunctivitis</td>
</tr>
<tr>
<td>- rhinitis</td>
</tr>
<tr>
<td>Photoinduced exanthems</td>
</tr>
<tr>
<td>Erythema nodosum</td>
</tr>
<tr>
<td>Severe cutaneous reactions</td>
</tr>
<tr>
<td>- DIHS/DRESS</td>
</tr>
<tr>
<td>- SJS/TEN</td>
</tr>
<tr>
<td>- Cutaneous vasculitis</td>
</tr>
<tr>
<td>- Cutaneous lupus erythematoses</td>
</tr>
<tr>
<td>etc.</td>
</tr>
</tbody>
</table>

Bircher A. Approach to the patient with … drug hypersensitivity, Karger, 2007
the diagnostic work-up for drug allergy

dependent on history / clinical manifestation
- Immediate / delayed
- Mild / severe / life-threatening
availability of safe test procedures
the importance of the drug
the specific situation of the patient
Knowledge of the relevant literature:
- Demoly P et al. Drug hypersensitivity questionnaire. Allergy 1999
- Brockow K et al. General considerations for skin tests. Allergy 2002
- Aberer W et al. Drug provocation testing. Allergy 2003
Experience
Test indication – no indication

- Urticaria, starting 20 min after intakte of penicillin tablet
- Angioedema starting 1 hour after intake of ACE-inhibitor
Drug hypersensitivity work-up

1st step: clinical picture and history
2nd step: appropriate testing
  - skin test
    - for immediate-type reactions
    - for delayed-type reactions
  - in vitro test
  - provocation test
Check for relevance
Inform the patient appropriately
Skin tests

- Brockow K et al. General considerations. Allergy 2002

Specific recommendations:
- Barbaud A. Cutaneous ADR. Contact Derm 2001
- Brockow K et al. Skin test concentrations for „all drugs“. Allergy 2013
<table>
<thead>
<tr>
<th>Condition</th>
<th>Patch test</th>
<th>Prick test</th>
<th>IDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash</td>
<td>useful</td>
<td>before IDT plus delayed reading</td>
<td>with immediate and delayed readings</td>
</tr>
<tr>
<td>Generalized eczema</td>
<td>useful</td>
<td>before IDT plus delayed reading</td>
<td>with immediate and delayed readings</td>
</tr>
<tr>
<td>Localized eczema caused by heparin</td>
<td>useful</td>
<td>no value but recommended</td>
<td>with immediate and delayed readings, frequently only positive &gt;3 days</td>
</tr>
<tr>
<td>SDRIFE (Baboon)</td>
<td>useful</td>
<td>unknown value</td>
<td>unknown value</td>
</tr>
<tr>
<td>AGEP</td>
<td>useful</td>
<td>unknown value</td>
<td>unknown value</td>
</tr>
<tr>
<td>Fixed drug erupt.</td>
<td>useful in patch</td>
<td>unknown value</td>
<td>unknown value</td>
</tr>
<tr>
<td>DRESS</td>
<td>probably helpful</td>
<td>value?</td>
<td>unknown value</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>no value</td>
<td>no value</td>
<td>no value, could be dangerous</td>
</tr>
<tr>
<td>TEN</td>
<td>can be done, rarely positive</td>
<td>no value</td>
<td>are rarely done, because could be dangerous</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>photopach test</td>
<td>no value</td>
<td>no value</td>
</tr>
</tbody>
</table>
Indications – no indications

- Immediate type reactions
  - Urticaria
  - Angioedema
  - Anaphylaxis
  - Conjunctivitis
  - Rhinitis
  - Bronchospasm / asthma
  - Erythematous eruption / flushing

- Delayed type reactions
  - Maculopapular rash
  - Generalized eczema
  - SDRIFE – Baboon syndrome
  - AGEP (pustulosis)
  - Fixed drug eruption
  - photosensitivity

- Drug-induced autoimmune diseases
  - Bullous pemphigoid
  - Pemphigus vulgaris
  - Systemic lupus erythematosus

- Severe exfoliative skin reactions
  - DRESS (hypersensitivity syndrome)
  - Exfoliative dermatitis
  - Multilocalized bullous FDE
  - Stevens Johnson syndrome
  - Toxic epidermal necrolysis

- Severe vasculitis syndromes

Barbaud Annick, Immunol Allergy Clin North Am 2009
Drugs with well-standardized test protocols

- Immediate type allergy:
  - Penicillins and cephalosporins
  - Neuromuscular blocking agents
  - Local anaesthetics
  - Iodinated contrast media
  - Chemotherapeutics (platinum salts)

- Contact allergy:
  - Many case reports
  - Several case series (iodinated contrast media, steroids, and others)
Timing

- After an interval that allows resolution of clinical symptoms and clearance of a suspected drug and drugs used for treatment
- 6 weeks to 6 months after the hypersensitivity reaction
- Drug-free intervals
  - H1-antihistamines  5 days
  - β-adrenergic drugs  5 days
  - Glucocorticosteroids
    - Long-term oral, i.v.  3 weeks
    - Short-term, high dose oral, i.v.  1 week
    - Short-term, <50 mg prednisolone oral, i.v.  3 days
    - Topical topical  > 2 weeks
Workflow and performance

- Patients should be in good condition
- Informed consent
- Start with skin prick test
- Almost no commercial test preparations
- Start at „safe“ concentrations
- Test drug and excipients
- If SPT is negative, perform intradermal testing
- To test controls is strongly recommended, but …
- Do readings at 15 min; late readings may be helpful
- Be aware of side effects
  - Pain
  - Flare-up of reaction
  - Systemic reaction
  - Skin necrosis, etc.
Reasons for false-positive reactions

- Spontaneous mast cell degranulation
- Non-specific irritation due to high concentration
- Physical trauma in patient with dermographism/urticaria factitia
- Reaction to diluent, preservative, or contaminant
- Improper interpretation of results (erythema vs. wheal)
- Lack of negative and positive test controls
- Patient is sensitized and may have (low-affinity) drug/hapten-specific IgE antibodies – but does not react!

- Even a positive reaction does not prove clinical relevance!
Reasons for false-negative reactions

- Application of too little antigen (inappropriate dilution, storage problem)
- Insufficient penetration of the antigen
- Blocking effect of medications
- Improper readings, inadequate scoring
- Missing co-factors at the time of testing
- Reaction requires metabolized drug
- Route of application might be important (e.g. for heparins)
- Improper testing, too early, etc.
- Individual variability
Adverse test reactions

- SPT, if performed correctly, is safe, but …
- IDT: several fatal or near-fatal reactions have been reported
- High risk:
  - Betalactams
  - Previous anaphylaxis
  - Complicating conditions, such as systemic mastocytosis
  - Unstable condition
  - etc.
- Essentials to treat anaphylaxis:
  - Adequate equipment
  - Specialist environment
Patch testing for delayed reactions

- Still experimental procedure
- Best done in large centers
- Few commercial test substances
- Problem of interpretation
  - Potential false-positive reactions
  - Potential false-negative reactions
  - Negative predictive value variable
- Safety concerns

Barbaud A et al.  
Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions.  
Contact Dermatitis 2001, 45, 321-328  
Immunol Allergy Clin North Am 2009
Some problems with patch testing

- Drug patch tests can re-induce the delayed CADR (even if test is negative):
  - Acyclovir, carbamazepine, pseudoephedrine, paracetamol
- Several drugs have been reported to induce false-positive results:
  - Colchicin, captopril, chloroquine, and others
- Testing in the most affected site of the initial CADR might be essential:
  - FDE, TEN, MPR and others
- Dilution in alcohol might be necessary
  - Steroids, estrogens
- Many drugs are irritants
- Photoallergic substances might also be contact allergens
- For many drugs, ideal concentrations, diluents and test procedure are not defined
- Healthy and previously exposed controls seem essential, but …
Summary – immediate type reactions

- SPTs and IDTs are bioassays
- detect rapidly biological response to mediators released from stimulated MC
- local reaction with wheal and flare
- do suggest, but not prove, IgE-mediated reaction
- big variability, dependent on many factors

- major characteristics:
  - simple, rapid, low cost, high sensitivity

- main limitations:
  - questionable relevance
  - low sensitivity
  - varying specificity
  - few standardized, commercial substances

- irreplacable in daily practice
In vitro-Testing

- IgE-detection if available
  - be aware of false-positive and false-negative reactions
  - IgE-detection and skin tests are frequently not equivalent

- Alternatives:
  - LTT, (specific IgG, histamine), tryptase?, HRT
  - CAST, FLOW-cytometry

- Relevance of in vitro testing frequently overestimated:
  - a positive test does not make „a diagnosis“
  - a negative test does not exclude allergy
Rechallenge often does establish a diagnosis, but:
- can cause severe or fatal reaction
- Contraindications: anaphylaxis, SJS, TEN, erythema multiforme, exfoliative dermatitis, erythroderma, etc.
- Great caution and a compelling need

Accurate identification of the responsible agent

Plans to avoid future allergic reactions should be formulated as a final phase of the management

Aberer et al., Drug provocation testing, Allergy 2003
Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations

- Allergy 2003: 58: 854-63
Principles and Indications

Drug Provocation Test (DPT) is considered to be the „gold standard“

But: it is not a golden standard!

Indications:

- Exclude hypersensitivity in non-suggestive history
- Provide safe pharmacologically and/or structurally non-related drugs in proven hypersensitivity
- Exclude cross-reactivity of related drugs in proven hypersensitivity
- Establish a firm diagnosis in suggestive history of drug hypersensitivity with negative, non-conclusive or non-available allergologic tests

ENDA – Position paper
Test methods

- Route of administration
- Test agents
- Dosage
- Time interval between reaction and DPT
- Ethical considerations
- Safeguards
- Documentation
- Practical aspects
- Test performance
- Assessment of test results

Chapters in the ENDA – Position paper
Published recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Doses (mg)</th>
<th>Route</th>
<th>Daily Dose for Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Penicillin</td>
<td>1, 5, 25, 100, 500, 1000</td>
<td>Oral</td>
<td>1000–2000 mg</td>
</tr>
<tr>
<td>Cefador</td>
<td>Cephalosporin</td>
<td>1, 5, 25, 125, 500</td>
<td>Oral</td>
<td>750 mg</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Cephalosporin</td>
<td>1, 5, 25, 100, 225</td>
<td>Oral</td>
<td>400 mg</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Cephalosporin</td>
<td>1, 5, 25, 100, 500, 1000</td>
<td>Intravenous</td>
<td>1000–2000 mg</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Macrolide</td>
<td>1, 5, 25, 75, 125, 250</td>
<td>Oral</td>
<td>500 mg</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Quinolone</td>
<td>1, 5, 25, 100, 500</td>
<td>Oral</td>
<td>500–1500 mg</td>
</tr>
<tr>
<td>Acetylsalicylic add</td>
<td>NSAID</td>
<td>1, 5, 20, 50, 100, 200, 500</td>
<td>Oral</td>
<td>500–3000 mg</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>NSAID</td>
<td>1, 3, 7.5</td>
<td>Oral</td>
<td>7.5–15 mg</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Steroid</td>
<td>2, 10, 20, 40</td>
<td>Oral</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>PPI</td>
<td>1, 5, 10, 20</td>
<td>Oral</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Tetrazepam</td>
<td>Benzodiazepine</td>
<td>1, 2.5, 25, 50</td>
<td>Oral</td>
<td>50–100 mg</td>
</tr>
<tr>
<td>Any vaccine</td>
<td>Vaccine</td>
<td>0.1, 0.5</td>
<td>Subcutaneous</td>
<td>0.5 (1.0) mL</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Local anesthetic</td>
<td>0.1, 1, 2</td>
<td>Subcutaneous</td>
<td>1–3 mL</td>
</tr>
</tbody>
</table>

Abbreviation: PPI, proton pump inhibitor.

*a Ten times less than the first dose for anaphylactic shock, individual approach.

*b Recommendations may vary in different countries.
# the golden standard?

## Table 4. Important considerations when interpreting DPT results

<table>
<thead>
<tr>
<th>Potential reasons for</th>
<th>false-positive reactions</th>
<th>false-negative results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological symptoms</td>
<td></td>
<td>Antiallergic drugs</td>
</tr>
<tr>
<td>Preexisting symptoms (e.g. urticaria)</td>
<td></td>
<td>Missing co-factors (light, co-medication, viral infection, physical exercise,...)</td>
</tr>
<tr>
<td>Drug-induced aggravation of preexisting disease</td>
<td></td>
<td>Exposure and/or observation time too short</td>
</tr>
<tr>
<td>Self infliction</td>
<td></td>
<td>Too short/too long time interval from reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosage too low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Desensitization” by testing</td>
</tr>
</tbody>
</table>
suspicion of drug hypersensitivity

ENDA questionnaire

drug hypersensitivity most unlikely

possible drug hypersensitivity?

yes

results

in vivo and/or in vitro tests available?

no

non-conclusive or negative

oral DPT

positive

proven drug hypersensitivity

negative

no drug hypersensitivity

not available or not adequate

parenteral DPT

positive

proven drug hypersensitivity

negative

no drug hypersensitivity

Aberer, Kränke Immunol Allergy Clin, 2009
Summary

- If you see suspicious skin lesions, always consider drug allergy
- Exact documentation is essential for the further work-up
- Make a correct diagnoses:
  - AGEP
- Decide for the appropriate testing technique
Diagnosis of drug allergy

If you want to know more:

- excellent books
- join the ENDA – European Network on Drug Allergy

Thanks for your attention