Type A reactions
- dose-dependent and predictable side effects
- due to the pharmacological activity of the drug

Type B “bizarre” reactions
- not predictable
- (partly) dose independent
- in susceptible patient

Adverse Drug Reactions (ADRs)

Type B “bizarre” reactions
- Often involve the skin
- 2-3% of hospitalized patients

- Comprise a broad spectrum of clinical features

1. Bigley et al. JAMA 1986;256:3358
Type B “bizarre” reactions – mild manifestations

- antibody-mediated effector functions (Type I - III)
- drug-specific T cell/cytokine-dependent functions (Type IV)

Maculopapular exanthema (MPE)

- Most common cutaneous drug reactions
- Non immediate-type reactions
- Usually develops within 7-14 days (1-3 days in sensitized individuals)
- Often on the trunk, neck and upper extremities
- Faint, pink or red macules, papules, progressively become confluent

Type B “bizarre” reactions - severe manifestations

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Stevens-Johnson Syndrome (SJS) → Toxic Epidermal Necrolysis (TEN)
- Acute Generalized Exanthematous Pustulosis (AGEP)

Mortality: 10 %
Mortality: 13-39 %
Mortality: 1-5 %
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

- Usually develops after 2-8 weeks. (slow recovery: weeks – months)
- Facial edema, maculopapular rash, erythroderma, exfoliative dermatitis
- Fever, lymphadenopathy, hepatitis, nephritis, carditis, pneumonitis, …
- Leukocytosis, eosinophilia, atypical lymphocytes

Stevens-Johnson Syndrome (SJS)
Toxic Epidermal Necrolysis (TEN)

- Usually develops within 4-8 weeks
- Mucous membrane involvement
- Atypical target lesions, painful purpuric macules, initially mainly on the trunk
- Blisters, epidermal detachment

Stevens-Johnson Syndrome (SJS)
Toxic Epidermal Necrolysis (TEN)

Represent a spectrum of disease with differing severity

<table>
<thead>
<tr>
<th>SJS</th>
<th>SJS/ TEN overlap</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 % of BSA</td>
<td>10-30 % of BSA</td>
<td>&gt;30 % of BSA</td>
</tr>
</tbody>
</table>

Acute Generalized Exanthematous Pustulosis (AGEP)

- usually develops within 48 hours
- acute occurrence of multiple sterile, non-follicular, pinhead-sized pustules
- arise on an edematous erythema
- the lesions are often accentuated in the main folds
- fever, elevated neutrophil counts (>7000/mm³)

Non-immediate reactions and typically involved drugs

<table>
<thead>
<tr>
<th>Non-immediate reactions</th>
<th>Typically involved drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPE</td>
<td>β-lactam antibiotics, sulfonamide antibiotics, macrolides, quinolones, diuretics and others</td>
</tr>
<tr>
<td>DRESS</td>
<td>Carbamazepine, phenytoin, lamotrigine, minocycline, atorvastatin, dapsone, sulfasalazine, co-trimoxazole, abacavir (without eosinophilia)</td>
</tr>
<tr>
<td>SJS and TEN</td>
<td>Allopurinol, phenytoin, carbamazepine, lamotrigine, co-trimoxazole, barbiturate, NSAID (oxicams), septraline, pantoprazole, tramadol, nevapirine</td>
</tr>
<tr>
<td>AGEP</td>
<td>Aminopenicillins, cephalosporins, macrolides sulfonamide antibiotics, celecoxib, diltiazem, quinolone, terbinafine, corticosteroids</td>
</tr>
</tbody>
</table>

Clinical approach

- Detailed history (which drugs are involved?)
- Interval between the introduction of a drug and onset of the eruption (immediate or non-immediate)
- Does the type of reaction correspond to known adverse reactions to (one of) the involved drug?
- Are there any risk factors or cofactors?
What are the risk factors?

- Underlying/concomitant illness
  - viral infections (HIV, EBV, CMV)
  - lymphoproliferative diseases
  - autoimmune disorders
- History of adverse drug reactions
  - prior sensitization
  - cross-reactivity
- Immunogenetic factors
  - certain HLA-B alleles predispose for drug allergies

Take home message

- eosinophils
- fever, lymphadenopathy
- involvement of internal organs
- widespread erythema (>60%)

Be aware of danger signs!

Danger signs in DRESS

- facial edema
- widespread erythema (>60%)
- fever, lymphadenopathy
- involvement of internal organs
Danger signs in SJS and TEN

- painful, burning skin
- atypical targets
- purpuric macules
- grey areas
- widespread erythema
- positive Nikolsky sign
- vesicles and bullae

Danger signs in AGEP

- fever
- leucocytosis
- widespread erythema
- non-follicular, pinhead-sized pustules

Drug tests

- IgE-mediated reactions
  - Scratch tests, intradermal tests
  - Serology
  - Basophil activation tests (BAT)

- T cell-mediated reactions
  - Patch tests
  - Lymphocyte transformation tests (LTT)
  - Elispot (cytokines)
  - FACS (CD69)