Classification of drug hypersensitivity by chronology and morphology

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Disclosure

In relation to this presentation, I declare that there are no conflicts of interest.

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1. Why?

2. How?
What is an immediate drug hypersensitivity reaction?
Proposed mechanisms of drug allergy

Immediate type I
- allergen
- IgE
- Fc receptor
- mast cell degranulation
- mediator release

Cytotoxic type II
- cell surface antigen
- IgG
- cytotoxic action
- antibody
- complement
- mediated lysis

Immunocomplex type III
- immune-complex deposition
- complement
- blood vessel
- tissue basement membrane

Delayed type IV
- antigens
- inflammatory mediators
- lymphokines
- activated macrophage

Hypothesis: drug hypersensitivity is always caused by these reaction types

Has proven wrong in its exclusiveness!

Coombs, Gell 1968
Proposed mechanisms of drug allergy

Immediate type I
- Allergen binds to IgE on mast cell
- Fc receptor
- Mast cell degranulation
- Mediator release

Cytotoxic type II
- Cell surface antigen binds to IgG
- Cytotoxic action
- Antibody
- Complement
- Complement-mediated lysis

Immunocomplex type III
- Immune-complex deposition
- Complement
- Blood vessel
- Tissue basement membrane

Delayed type IV
- Antigens
- Inflammatory mediators
- T lymphocytes
- Lymphokines
- Activated macrophage

Proposed mechanisms of drug allergy

Immediate

Delayed
Non-immediate

Coombs, Gell 1968
Immediate hypersensitivity: common associations

- **Chronology**
  - Within minutes to 1(-6) hours after last drug intake, if drug given iv > im > sc > po

- **Clinical manifestation**
  - Urticaria, angioedema, bronchospasm, anaphylaxis

- **Effector cells**
  - Mostly mast cells/basophils

- **Pathophysiology**
  - IgE-mediated anaphylaxis/urticaria (type I)
  - Nonallergic (direct mast cell/basophil activation)
  - IgG-immune complex anaphylaxis?

adapted from: Andreas Bircher
Non-immediate (delayed): common associations

- Chronology
  - Typically from 1- (6 - 12 to 24/48) hours if drug given iv > im > sc > po

- Clinical manifestation
  - Maculopapular exanthems > many others

- Effector cells
  - T lymphocytes (+ other effector cells)

- Pathophysiology
  - T cell-mediated and -orchestrated cytotoxicity or inflammation

adapted from: Andreas Bircher
### Time cutoff differences for acute/delayed immediate/non-immediate

**Table 1** Classification of hypersensitivity reactions to ASA and other nonsteroidal anti-inflammatory drugs (NSAIDs) (Modified from [3])

<table>
<thead>
<tr>
<th>Timing of reaction</th>
<th>Clinical manifestation</th>
<th>Type of reaction</th>
<th>Underlying disease</th>
<th>Putative mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (immediate to several hours after exposure)</td>
<td>Rhinitis/asthma</td>
<td>Cross-reactive</td>
<td>Asthma/rhinosinusitis/nasal polyps</td>
<td>Inhibition of COX-1</td>
</tr>
<tr>
<td></td>
<td>Urticaria/angioedema</td>
<td>Cross-reactive</td>
<td>Chronic urticaria</td>
<td>Inhibition of COX-1</td>
</tr>
<tr>
<td></td>
<td>Urticaria/angioedema</td>
<td>Multiple NSAIDs-induced</td>
<td>No underlying chronic disease (in some patients, the reaction to NSAIDs may precede development of chronic urticaria)</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Urticaria/angioedema/ anaphylaxis</td>
<td>Single drug-induced</td>
<td>Atopy, Food allergy, Drug allergy</td>
<td>IgE-mediated</td>
</tr>
<tr>
<td>Delayed (more than 24 h after exposure)</td>
<td>Fixed drug eruptions. Severe bullous skin reaction</td>
<td>Single drug or multiple drug-induced</td>
<td>Usually no</td>
<td>T-cell-mediated (Type IV) Cytotoxic T cells NK cells Other</td>
</tr>
</tbody>
</table>
Table 2. Clinical reactions to id skin test.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria/urticaria</td>
<td>80</td>
</tr>
<tr>
<td>Angioedema</td>
<td>60</td>
</tr>
<tr>
<td>Exanthema</td>
<td>40</td>
</tr>
<tr>
<td>Erythema</td>
<td>20</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>20</td>
</tr>
<tr>
<td>Nausea/vomit</td>
<td>20</td>
</tr>
<tr>
<td>Hypotension</td>
<td>20</td>
</tr>
<tr>
<td>Collapse</td>
<td>20</td>
</tr>
</tbody>
</table>

A. Time to onset of reaction (min)

B. Time to onset of reaction (days)
Chronology as indicator for mechanism

- Intradermal tests positive in 30 (24.6%) of 122 immediate reactions (read immediately), and only in 3 (2.4%) read delayed.
- Intradermal tests positive in 31 (31.6%) of 98 non-immediate reactors read delayed, and only in 2 (2%) read immediately.

For contrast media chronology of history and skin tests correlate well, probably because iv and one shot.
Position paper

Diagnosis of immediate allergic reactions to beta-lactam antibiotics

M. J. Torres¹, M. Blanca², J. Fernandez³, A. Romano⁴, A. de Weck⁵, W. Aberer⁶, K. Brockow⁷, W. J. Pichler⁸, P. Demoly⁹ for ENDA*, and the EAACI interest group on drug hypersensitivity

Review article

Diagnosis of nonimmediate reactions to β-lactam antibiotics

Nonimmediate manifestations (i.e. occurring more than 1 h after drug administration), particularly maculopapular and urticarial eruptions, are common during β-lactam treatment. The mechanisms involved in most nonimmediate reactions seem to be heterogeneous and are not yet completely understood. However, clinical and immunohistological studies, as well as analysis of drug-specific T-cell clones obtained from the circulating blood and the skin, suggest that different mechanisms may be involved in the pathogenesis of these reactions.

A. Romano¹, M. Blanca², M. J. Torres², A. Bircher³, W. Aberer⁴, K. Brockow⁵, W. J. Pichler⁶, P. Demoly⁷, for ENDA and the EAACI interest group on drug hypersensitivity*
More complicated:

1. Is really only the chronology meant or also the manifestations?
2. Time interval to the last intake or start of therapy?

Diagnosis of nonimmediate reactions to β-lactam antibiotics

Nonimmediate manifestations (i.e. occurring more than 1 h after drug administration), particularly maculopapular and urticarial eruptions, are common during β-lactam treatment. The mechanisms involved in most nonimmediate reactions seem to be heterogeneous and are not yet completely understood. However, clinical and immunohistological studies, as well as analysis of drug-specific T-cell clones obtained from the circulating blood and the skin, suggest that...
Chronology in ICON for DHR

Problems arising from a chronological approach

- None
  - If just used to describe the clinical onset and evolution
- Not precise
  - If based on patient’s history alone
  - With regard to the dynamic process
- Problematic
  - If used for classification without further information
  - If transporting information about pathophysiology
  - If used primary instead of clinical manifestations
  - If used to validate diagnostic tests, which are based on pathophysiology

adapted from: Andreas Bircher
The GIGO principle (Garbage in – garbage out) in DHR diagnosis

- **Optimal pretest procedure (correct morph/chron)**
- **Correctly applied, adequate tests**
- **Best possible diagnosis**

- **Optimal pretest procedure (correct chron/morph)**
- **Inadequate test system**
- **False +/- diagnosis**

- **Inadequate pretest procedure (wrong chron/morph)**
- **Optimal test system**
- **False +/- diagnosis**

adapted from: Andreas Bircher
Why classification?

- Exact description of one patient
- Classification determines test plan
- Comparison of studies and patients!
- Development of new tests
- Have standardised procedures, need to phenotype in multicenter studies now
Case report

- For tonsillitis amoxicillin over 7 days
- One day afterwards itching skin lesions trunk, spreading
- No fever, FBC ok, CRP, ASAT, ALAT, $\gamma$-GT slightly elevated
- Hospitalisation, topical and systemic CS, AH
- Fast improvement
How to classify?
Different levels of classification!

- **Elicitor**
  - Has to be avoided!

- **Manifestation / morphology**
  - Primary manifestations and lesions (and their evolution)

- **Severity**
  - Danger for the patient upon reexposition

- **Chronology**
  - Time interval between intake of drug and manifestations
  - Duration of total intake vs interval from the last intake

- **Pathophysiology**
  - If known (not if only suspected)
Case report

- For tonsillitis, amoxicillin over 7 days
- One day afterwards, itching skin lesions on trunk, spreading
- No fever, FBC ok, CRP, ASAT, ALAT, γ-GT slightly elevated
- Hospitalisation, topical and systemic CS, AH
- Fast improvement
Terminology of chronology?

- Instantaneous (C)
- Immediate (C, P)
- Acute (C)
- Early (C)
- Non-immediate (C)
- Accelerated (C)
- Late (C), very late
- Delayed (C, P)

C = Chronology: time-related
P = Pathophysiology: mechanism-related

from: Andreas Bircher
How would you like to classify drug reactions purely according to chronology?
Advantages of a chronological approach

Tab. 3: Typical time intervals between initial drug use and first onset of symptoms

<table>
<thead>
<tr>
<th>Hypersensitivity reaction</th>
<th>Time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria, asthma, anaphylaxis</td>
<td>typically within 1 h, in rare cases up to 12 h after exposure</td>
</tr>
<tr>
<td>Maculopapular drug eruption</td>
<td>4–14 Days after start of use(^a)</td>
</tr>
<tr>
<td>AGEP</td>
<td>1–12 Days after start of use(^b)</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>4–28 Days after start of use(^c)</td>
</tr>
<tr>
<td>DRESS</td>
<td>2–8 Weeks after start of use</td>
</tr>
</tbody>
</table>

AGEP, acute generalized exanthematous pustulosis; SJS, Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms.

\(^a\)Time interval in repeat reactions typically shorter compared with the first reaction. In maculopapular drug eruptions, reaction typically seen after 1–4 days, typical time interval for repeat reactions has not been investigated in AGEP, SJS, TEN, and DRESS;

\(^b\)mostly 1–2 days with antibiotics, often 7–12 days with other medications;\(^c\)sometimes longer with allopurinol
What is an exanthem?
Exanthem (*exantheo* = blooming up)

- An exanthem (from Greek "exanthema", a breaking out) is a widespread rash usually occurring in children. Exanthems can be caused by toxins or drugs, microorganisms, or can result from autoimmune disease (Wikipedia)
- an eruptive disease (as measles) or its symptomatic eruption (Merriam Webster)
- a rapidly erupting rash that may have specific diagnostic features of an infectious disease. Chickenpox, measles, roseola infantum, and rubella are usually characterized by a particular type of exanthem. (Mosby’s medical dictionary)
<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macule</td>
<td>Circumscribed area of changed skin color, no skin elevation or depression; may be any size</td>
</tr>
<tr>
<td>Papule</td>
<td>Solid, raised lesion up to 0.5 cm in greatest diameter</td>
</tr>
<tr>
<td>Pustule</td>
<td>Elevation of skin containing purulent fluid</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Elevated fluid-containing lesion less than 0.5 cm in greatest diameter</td>
</tr>
<tr>
<td>Bulla</td>
<td>Same as vesicle, except lesion is more than 0.5 cm in greatest diameter</td>
</tr>
<tr>
<td>(Urtica (wheal))</td>
<td>(Solid raised pruritic edematous, which only lasts for hours and may return at a different spot)</td>
</tr>
<tr>
<td>(Angioedema)</td>
<td>(Swelling of deeper skin tissue mostly no pruritus)</td>
</tr>
</tbody>
</table>
Description of exanthema

Distribution: \textit{localised} or \textit{disseminated} or \textit{generalised}

Lesions: maculopapular with atypical target lesions

\textit{=>} Disseminated maculopapular (targetoid) exanthem
Description of exanthema

**Distribution:**
- Localised
- Disseminated or generalised

**Lesions:**
- Maculopapular with atypical target lesions

=> Disseminated maculopapular (targetoid) exanthem
Classification of the case

- **Elicitor**
  - Suspicion of amoxicillin hypersensitivity

- **Manifestation / morphology**
  - General. maculopapular (targetoid) exanthem
  - Systemic involvement (hepatitis), no DRESS

- **(Severity)**
  - Moderate (hospitalisation, not life-threatening)

- **Chronology**
  - Non-immediate (late)

- **(Pathophysiology)**
  - Known only after test: type IV or „non-allergic“
A common classification is needed

There are different ways to classify: elicitor > manifestation / morphology > chronology > (severity >) mechanism

Elicitor and manifestation most important

The others carry important information for probability assessment and risk

Do not mix up different levels of classification but give independent information!

Reliability beats quantity of information
Thank you very much!