ADR AC GmbH
Adverse Drug Reactions - Analysis & Consulting

RIA Rheumatology Immunology Allergology

DRUG REACTIONS

1st WAO Allied Health Session – December 4th, 2011, Cancún, México

Barbara Daubner, PhD

ADR-AC GmbH, Bern & Clinic for Rheumatology and Clinical Immunology/Allergology
Division of Allergology, Inselspital Bern, Switzerland

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DRUG REACTIONS

Type A reactions

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

i.e.
Gastrointestinal bleeding after NSAIDs

Type B "bizarre" reactions

- not predictable
- (partly) dose independent
- in susceptible patient

drug hypersensitivity: classification into 4 categories: Type I – Type IV

i.e.
Urticaria after NSAIDs

Type B "bizarre" reactions

Often involve the skin

- 2-3% of hospitalized patients[1]

rather mild — life-threatening

„great imitator"

- Comprise a broad spectrum of clinical features

1. Bigby et al. JAMA 1986;256:3358

Type B "bizarre" reactions – mild manifestations

Urticaria | Maculopapular exanthema (MPE)

- 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

Maculopapular exanthema (MPE)

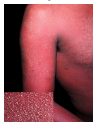
Pichler. Ann Intern Med. 2003 ;139:683

Type B "bizarre" reactions - severe manifestations

Mortality: 10 % | Mortality: 13-39 % | Mortality: 1-5%

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

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



Acute Generalized Exanthematous Pustulosis (AGEP)

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

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

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

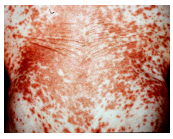
- Usually develops within 4-8 weeks
- Mucus membrane involvement
- Atypical target lesions, painful purpuric macules, initially mainly on the trunk
- Blisters, epidermal detachment

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

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

Represent a spectrum of disease with differing severity

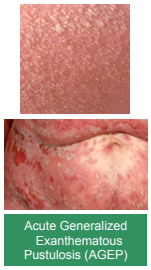
skin detachment

SJS	SJS/ TEN overlap	TEN
		
<10 % of BSA	10-30 % of BSA	>30 % of BSA

1. Bachot et al. Am J Clin Dermatol 2003; 4:561
2. Bastuji-Garin et al. Arch. Dermatol 1993;129:92
3. Mockenhaupt. JDDG 2009;2:142

Acute Generalized Exanthematous Pustulosis (AGEP)

- usually develops within 48 hours recovery: about 2 weeks
- acute occurrence of multiple sterile, non-follucilar, pinhead-sized pustules
- arise on an edematous erythema
- the lesions are often accentuated in the main folds
- fever, elevated neutrophil counts (>7000/mm^3)



Acute Generalized Exanthematous Pustulosis (AGEP)

Roujeau et al. Arch Dermatol 1991; 127: 1333

Non-immediate reactions and typically involved drugs	
MPE	β-lactam antibiotics, sufonamide antibiotics, macrolides, quinolones, diuretics and others
DRESS	Carbamazepine, phenytoin, lamotrigine, minocycline, allopurinol, dapsone, sulfasalazine, co-trimoxazole, abacavir (without eosinophilia)
SJS and TEN	Allopurinol, phenytoin, carbamazepine, lamotrigine, co-trimoxazole, barbiturate, NSAID (oxicams), sertraline, pantoprazole, tramadol, nevirapine
AGEP	Aminopenicillins, cephalosporins, macrolides sulfonamide antibiotics, celecoxib, diltiazem, quinolone, terbinafine, corticosteroids

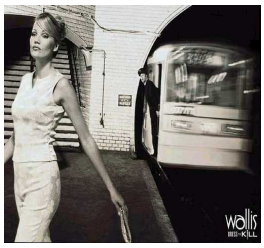
Clinical approach

- 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



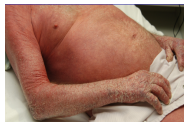
Be aware of danger signs!

Danger sings in DRESS

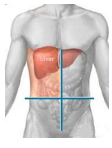
facial edema

eosinophils

⚠ DANGER



widespread erythema (>60%)



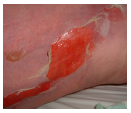
fever, lymphadenopathy
involvement of internal organs

Danger sings in SJS and TEN

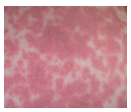
painful, burning skin

mucosal involvement

⚠ DANGER



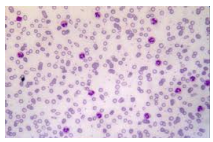
atypical targets
purpuric macules
grey areas



widespread erythema
pos. Nikolsky sign
vesicles and bullae

Danger sings in AGEP

fever



leucocytosis

⚠ DANGER

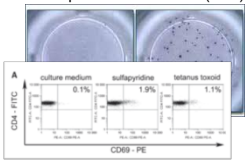
widespread erythema

non-follicular,
pinhead-sized pustules

DRUG TESTS

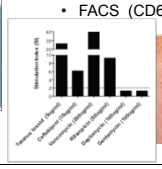
IgE-mediated reactions

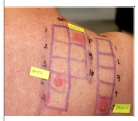
- Scratch tests, intradermal tests
- Serology
- Basophil activation tests (BAT)



T cell-mediated reactions

- Patch tests
- Lymphocyte transformation tests (LTT)
- Elispot (cytokines)
- FACS (CD69)






Prof. Werner J. Pichler
INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL
ADR AC GmbH
Adverse Drug Reactions - Analysis & Consulting
RIA
Rheumatology
Immunology
Allergology
Thomas Gentinetta
Dr. Tatjana Petkovic
Dr. Yuttana Srinoulprasert
Adam Jacqueline
Dr. Klara Eriksson
Heidi Jamin
Karin Schnyder
Steve Watkins
Natascha Wuillemin
Dr. Daniel Yerly
Dr. James Yun