

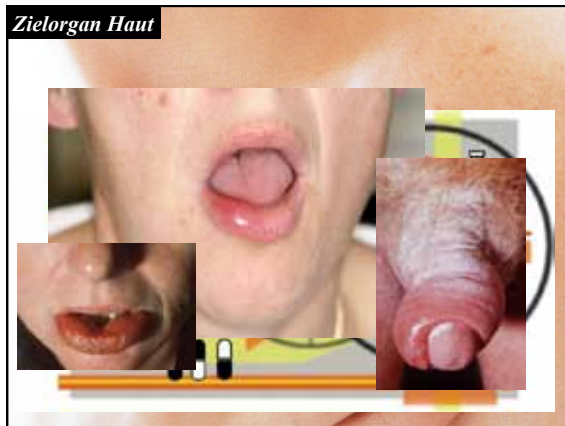
Die Haut als erstes Zielorgan allergischer Reaktionen

braucht es Laboruntersuchungen um das klinische Bild zu bestätigen ?

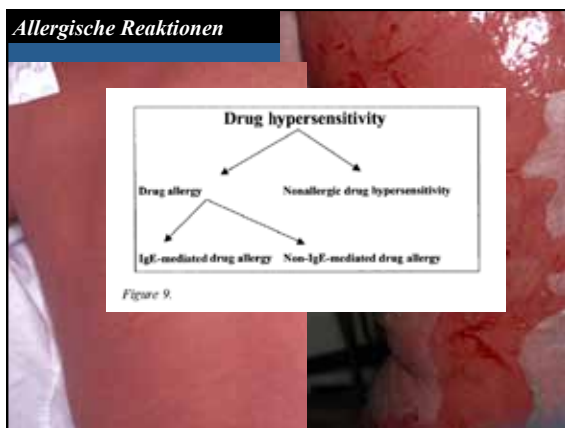
Paul Scheidegger











Coombs and Gell's Klassifikation der Hypersensitivität

	Type I	Type II	Type III	Type IV
Immune reaction	IgE antibody, T _H cells	IgG antibody	IgG antibody	T cells

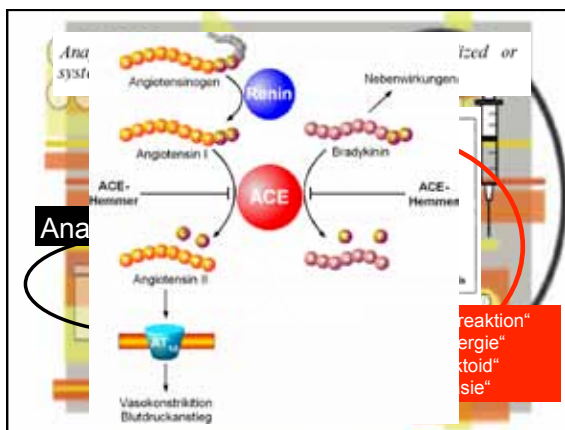
Coombs and Gell's Klassifikation der Hypersensitivität

	Type I	Type II	Type III	Type IV
Immune reaction	IgE antibody, T _H cells	IgG antibody	IgG antibody	T cells
Antigen	Soluble antigen	Cell or membrane-associated antigen	Soluble antigen	Soluble antigen
Effector mechanism	Allergic activation	Complement, FcγR cells, phagocytes, NK cells	Complement, Phagocytes	Macrophage activation
Examples of hypersensitivity reaction	Allergy, Hay fever, asthma, anaphylaxis, urticaria, rhinitis	Transfusion, drug rash (penicillin)	Drug rash	Serum sickness, rheumatoid arthritis, contact dermatitis

Unerwünschte Arzneimittelreaktionen – Typ I

	Type I
Immune reaction	IgE antibody, T _H cells
Antigen	Soluble antigen
Effector mechanism	Allergic activation
Examples of hypersensitivity reaction	Allergy, Hay fever, asthma, anaphylaxis, urticaria, rhinitis







EEM – SJS – TEN/Lyell

AGEP

DRESS
Baboon / STRIFE
TSS

EEM – SJS – TEN

Stevens-Johnson Syn. & TEN: ein Spektrum !

Condition	Mortality	Epidermal Detachment
Makulo-papulöses Exanthem	0%	Keine Epidermisablösung
Stevens-Johnson Syndrom	1-5%	Epidermisablösung
Toxische Epid. Nekrolyse (TEN)	25-35%	Epidermisablösung

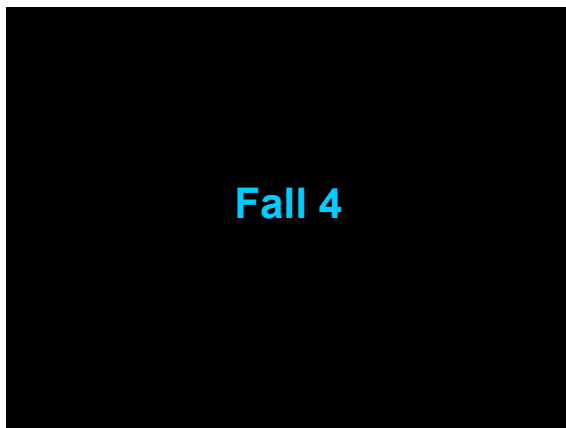
Fall 1











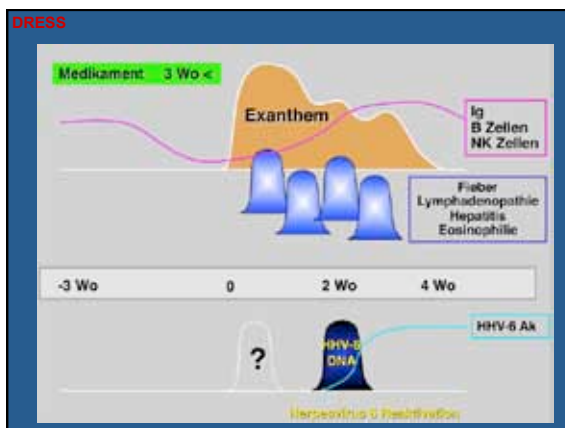


DRESS

Hypersensitivität Syndrom (DRESS)

- Anzeichen & Symptome:
 - Diffuse Makulo-Papulose +/- Pustulöses Exanthem
 - Gesicht's Oedem
 - Fieber
 - Lymphadenopathie
 - Häufig Eosinophilie (>1500/mm³)
 - Leukozytose > 10 x 10⁹/ml + atypische Lymphozytose
 - Systemische Beteiligung hauptsächlich Hepatitis (ASAT > 100), Arthritis, Pulmonale Infiltrate, interstitielle Nephritis...
- Mortalität: 5-10%





Fall 5







Kind mit Fieber und Pneumonie

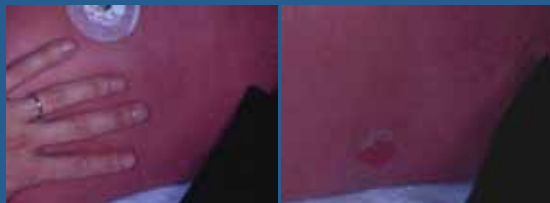


Stevens-Johnson-Syndrom
bei Mykoplasmeninfektion



Fall 7

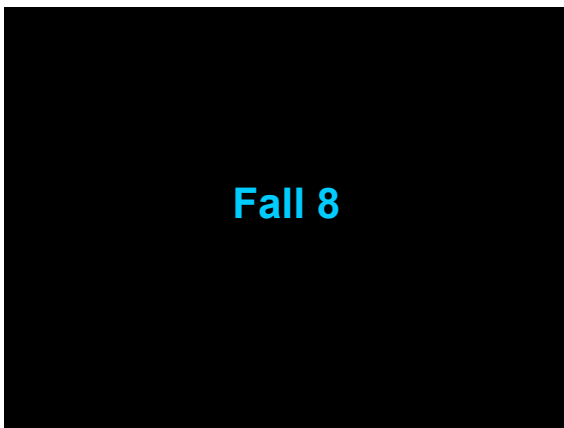
68 Jähriger mit St.n. Lyell Syndrom auf Mefenaminsäure vor 1 Jahr
nach einer Schnittverletzung erhielt der Patient von einem Nachbar
Ponstan nach 5 Stunden Erythrodermie



Nikolski positiv









12h später....

erneute Medikamentenanamnese:
 während 3 Tagen vor Beginn des Exanthems Einnahme von Pretuval

Pretuval®

Bei Grippe und Erkältungen

Tablette
 Wirkstoffe: 20 mg Dextromethorphanhydrobromid, 30 mg Pseudoephedrinhydrochlorid und 300 mg Paracetamol pro Tablette.

Acute generalized exanthematous pustulosis associated with polysensitivity to paracetamol and bromhexine: the diagnostic role of *in vitro* interferon- γ release test

S. Halevy, A. D. Cohen and E. Livni**
 Department of Dermatology, Joseph Shatzkin Laboratory, Center for Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva and Tissue Bank Laboratory, Ben-Gurion Medical Center, Beilinson Campus, Petah Tikva, Israel

Clin Exp Dermatol 2009; 35: 612

AGEP

Akute Generalisierte Exanthematöse Pustulose (AGEP)

Diagnostische Kriterien:

1. Akutes Pustulöses Exanthem
2. Fieber > 38°C
3. Neutrophilie \pm Eosinophilie
4. Subkorneale oder Intraepidermale Pusteln (Histo)
5. Spontane Verbesserung innerhalb 15 Tagen

Differentialdiagnose – Exanthem

1. genaue Anamnese – Hitliste Medikamente

Geschätzte absolute und relative Häufigkeiten der Auslösung kutaner allergischer UAW durch bestimmte Arzneimittelgruppen. (Mod. nach [3, 4, 16, 23, 31])

Auslöser kutaner allergischer UAW nach absoluter Häufigkeit (innerhalb der Anzahl kutaner allergischer UAW)	Auslöser kutaner allergischer UAW nach relativer Häufigkeit (bezogen auf die Exposition mit dem Arzneimittel)
1. Antibiotika (v. a. Betalaktame, Sulfonamide): ca. 50%	1. Gold
2. NSAR (v. a. Intoleranzreaktionen*): ca. 20%	2. Trimethoprim/Sulfonamid
3. ZNS-wirksame Arzneimittel (v. a. Antikonvulsiva): ca. 10%	3. Cephalosporine
4. Kardiovaskuläre Arzneimittel: ca. 6%	4. ACE-Hemmer*

* Den durch diese Arzneimittel ausgelösten Intoleranzreaktionen liegen keine immunologischen Mechanismen zugrunde.

Hitlisten

1. Hitliste

Table 2. Frequency of various classes of drugs associated with an eruption in cases with ≤ 6 suspected drugs†

Class of drug	No. of cases (%) (n=102)
Antibiotic	37
Antiepileptic	12
Phenolphthalein	9
Antiarrhythmic	6
Calcium ion inhibitor	3
Anticoagulant	5
Enoxaparin	2
Clopidogrel	2
Warfarin	1
Antiulcer	4
Aspirin	4
Proton pump inhibitors	4
ACE inhibitors	3
Contraceptives	3
Diuretics	3
Anti-inflammatory	2
Antiretroviral (HIV)	2
Antiviral	2
Beta-blockers	2
Chemotherapeutic	2
Other	11

† ACE, angiotensin-converting enzyme.

Differential Diagnose Exanthem

2. Hitlisten – diagnostic clues Br J Dermatol 2002; 147

Table 3. Diagnostic clues and their likelihood

Diagnostic clues	Suspected agent	Odds ratio
Fever	Infection	5.6
Headache + diarrhoea + abdominal pain	Rotaviruses and picornaviruses	49.8
Constitutional symptoms	Infection	11.6
Severe pruritus	Drugs	4.3
Seasonality	Picornaviruses	0.8
Enanthema	Picornaviruses	11.7
Pustular pattern	Drugs	16.4
Papular pattern	Drugs	3.9
Dusky-red erythema	Drugs	10.2
Vesicular pattern	Picornaviruses	158.3
Children	Infection	1.3

Quo vadis – Exanthem?

3. Hitlisten – Risikopersonen

Patient Risk Factors for Adverse Drug Reactions

General drug reactions (nonimmune)	Hypersensitivity drug reactions (immune)
Female gender ¹²	Female gender ¹²
Serious illness	Adult
Renal insufficiency	HIV infection ¹³
Liver disease	Concomitant viral infection ¹⁴
Polypharmacy	Previous hypersensitivity to chemically-related drug
HIV infection ¹³	Asthma ¹⁵
Herpes infection	Use of beta blockers ¹⁶
Alcoholism	Specific genetic polymorphisms
Systemic lupus erythematosus ¹⁶	Systemic lupus erythematosus ¹⁶

Quo vadis – Exanthem?

4. Morphologie des Exantheme

Table 2. Prevalence (%) of exanthem patterns and their causative agents

Pattern	Causative agent			
	Drugs	Viruses	Bacteria	Parasites
Macular	9.8	5.4	3.6	0.9
Maculopapular	5.3	8.9	6.2	0.9
Papular	3.6	0	0	0
Maculopapular with petechiae	0	2.7	2.7	0
Erythematovesicular	0	9.8	0	0
Erythematopustular	3.6	0	0	0
Urticarial	0	1.8	1.8	0.9
Total	22.3	28.6	14.3	2.7

Br J Dermatol 2002; 147

Quo vadis – Exanthem?

5. Liegt ein Exanthem und oder Lnn-Befund vor ?

Quo vadis – Exanthem?

6. Wie ist das periphere Blutbild/ sind die Leberenzyme?

Segk. Neutroph.	80-75	1,8-7,5	48,1	8,88	86,7	8,50	22,3	1,40
Eosinophile	1-5	0-4	8,8	1,58	0,0	1,82	7,8	0,47
Neutrophile	50-70	1,2-7,7	7,8	0,18	1,0	8,11	1,7	0,10

Enzyme		Einheit	Wert	Norm
AsAT (GPT)	20-40	U/l	32	30
AlAT (GPT)	10-30	U/l	88	30
Gamma-GT	10-30	U/l	108	30
LDH	100-250	U/l	108	100

Lymphozyten	20-40	0,60-0	11,8	0,15	28,3	0,48
Plasmazellen	1	0-11	1,2	0,11	13,2	0,11
Atyp. Lymphozyten	0	0	3,0	0,07	2,1	0,08

37,2 Temperatur, generalisiertes diskretes fein-

Cave – Wenn es gefährlich wird.....

Palmoplantare Beteiligung
 Schleimhautbeteiligung
 Erythrodermie

hämorrhagische Läsionen
 generalisierte Pustulose
 Blasen
 Ablösung der Haut

Dx und DD Drug Hypersensitivität „Akute Phase“ intra festum

1. genaue Anamnese – Hitlisten
2. sog Diagnostic Clues / „Settings“
3. Risikopersonen
4. Morphologie/Typ des Exanths
5. Enanthe/Lnn beurteilen
6. Peripheres Blutbild
7. Danger signs kennen

**Dx und DD Drug Hypersensitivität
„after the fact“ post festum**

1. genaue Anamnese – Hitlisten
2. sog Diagnostic Clues / „Settings“
3. Risikopersonen
4. Morphologie/Typ des Exantheme

**Dx und DD Drug Hypersensitivität
„after the fact“ post festum**

1. Anamnese
2. Hauttestungen prick (ic, Scratch, Epikutan) bei Soforttyp
3. LTT (BAT, spezifisch IgE, Leukotrien, CD63, CD69) bei Spättypreaktionen
4. Provokationstestungen

In vivo veritas !



Sensitivity & Specificity of the Lymphocyte transformation test (LTT)

Author	n	sensitivity	specificity	disease
Nyfelner & Pichler, 1997	100	74	85	All
Luque E et al., 2001	50	62	93	Penicillins (imm. & non-immEDIATE)
Harl Y e t val, 2001	21	67	98	MPE & bullous E.
Naisbitt D et al, 2003	36	94	100	DRESS/ DiHS

**Diagnosis of drug hypersensitivity:
which mechanism is involved ?**

Type I:	Type II:	Type III:	Type IV a,b,c,d:
IgE	IgG	IgG	T cells
Soluble antigen	Cell- or matrix associated antigen	Soluble antigen	MHC-presented antigen p-1 concept stimulated cells
Urticaria, Anaphylaxis, Asthma, Allergic rhinitis	Blood cell dyscrasia: haemolytic anemia and thrombocytopenia	Immune complex mediated diseases: vasculitis, serum sickness	MPE, DIHS/DRESS, SJS/TEN, hepatitis
Specific IgE Prick i.d. BAT LTT/LAT provocation	Coombs test with drug	No tests available	i.d. epicutaneous LTT / LAT cytotoxicity

Klassifikation nach Naisbitt

Table 1. Classification of adverse drug reactions

Type A (augmented) reactions: predicted from the known pharmacology of the drug. These reactions are dose-dependent: examples are bleeding with anticoagulants

Type B (bizarre) reactions: reactions are not predicted from the known pharmacology of the drug. They appear (but actually are not) relatively dose-independent, as very small doses might already elicit symptoms. They include immune-mediated side-effects like maculopapular exanthema, but also other hypersensitivity reactions, like aspirin-induced asthma

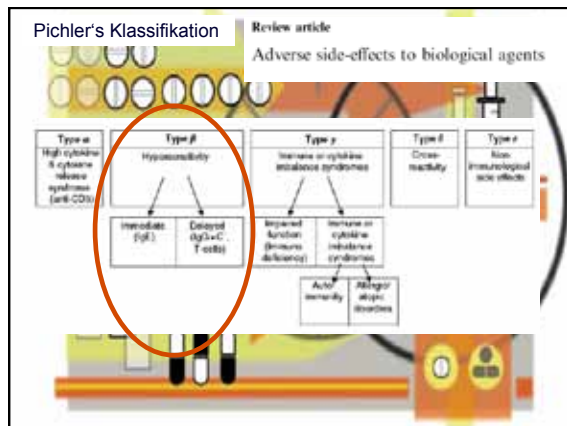
Type C (chemical) reactions*: which are related to the chemical structure and its metabolism, e.g. paracetamol hepatotoxicity

Type D (delayed) reactions*: which appear after many years of treatment, e.g. bladder carcinoma after treatment with cyclophosphamide

Type E (end of treatment) reactions*: occur after drug withdrawal, e.g. seizures after stopping phenytoin

Source: Naisbitt et al. (3).

*Type C and D are rarely used.



Pichler's Klassifikation Review article
Adverse side-effects to biological agents

Table 4. Subclassifying side-effects of TNF- α and anti-TNF- α

	TNF- α	Anti-TNF- α (infliximab)
Type α High dose	<ul style="list-style-type: none"> Infectious syndromes Meningitis Arthritis Leak 	-
Type β Hypersensitivity	<ul style="list-style-type: none"> Local and generalized urticaria Local dermatitis 	<ul style="list-style-type: none"> Local and systemic urticaria, erythema, serum sickness Loss of efficiency Anaphylaxis and related adverse reactions, local dermatitis
Type γ Cytokine or immune mediated syndromes	<ul style="list-style-type: none"> Immunoallergic Autoimmune/autoantibody disorders 	<ul style="list-style-type: none"> Autoimmune, idiopathic, other granulomatous infectious diseases Immune-mediated pneumonitis, acute fibrosis, systemic sclerosis, SLE, demyelinating disease, paraneoplasia, tuberculous-like reaction, sarcoidosis Altered dermatitis ITC
Other atypic	-	Altered dermatitis
Type δ Cross-reactivity	-	ITC
Type ϵ Non-immunological side-effects	<ul style="list-style-type: none"> Neurological symptoms like B6/12 deficiency, hearing loss, depression, diabetes, multiple myeloma 	Heart malfunctions

TNF, tumor necrosis factor; ITC, immunologic T cell; SLE, systemic lupus erythematosus; IT, unknown
