

ALLERGIEPRAXIS  
HAUTPRAXIS



Die Haut als erstes Zielorgan allergischer Reaktionen

braucht es Laboruntersuchungen um das klinische Bild zu bestätigen ?

Paul Scheidegger

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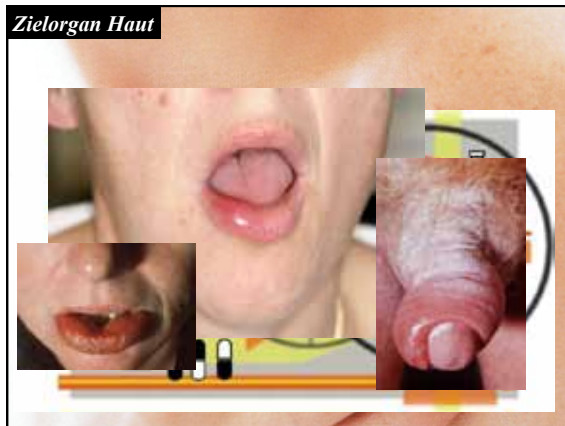
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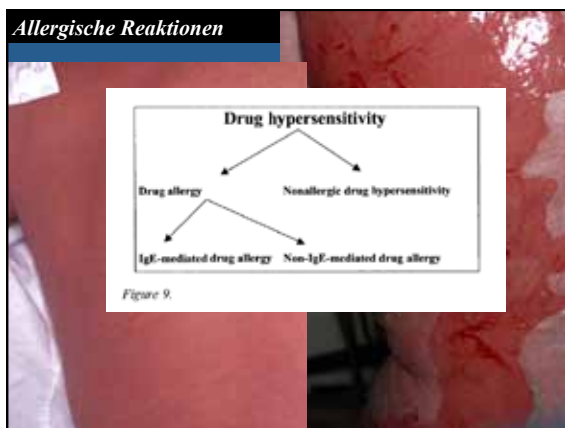
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**Coombs and Gell's Klassifikation der Hypersensitivität**

	Type I	Type II	Type III	Type IV
<b>Immune reaction</b>	IgE antibody, T <sub>H</sub> cells	IgG antibody	IgG antibody	T cells

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**Coombs and Gell's Klassifikation der Hypersensitivität**

	Type I	Type II	Type III	Type IV
<b>Immune reaction</b>	IgE antibody, T <sub>H</sub> cells	IgG antibody	IgG antibody	T cells
<b>Antigen</b>	Soluble antigen	Cell or membrane-associated antigen	Soluble antigen	Soluble antigen
<b>Effector mechanism</b>	Allergic activation	Complement, FcγR cells, phagocytes, NK cells	Complement, Phagocytes	Macrophage activation
<b>Examples of hypersensitivity reaction</b>	Allergy, Asthma, Anaphylaxis, Systemic mastocytosis	Transfusion, Rh incompatibility (neonatal)	Drug allergy	Serum sickness, Contact dermatitis

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**Unerwünschte Arzneimittelreaktionen – Typ I**

	Type I
<b>Immune reaction</b>	IgE antibody, T <sub>H</sub> cells
<b>Antigen</b>	Soluble antigen
<b>Effector mechanism</b>	Allergic activation
<b>Examples of hypersensitivity reaction</b>	Allergy, Asthma, Anaphylaxis, Systemic mastocytosis

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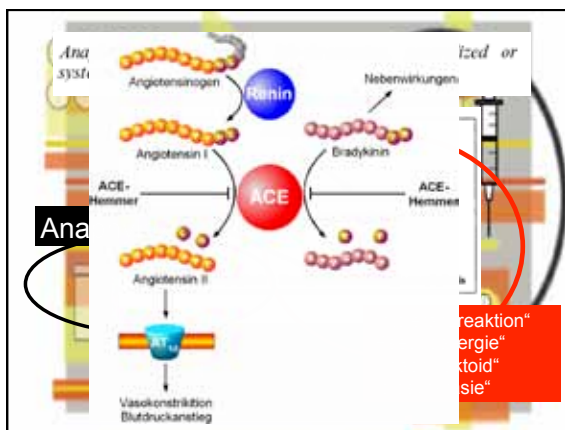
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# EEM – SJS – TEN/Lyell

## AGEP

DRESS  
Baboon / STRIFE  
TSS

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## EEM – SJS – TEN

### Stevens-Johnson Syn. & TEN: ein Spektrum !

Klinisches Bild	Mortalität	Epidermisablösung
Makulo-papulöses Exanthem	0%	Keine Epidermisablösung
Stevens-Johnson Syndrom	1-5%	Epidermisablösung
Toxische Epid. Nekrolyse (TEN)	25-35%	Epidermisablösung

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# Fall 1

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19 j. Patient mit Fieber 37.8, Kopfschmerzen, Arthralgien,  
Nicht juckendem stammbetontem Exanthem  
In den letzten 3 Tagen regelmässig Paracetamol eingenommen




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Parameter	Value	Unit	Ref.	Unit	Value
Neutrophile	176-280	/l	117 *		309 *
Basophile	0-0-0,33	/l	0,380 *		0,390 *
Erythrozyten	4,2-5,2	/l	4,380 *		4,480 *
HbC	130-160	g/l	133		131
MCV	107-124	fl	104 *		104,3 *
MCH	30-36	pg	29,4 *		29,1 *
MCHC	32-36	g/l	28,4 *		28,1 *
Retikulozyten abs.	0-2-1,8	%	0,4 *		0,4 *
Retikulozyten abs.	20-100	/l	18 *		18 *
Thrombozyten	140-400	/l	312,2		28 *
Leukozyten	4-10	/l	6,2 *		5,8 *
Leukozyten segment.	4-10	/l	5,2 *		5,8 *

**Blutbild**

Parameter	Value	Unit	Ref.	Unit	Value
Stark Neuroph.	0	abs.	0	abs.	0
Stark Neuroph.	-10	-1	12,3 *	0,28	0,7
Segm. Neuroph.	40-75	1,8-7,3	62,3 *	1,16	30,7 *
Sarkozyten	-5	-0,5	0,5	0,20	1,3
Basophile	-2	-0,2	1,2	0,03	1,8
Monocyten	2-10	0,20-1	0,5	0,10	14,0 *
Lymphocyten	20-40	0,20-4	17,8 *	0,28	28,1 *
Plasmazellen	-	-	0-5	0,11	<0,1
Atyp. Lymphocyten	0	0	1,8 *	0,07 *	0,3 *

Untersuchungsbefund vom 23.10.2001: 37,2 Temperatur, generalisiertes diskretes Erythematöses Exanthem, leichte Konjunktivitis, mukohalber und Theodor'scher LKN, Hämoglobinie, Leukopenie und Plasmazytose.

Diagnose: Röteln

**ELISA (Vidas)**  
Röteln **IgM positiv**

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Fall 2

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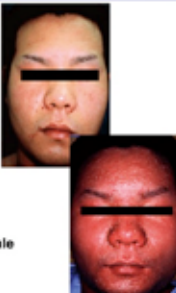
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**DRESS**

### Hypersensitivität Syndrom (DRESS)

- **Anzeichen & Symptome:**
  - Diffuse Makulo-Papulose +/- Pustulöses Exanthem
  - Gesicht's Oedem
  - Fieber
  - Lymphadenopathie
  - Häufig Eosinophilie (>1500/mm<sup>3</sup>)
  - Leukozytose > 10 x 10<sup>9</sup>/ml + atypische Lymphozytose
  - Systemische Beteiligung hauptsächlich Hepatitis (ASAT > 100), Arthritis, Pulmonale Infiltrate, interstielle Nephritis...
- **Mortalität: 5-10%**




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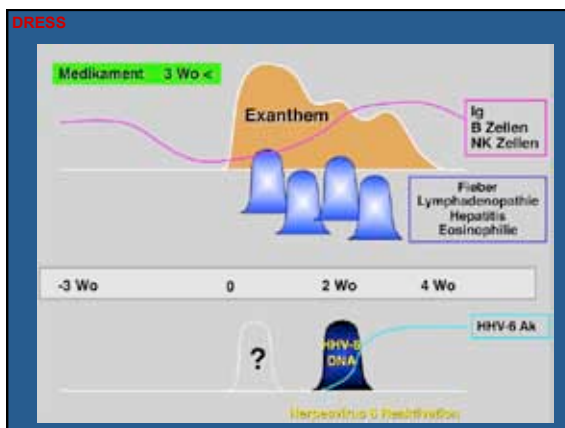
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**Fall 5**

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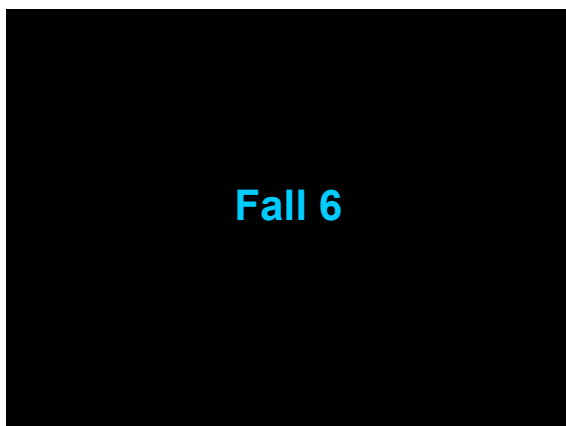
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Kind mit Fieber und Pneumonie



Stevens-Johnson-Syndrom  
bei Mykoplasmeninfektion



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## Fall 7

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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

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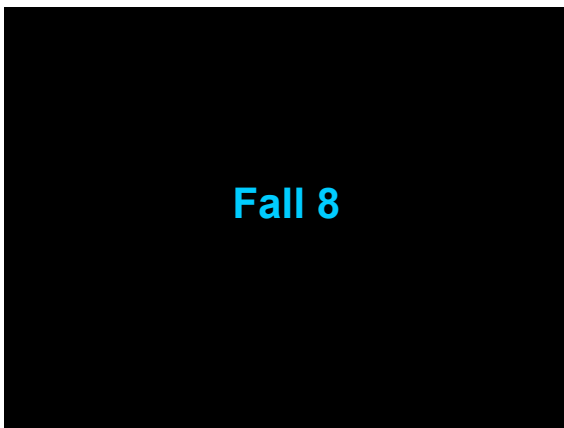
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**35 jähriger Patient**

Schwindel, Gliederschmerzen, Schnupfen, Husten, Fieber 39 Grad  
 juckender Ausschlag am ganzen Körper  
 Ehefrau vor 2 Wo wegen Halsschmerzen antibiotisch behandelt




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**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- $\gamma$  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  
 \*Translational Laboratory, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel

*Clin Exp Dermatol* 2009; 34: 612

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**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

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### 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.

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### Hitlisten

1. Hitliste

**Table 2.** Frequency of various classes of drugs associated with an eruption in cases with <math>\leq 6</math> suspected drugs†

Class of drug	No. of cases (%) (n=102)
Antibiotics	37
Antiepileptic	12
Phenylethol	9
Antiarrhythmic	6
Calcium ion inhibition	3
Anticoagulant	5
Enoxaparin	2
Cepidogrel	2
Warfarin	1
Acetaminophen	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.

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### 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

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### Quo vadis – Exanthem?

**3. Hitlisten – Risikopersonen**

**Patient Risk Factors for Adverse Drug Reactions**

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

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### Quo vadis – Exanthem?

**4. Morphologie des Exanths**

**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

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### Quo vadis – Exanthem?

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

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### 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	1,50	12,3	1,40
Eosinophile	1-5	0-4	0,8	1,58	0,0	1,82	7,8	0,47
Basophile	0-2	0-2	1,2	0,18	1,0	8,11	1,1	0,10

Enzyme		Einheit	Wert	Norm
ALT (GPT)	25-40	U/l	11,8	0-35
AST (GPT)	10-30	U/l	8,8	0-37
Gamma-GT	10-30	U/l	11,8	0-35

Leukozyten	4-10	10 <sup>9</sup> /l	11,8	4-10
Lymphozyten	20-40	%	11,8	20-40
Thrombozyten	150-400	10 <sup>9</sup> /l	11,8	150-400

17,2 Temperatur, generalisiertes diskretes fein-

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### Cave – Wenn es gefährlich wird.....

Palmoplantare Beteiligung

Schleimhautbeteiligung

Erythrodermie

hämorrhagische Läsionen

generalisierte Pustulose

Blasens

Ablösung der Haut

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### 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

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**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

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**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

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**In vivo veritas !**



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### 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)
Hari Y et al., 2001	21	67	98	MPE & bullous E.
Naisbitt D et al., 2003	36	94	100	DRESS/ DiHS

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

Type I:	Type II:	Type III:	Type IV a,b,c,d:
<b>IgE</b>	<b>IgG</b>	<b>IgG</b>	<b>T cells</b>
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
<b>Specific IgE</b> Prick i.d. BAT LTT/LAT provocation	<b>Coombs test</b> with drug	<b>No tests</b> available	i.d. epicutaneous LTT / LAT cytotoxicity

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### 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.

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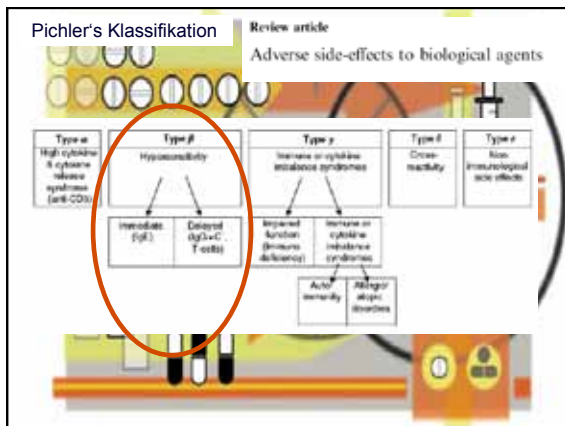
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Pichler's Klassifikation Review article  
**Adverse side-effects to biological agents**

Table 4. Subclassifying side-effects of TNF- $\alpha$  and anti-TNF- $\alpha$

	TNF- $\alpha$	Anti-TNF- $\alpha$ (infliximab)
Type $\alpha$ High dose	<ul style="list-style-type: none"> <li>Infectious syndromes</li> <li>Myalgia</li> <li>Arthralgia</li> <li>Head</li> </ul>	-
Type $\beta$ Hypersensitivity	<ul style="list-style-type: none"> <li>Local and generalised urticaria</li> <li>Local dermatitis</li> </ul>	<ul style="list-style-type: none"> <li>Local and systemic urticaria, erythema, serum sickness</li> <li>Loss of efficiency</li> <li>Anaphylaxis and related adverse reactions, local dermatitis</li> </ul>
Type $\gamma$ Cytokine or immune mediated syndromes	<ul style="list-style-type: none"> <li>Immunoallergic</li> <li>Autoimmune/interferon-related disorders</li> </ul>	<ul style="list-style-type: none"> <li>Subcutaneous, fibrotic, other granulomatous infectious diseases</li> <li>Immune-mediated pneumonitis, acute fibrosis, systemic sclerosis, SLE, demyelinating disease, paraneoplasia, tuberculous-like reaction, sarcoid</li> <li>Altered dermatitis</li> </ul>
Other effects	-	<ul style="list-style-type: none"> <li>Altered dermatitis</li> <li>IT</li> </ul>
Type $\delta$ Cross-reactivity	-	<ul style="list-style-type: none"> <li>Headache</li> </ul>
Type $\epsilon$ Non-immunological side-effects	<ul style="list-style-type: none"> <li>Neurological symptoms like B6/12 deficiency, hearing loss, depression, dizziness, restless legs</li> </ul>	<ul style="list-style-type: none"> <li>Headache</li> </ul>

TNF, tumour necrosis factor; IgE, immunoglobulin E; SLE, systemic lupus erythematosus; IT, interstitial

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