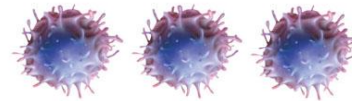


# *Patterns of cross-reactivity*

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Holligenstr 91, CH-3008-Bern,  
Switzerland

# **D.H. 1927**

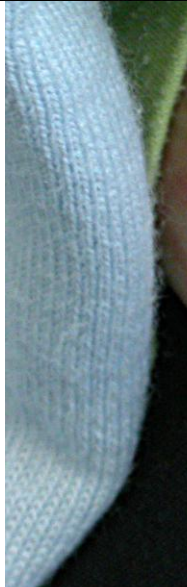
- **Endocarditis (due to Enterococcus faecalis, blood culture positive 22.4.07)**
- **Valvulopathie (aortal stenosis, sick-sinus-syndrome, pace maker implantation 2004)**
- **Breast cancer and mastectomy 1997 and 2003**
- **Hypothyreosis (substituted)**
- **Renale insufficiency (clearance 40ml/min).**
- **Multiple ulcerationen on digits of both feets**

# D.H. 1927

Therapy of endocarditis:

scheduled for 6 weeks:  $\beta$ -Lactams or Vancomycin  
and Garamycin

- 23.4. – 26.4. Amoxicillin & clavulanic acid i.v.
- 26.4. – 1.5. Amoxicillin i.v.
- Exanthem 1.5. (itchy)



# What now ?

## D.H. 1927

### Acute situation

1. **Severity of exanthem ?**
2. **Type of exanthem/of immune reaction (immediate/delayed)**
3. **Stop of amoxicillin; other therapy**

### Advice for future

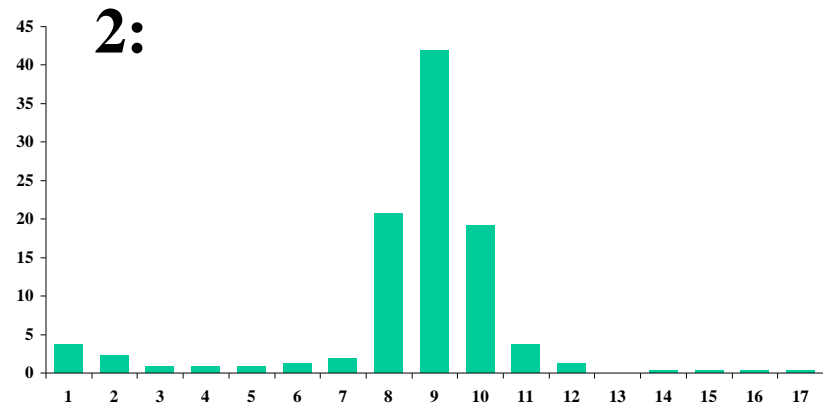
1. **Can one use cephalosporin in future?**
2. **Can one use other penicillins (i.e. piperacillin, flucloxacillin?)**
3. **Can one use monobactam or carbapenem?**

# D.H. 1927

1. **Severity of exanthem ?**
2. **Type of exanthem/of immune reaction (immediate/delayed)**
3. **Stop of amoxicillin, continue with vancomycin (kidney !). alternative ?**
4. **Desensibilisation ?**

**1:** no bullae oder mucosal involvement  
ALAT/ASAT/gGT/AP constant

No eosinophilia, no increase of creatinine



23.4. → 1.5.

# What now ?

## D.H. 1927

### Acute situation

1. Severity of exanthem ?
2. Type of exanthem/of immune reaction (immediate/delayed)
3. Stop of amoxicillin; other therapy

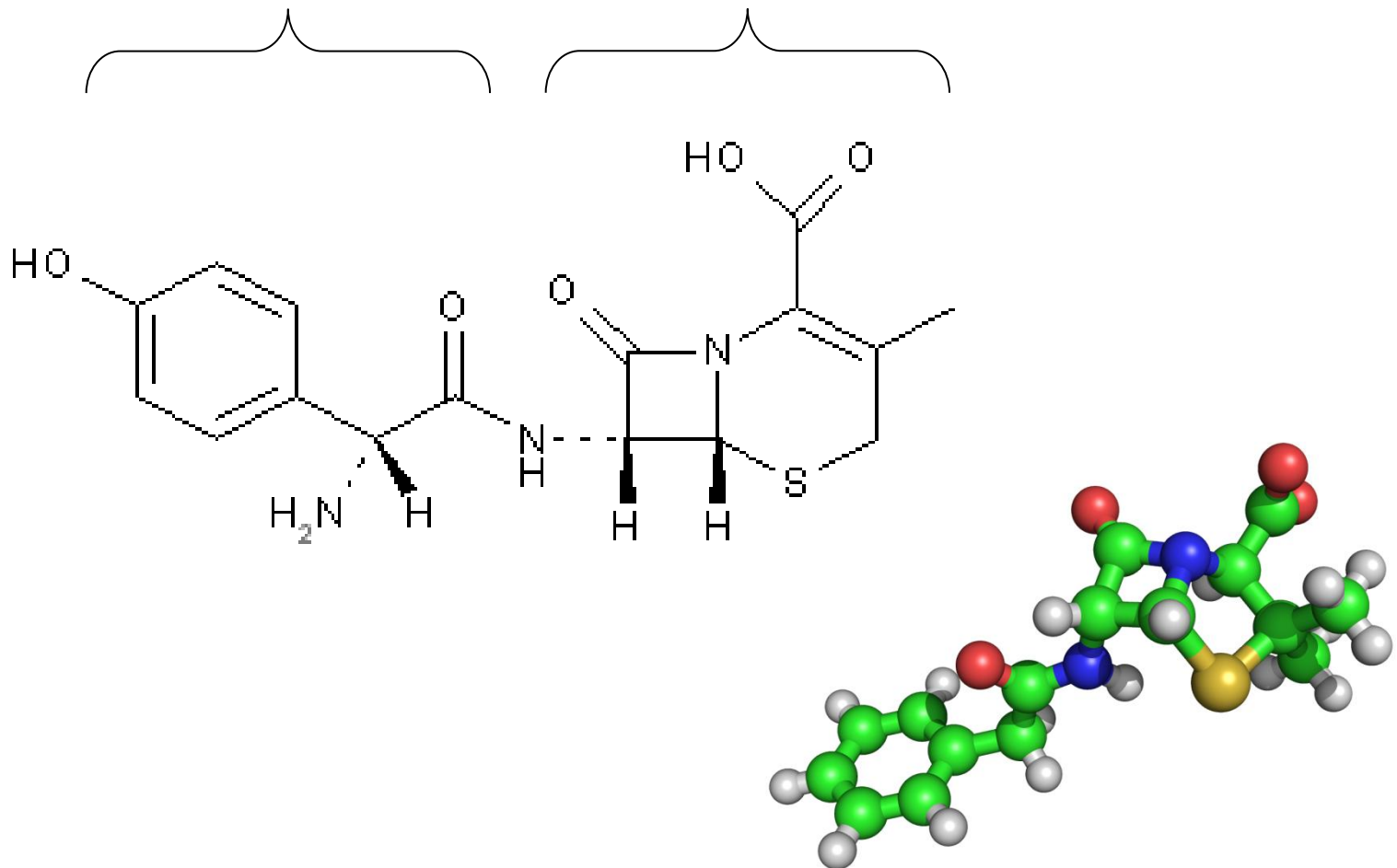
### Advice for future

1. Can one use cephalosporin in future?
2. Can one use other penicillins (i.e. piperacillin, flucloxacillin?)
3. Can one use monobactam or carbapenem?

# Core structure and side-chain

Side chain

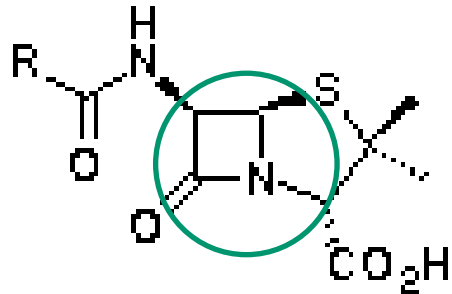
Core-structure (Cephem)



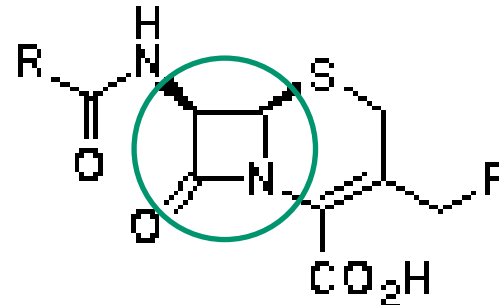


# Cross-reactivity

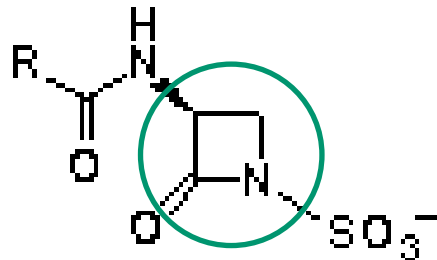
## $\beta$ -Lactam Antibiotika



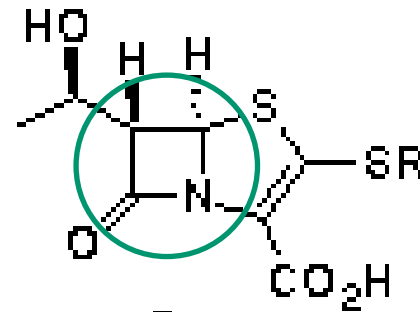
Penam



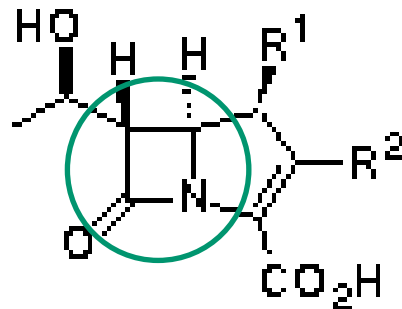
Cephem



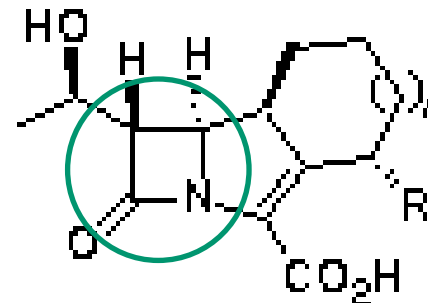
Monobactam



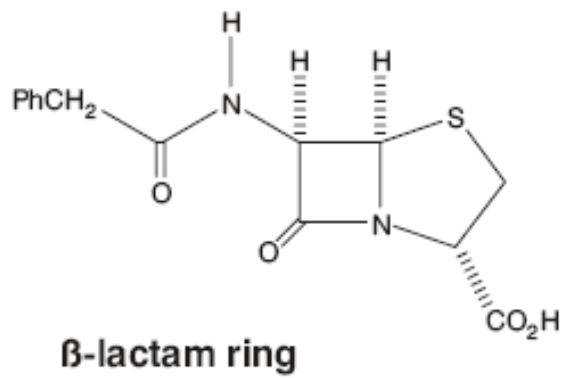
Penem



Carbapenem

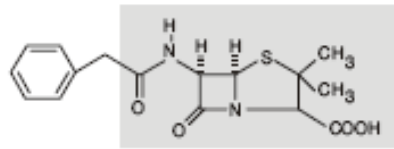
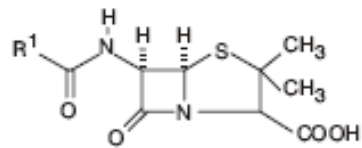


Trinem

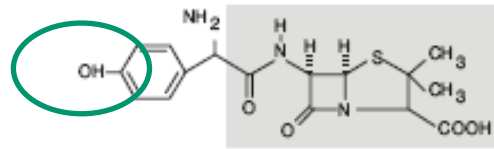


**IgE:** 4-11% in penicillin/amoxicillin allergic patients with cephalosporins  
 Cefadroxil and Amoxicillin: same side chain  
**T cells:** < 1% between penicillins and cephalosporins, but frequent in between penicillins, cephalosporins...

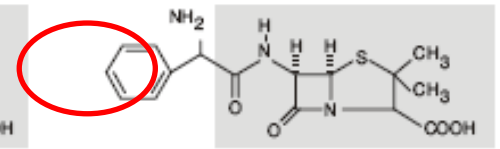
**Penicillin**



Benzylpenicillin

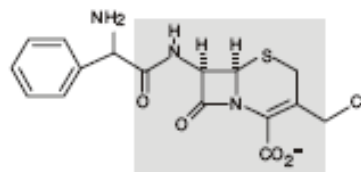
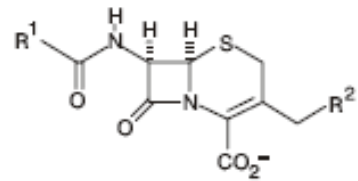


Amoxicillin

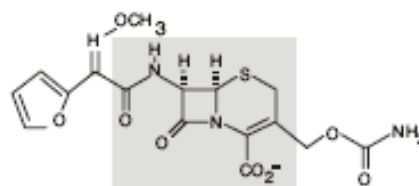


Ampicillin

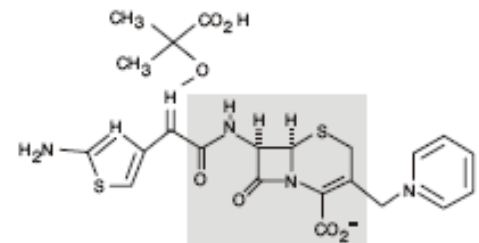
**Cephalosporin**



Cefaclor

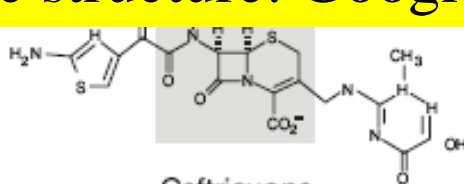


Cefuroxime

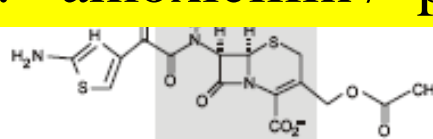


Ceftazidime

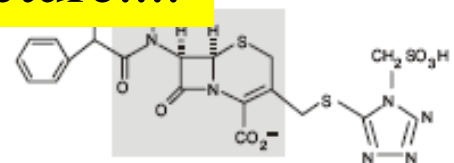
Check the structure: Google: amoxicillin / picture....



Ceftriaxone

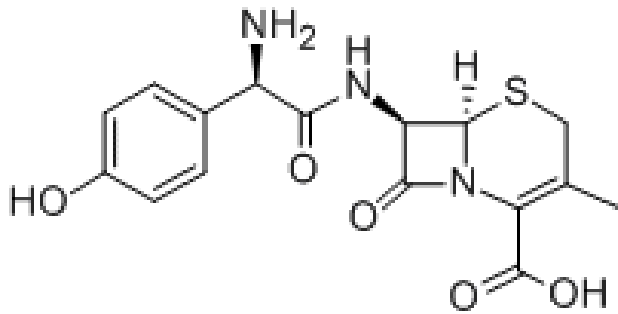


Cefotaxime

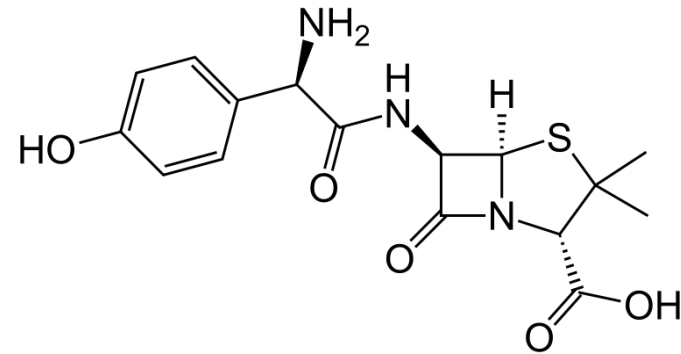


Cefonicid

# Cephadroxil



# Amoxicillin

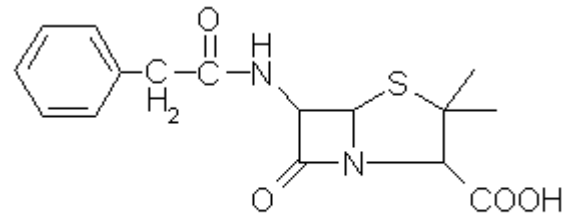


Cross-reactivity based on identical side chain

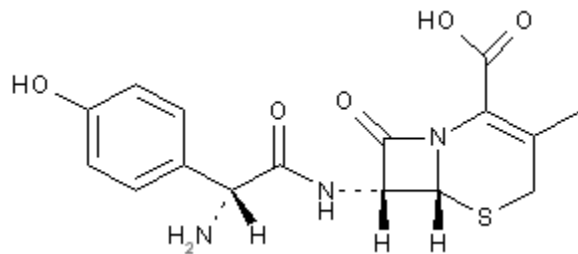
# Patterns of cross-reactivity

- **Differentiate between IgE and T-cell reactions:** antibodies and T-cells recognize different parts of the same molecule
- **Cross-reactivity of IgE** appears to be more common, as minor determinants might be responsible
- **Cross-reactivity of T-cells** is often less severe

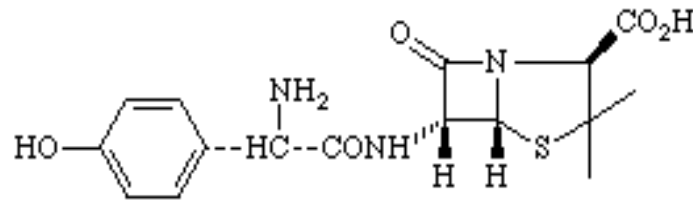
# IgE or T-cell cross-reactivity Amoxicillin and Cefadroxil ?



penicillin G



cefadroxil



amoxicillin

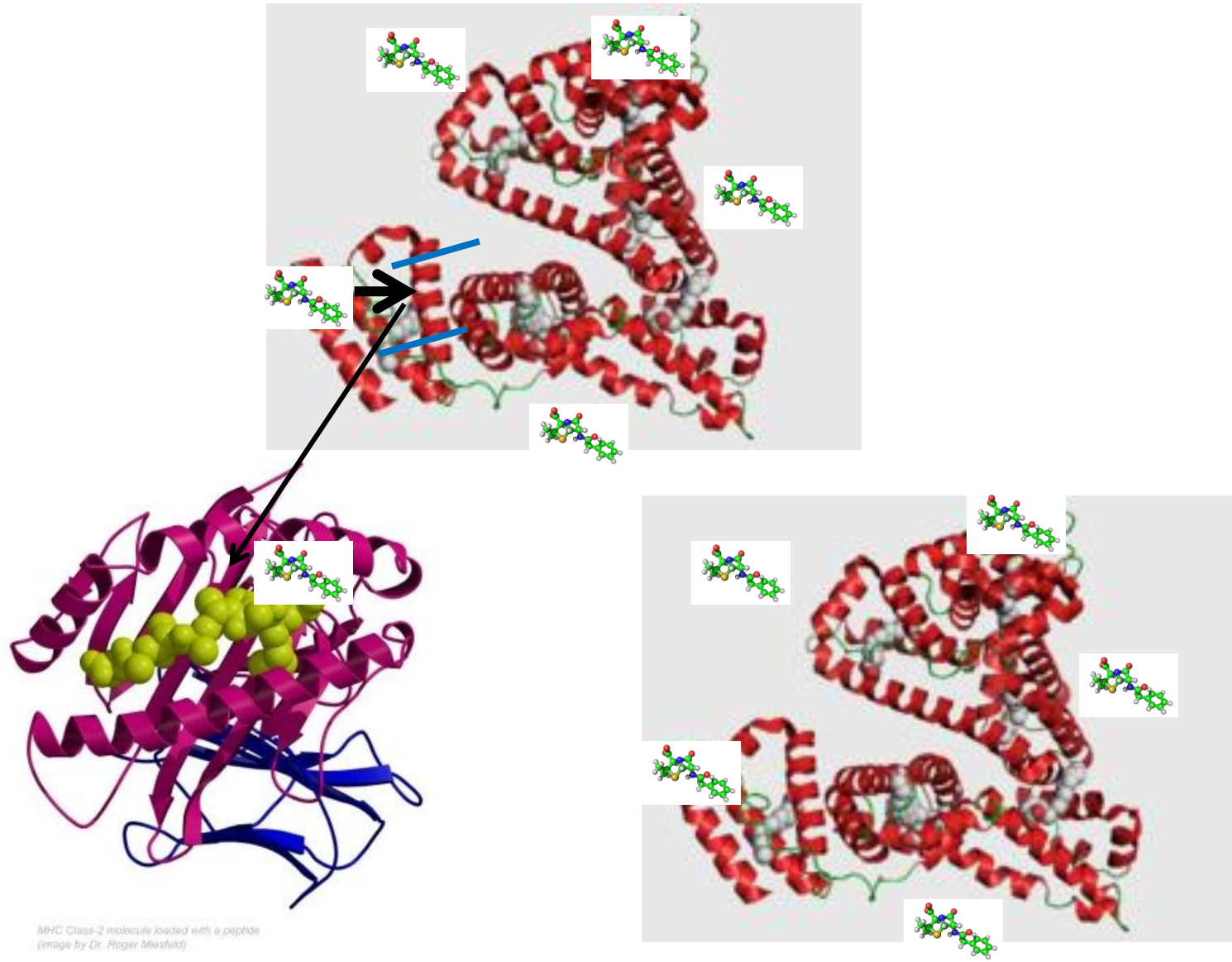
Same  
core  
structure

T & IgE

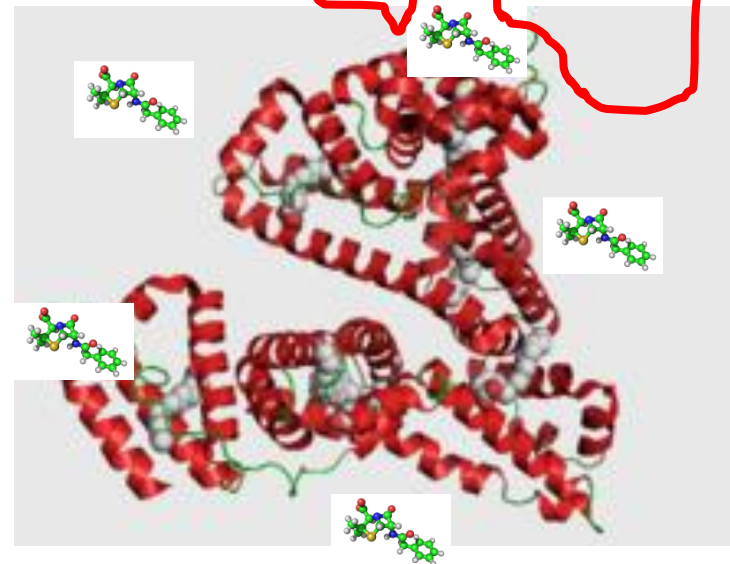
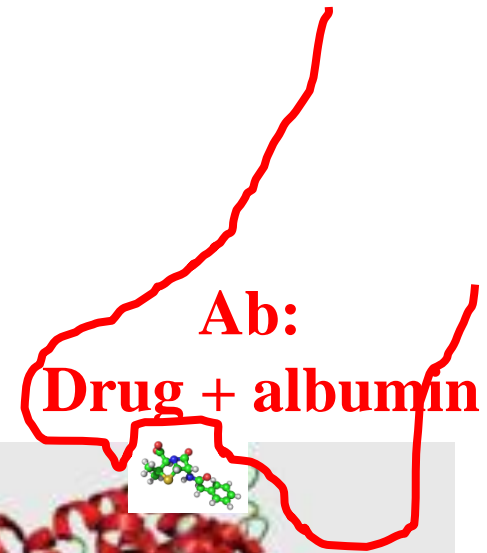
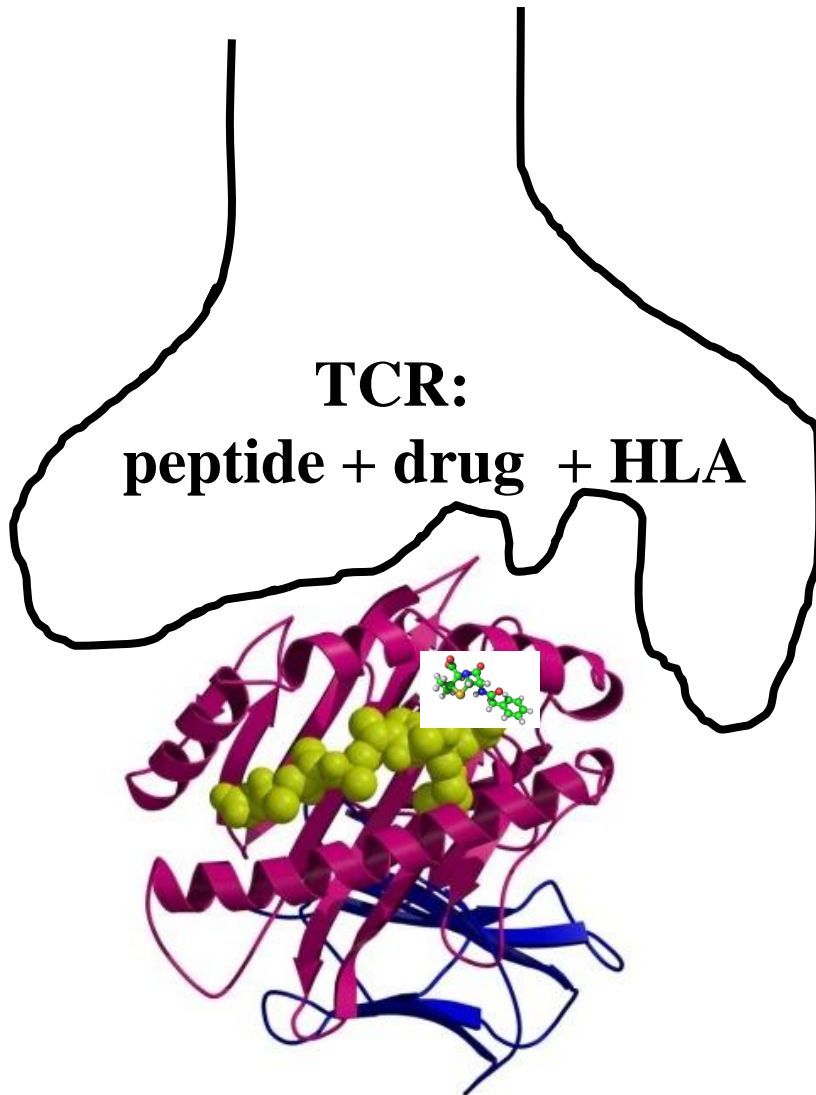
Same side chain

Seldom IgE, even more rarely T

# T cells and antibodies recognize different parts of the molecule (albumin)



# T cells and antibodies recognize different parts of the molecule (albumin)



# Patterns of cross-reactivity

- **Differentiate between IgE and T-cell reactions:** antibodies and T-cells recognize different parts of the same molecule
- **Cross-reactivity of IgE** appears to be more common, as minor determinants might be responsible
- **Cross-reactivity of T-cells** is often less severe: only part of reactive T-cells is cross-reactive; the same for IgE, but very few IgE may already cause symptoms



# Cross reactivity

- Patient with anaphylactic shock after Kefzol
  - Can you give him Augmentin ?
  - Can you give him Ciproxin ?
  - Can you give him Zinazef ?
  
- Patient with maculopapular exanthem after Amoxillin
  - Can you give him Augmentin ?
  - Can you give him Ciproxin?
  - Can you give him Zinazef?

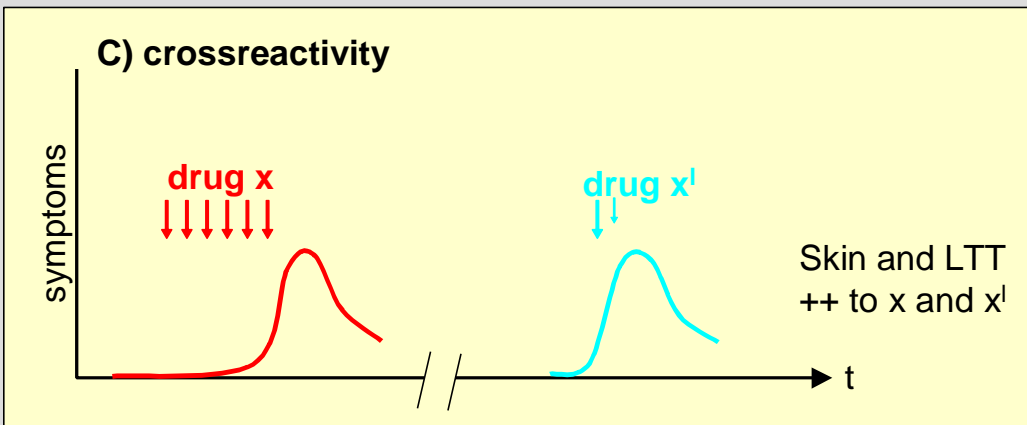
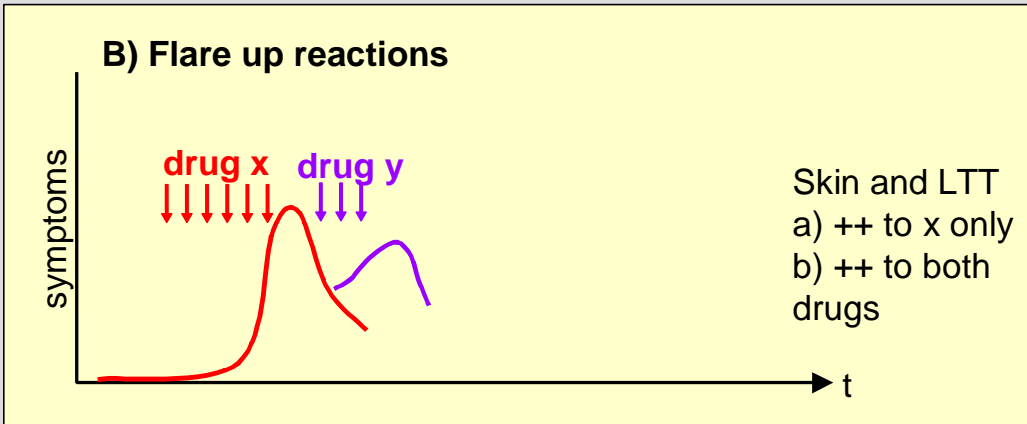
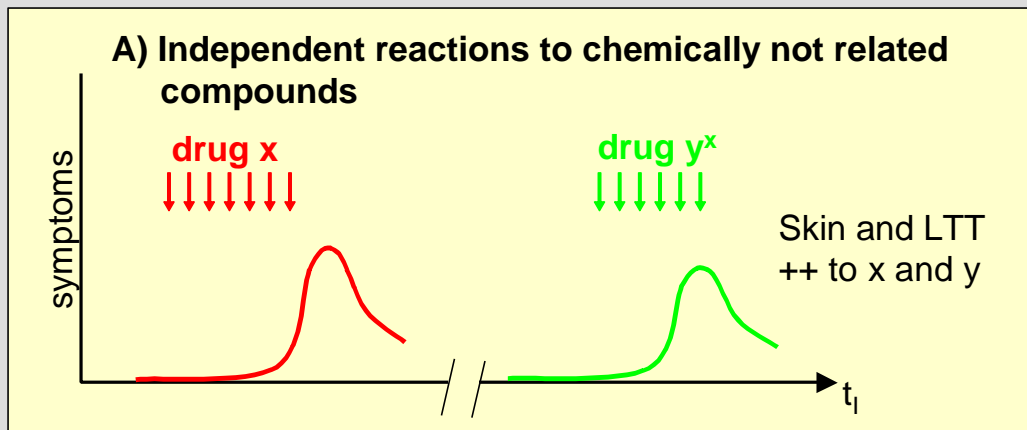
# Cross-reactivity

- Patient with allergy to ciproxin (urticaria)
  - can you give him Norfloxazin ?
  - can you give him Augmentin ?
  
- Patient with allergy to ciproxin (exanthem with hepatitis)
  - can you give him Norfloxazin ?
  - can you give him Augmentin?

2

Flare up reactions

# Multiple drug hypersensitivity, flare up reactions, cross-reactivity



Multiple  
Drug Hyper-  
sensitivity s.s.

**Frequent**, try  
to make an  
interval

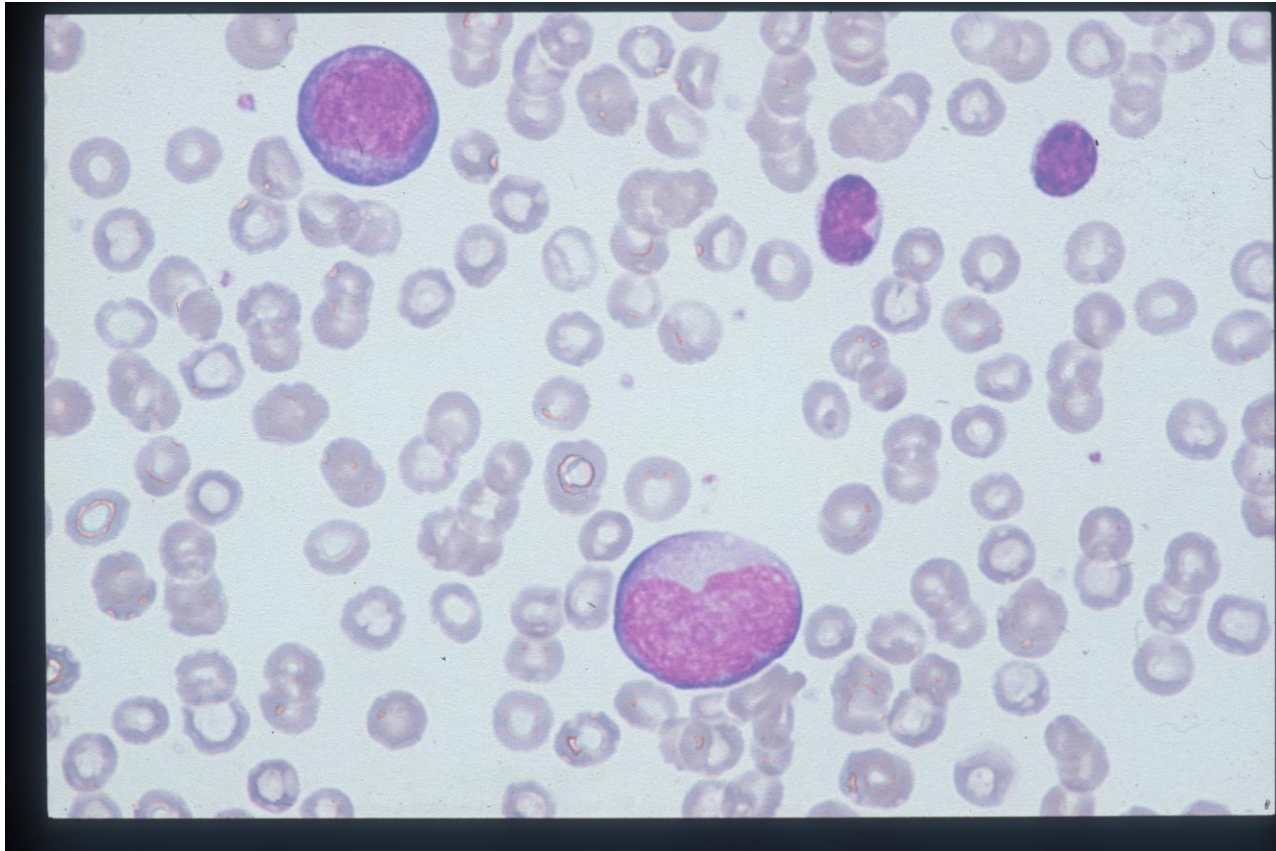
Look to the  
chemical structure  
(e.g. google-pictures)

# Dangerous symptoms:

- 19 year old female, coeliac disease, DM I with neuropathy
- Tegretol (Carbamazepine; 2x200mg); later Neurontine (Gabapentin 3x300mg)
- after 10 weeks treatment with Gabapentine



„atypical lymphocytes “  
(= activated CD8+ T-cells) in the blood at  
massive immune reactions  
(e.g. generalised drug allergy,  
acute EBV und HIV-infection, acute Still syndrom...)



# Flare up Reactions

- Drug hypersensitivity causes a massive immune stimulation
- Immune stimulations are risk factors for drug hypersensitivity reactions
- Addition of a new drug (antibiotic) into an ongoing drug hypersensitivity may lead to flare up reactions, resulting in aggravation of clinical symptoms

# Flare up Reactions (?)

The allergy is directed against the first antibiotic (e.g. clamoxyl),

The second drug stimulates preactivated T cells

Examples: Staph. aureus in artificial knee joints

Therapy with Clamoxyl®: severe exanthema on day 10;

Addition of rimactan and vibramycin 2 days after stopping clamoxyl aggravates the exanthema

Is it an allergy to rimactan or vibramycin as well?

Or are the clamoxyl activated T cells also reacting with rimactan as well (?)



# Take home message

## *Cross-reactivity and flare up reactions*

- Cross-reactivity occurs mainly in the same chemical group
- Cross-reactivity is mainly a problem with acute reactions, it is overestimated in delayed reactions (DD flare up reactions).
- Delayed reactions to penicillins like amoxicillin (exanthem) are NO contraindications for cephalosporins (and vice versa)
- Massive immune stimulations like severe drug allergies can lead to flare up reactions

Thank you very much....

*Allergology Bern*

