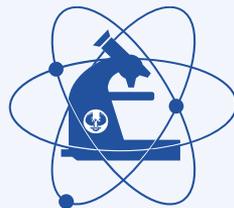


The mechanisms of common drug hypersensitivities and implications for testing

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17 May 2016



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Adverse Drug Reactions (ADR)

- **Type A**

- 85-90% of ADR
- Any individual, given sufficient dose & exposure
- Predictable from a known pharmacologic property
- Eg. Diarrhoea from antibiotics, gastritis from NSAIDs, aminoglycoside nephrotoxicity

- **Type B:**

- 10-15% of ADR
- In a susceptible subgroup of patients
- At doses that are usually tolerated
- Signs & symptoms different from pharmacologic actions of the drug
- Include hypersensitivity reactions mediated by immunologic mechanism “allergy”** and others which result from unique susceptibility to unwanted pharmacological effects.
- Unpredictable (until modern genetic studies)



Type B reactions

- **Exaggerated sensitivity to known drug toxicities/intolerance**
aspirin → tinnitus
- **Idiosyncratic drug reactions**
primaquine → non-immune haemolytic anaemia in glucose-6-phosphate dehydrogenase (G6PD) deficiency
azathioprine toxicity in thiopurine methyl transferase (TPMT) deficiency
- **Immunologic drug reaction (drug allergy)**
drug allergies result from specific immunologic responses to medications
allergic drug reactions account for about 6-10% of all ADRs
up to 10% of fatal reactions



Gell and Coombs classification of immunologic drug reactions

Type	Description	Mechanism	Clinical features
I	IgE-mediated; immediate type	IgE-mediated activation of mast cells & basophils → release of vasoactive substance (histamines, prostaglandins, leukotrienes)	Anaphylaxis Angioedema Bronchospasm Urticaria (hives)
II	Antibody-dependent cytotoxicity	An antigen/hapten intimately a/w a cell binds to antibody → cell or tissue injury.	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Deposition of antigen-antibody complexes in vessels or tissue → complement activation +/- recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors.	Serum sickness Arthus reaction
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (IVa to IVd).	Contact dermatitis Morbilliform reactions Exfoliative dermatoses (SJS/TEN) AGEP DRESS/DiHS



Type I reactions

- Require prior exposure (exceptions follow) and the presence of drug specific IgE
- Itch, urticaria, angioedema, wheeze, vomiting, hypotension
- Timing is rapid; influenced by route of administration
- IV – sec to min
- Oral – 3-30 min (empty stomach); 10-60 min (with food)
- IgE-mediated anaphylactic reactions should NOT begin several days into a course of therapy, if the patient's exposure to the drug has been continuous
- If several doses are skipped, symptoms can appear when the drug is resumed.

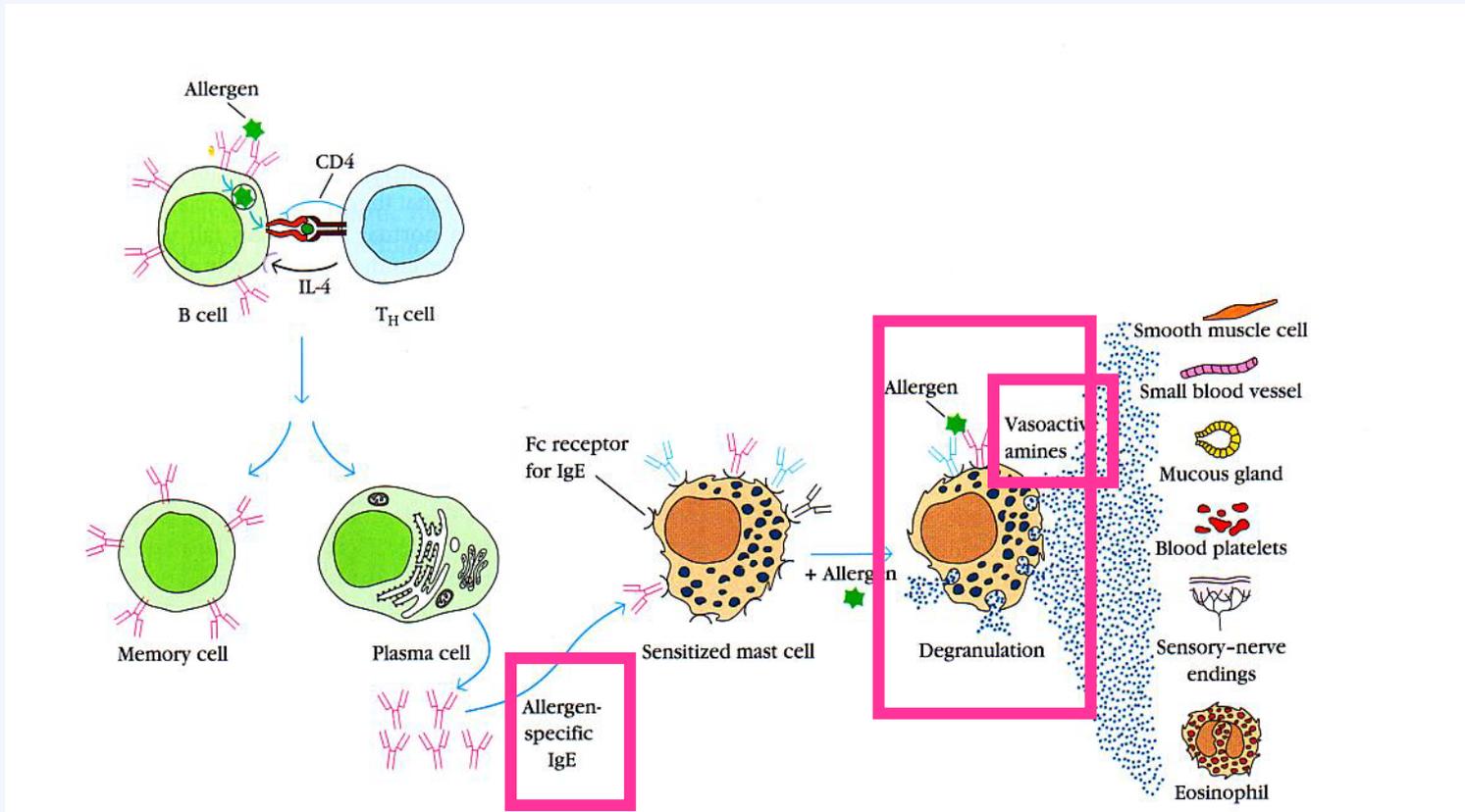


Commonly implicated drugs

- Beta-lactam drugs (penicillins, cephalosporins)
- Neuromuscular blocking agents
- Platinum containing chemotherapeutic agents (carboplatin, oxaliplatin)
- Chimeric antibodies (cetuximab, rituximab)
- Agents ancillary to medical/surgical procedures; latex and chlorhexidine, some reactions to RCM
- BUT a very wide range of drugs give rise to anaphylaxis; e.g. quinalones, PPI, NSAID, opiates, paracetamol- mechanism often unproven



Laboratory measurements



Sensitisation

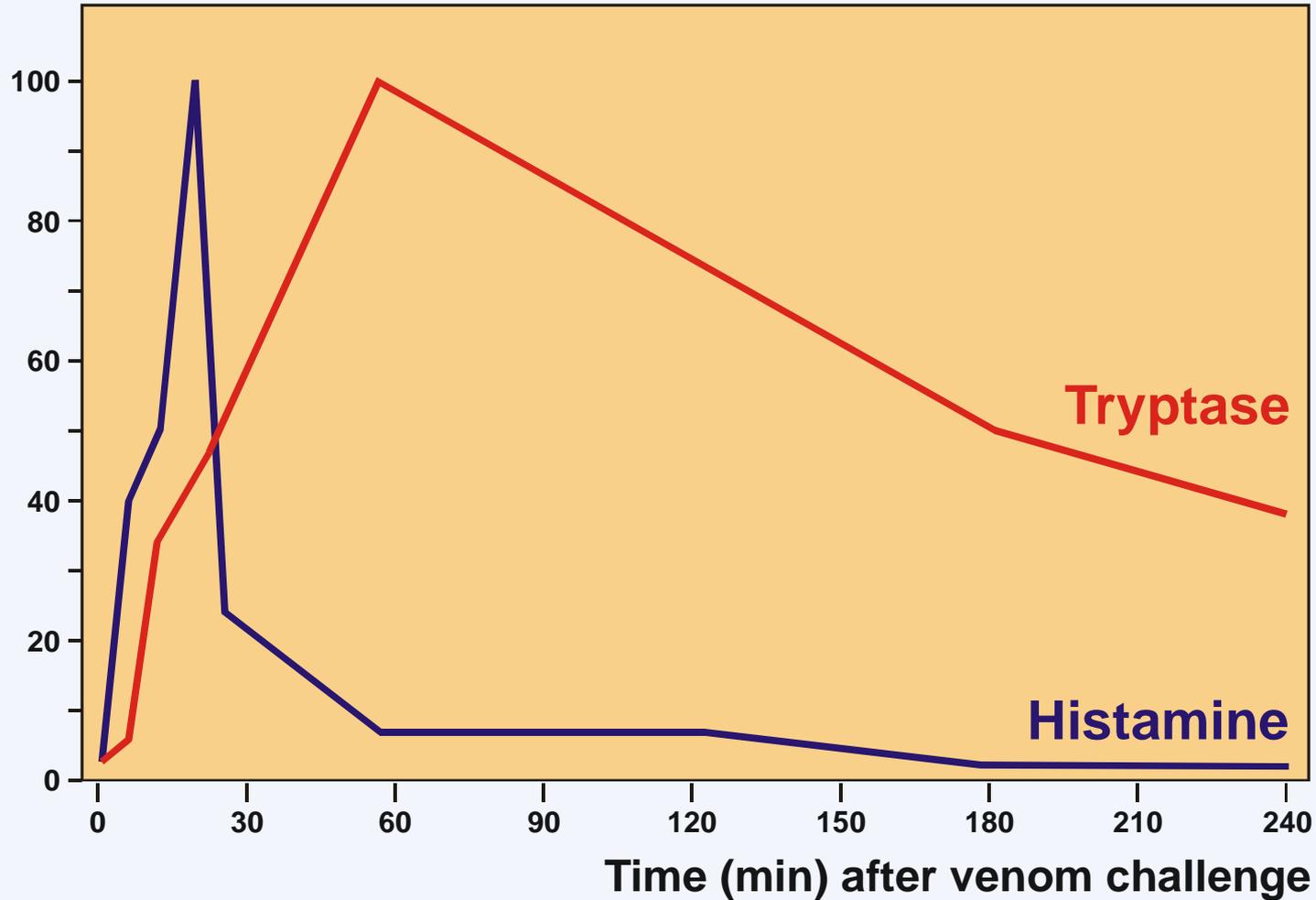
Clinical Allergy



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Time course – mature β -tryptase

% Maximal level of mediator



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Beta lactam antibiotic allergy

- Specific IgE
- Skin testing and challenge
- Cross reactivity



Diagnosis of type 1 allergy has 4 parameters

History

- most important

In vitro testing –

- specific IgE (previously RAST)
- highly specific with low sensitivity (only helpful if +ve)
- available for penicilloyl V, penicilloyl G, amoxylloyl, ampicilloyl, cefaclor
- also for chlorhexidine, latex and among others

In vivo testing

- skin prick and intradermal testing
- can test with more drugs
- need to ensure they are not irritants
- more sensitive (70-95%) and specific
- small risk of severe reaction

Challenge

- to the implicated drug or to an alternative



SIgE to antibiotics

- Poor negative predictive value (cannot exclude on the basis of a negative result)
- High positive predictive value (virtually confirms a Type I hypersensitivity)



RAST positive –
Confirms
penicillin allergy

Avoid, needs
medic alert



RAST negative –
Cant exclude
penicillin allergy

Refer for skin
testing +/-
challenge



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High pretest
Probability of
Type I allergy

Skin testing



Positive

Negative



Intradermal testing



Positive

Negative



Challenge



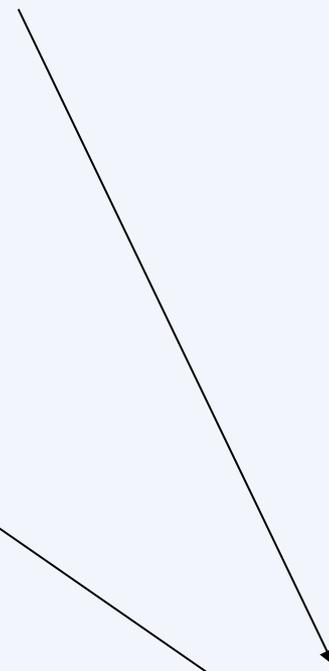
Positive

Negative



NOT ALLERGIC

ALLERGIC



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Prick skin testing Technique

Technique :

1. A drop of allergen extract is placed on skin.
2. Lancet prick and lifts skin.
3. Wheal and flare response evident at 20mins

Wheal mean diameter 3mm or more greater than negative control is **immunologically but not clinically specific**

Note positive (histamine) and negative control (glycerine)

- painless
- simple
- quick
- safe (with qualifications)
- inexpensive



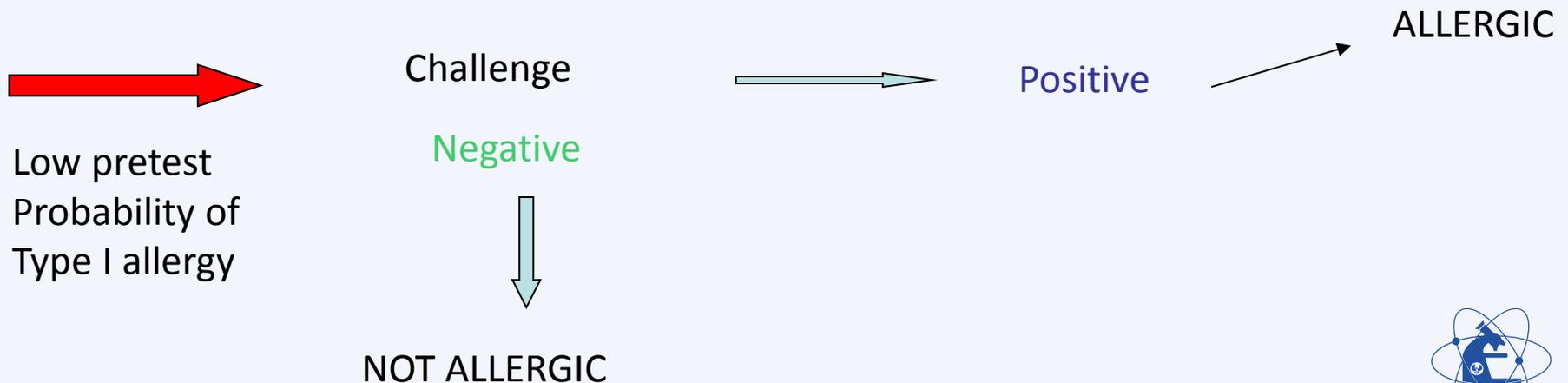
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Intradermal testing

- Immediate sensitivity; read at 20 minutes
- Too sensitive, very low specificity in testing for aeroallergen or food sensitivity
- Painful, substantial risk anaphylaxis, greater expertise to read/interpret
- Used in hospital in assessing non-atopic IgE type allergy to venom and drugs



Challenge often 1/100 dose, 1/10 dose, full dose
Followed by a course of the drug (i.e. antibiotic)



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Penicillin allergy

- Common Beta lactam immunogenic isotopes:
 - Major determinants (95% of the degradation metabolites) BUT less associated with anaphylaxis
 - Minor determinants (5% of metabolites) AND most associated with anaphylaxis
- B lactam side-chains:
 - Also test for amoxicillin

Blood test request:

Penicilloyl V
Penicilloyl G
Amoxicilloyl

Skin test:

The major determinants:

- Prepen (penicilloyl-polylysine)

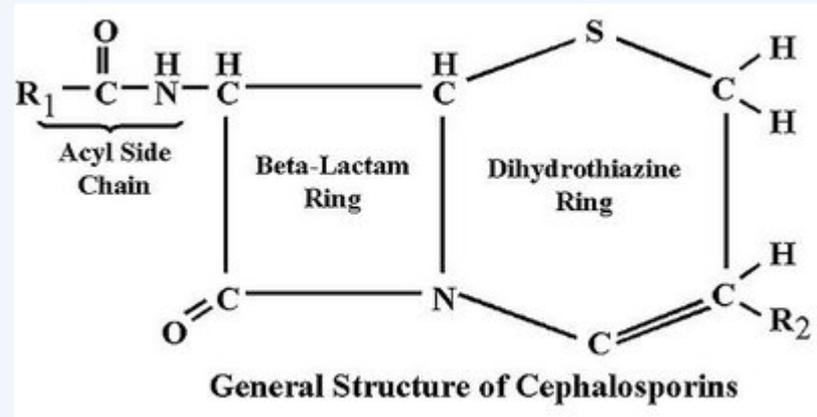
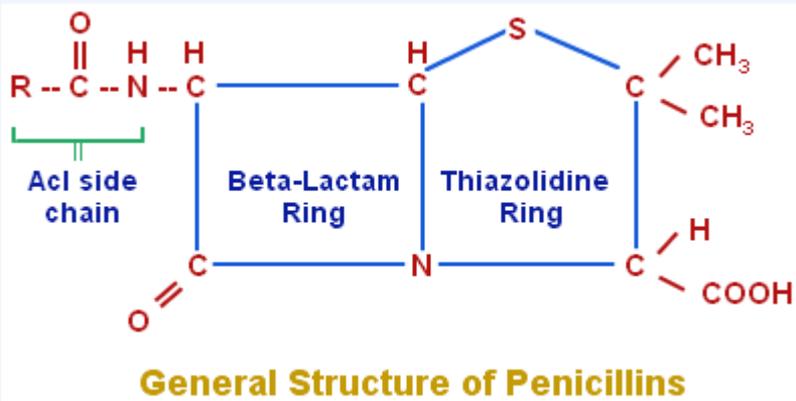
The minor determinants:

MDM (minor determinant mixture)
(Penicilloate)

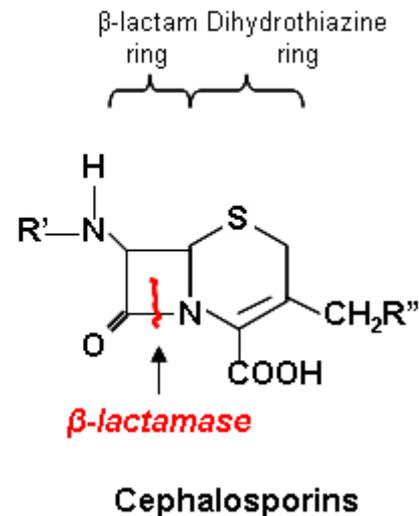
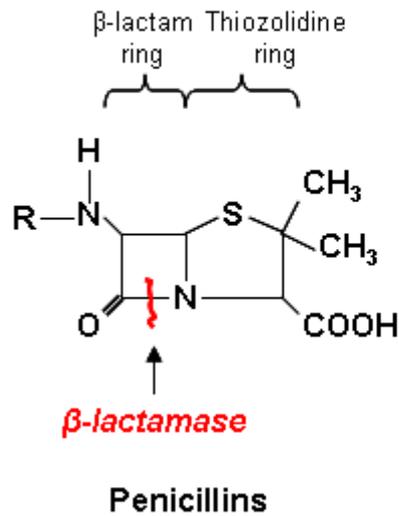
Ampicillin/amoxycillin



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β -Lactam Antibiotics



Cross Reactivity

- Penicillins and cephalosporins <5%
- Penicillins and carbapenem <5%
- Penicillins and monobactams 0%

- Amoxicillin, ampicillin, cephalexin and cefaclor share a side chain which is allergenic in a minority of subjects



Penicillin Allergy

All drug allergies and their reactions must be specified in the allergy section on medication chart and the alert sheet. Contact ward pharmacist or ID team if any concerns/queries.



Contra-indicated

Antibiotics to be **avoided** in penicillin allergy

Amoxycillin
Amoxycillin/Clavulanic acid (*Augmentin, Curam*)
Benzathine penicillin
Benzylpenicillin (*Penicillin G*)
Penicillamine
Phenoxyethylpenicillin (*Penicillin V*)
Dicloxacillin
Flucloxacillin
Piperacillin/Tazobactam (*Tazocin*)
Ticarcillin/Clavulanic acid (*Timentin*)

Caution

Avoid if serious penicillin allergy
(e.g. anaphylaxis)

Use with caution if non-severe
allergy (e.g. minor rash)

Seek specialist advice

Antibiotics to be **used with caution or might need to be avoided** in penicillin allergy

Cefaclor
Cephalexin
Cefepime
Cefotaxime
Cefoxitin
Ceftazidime
Ceftriaxone
Cefuroxime
Cephazolin
Ertapenem
Imipenem/Cilastatin
Meropenem

Considered Safe

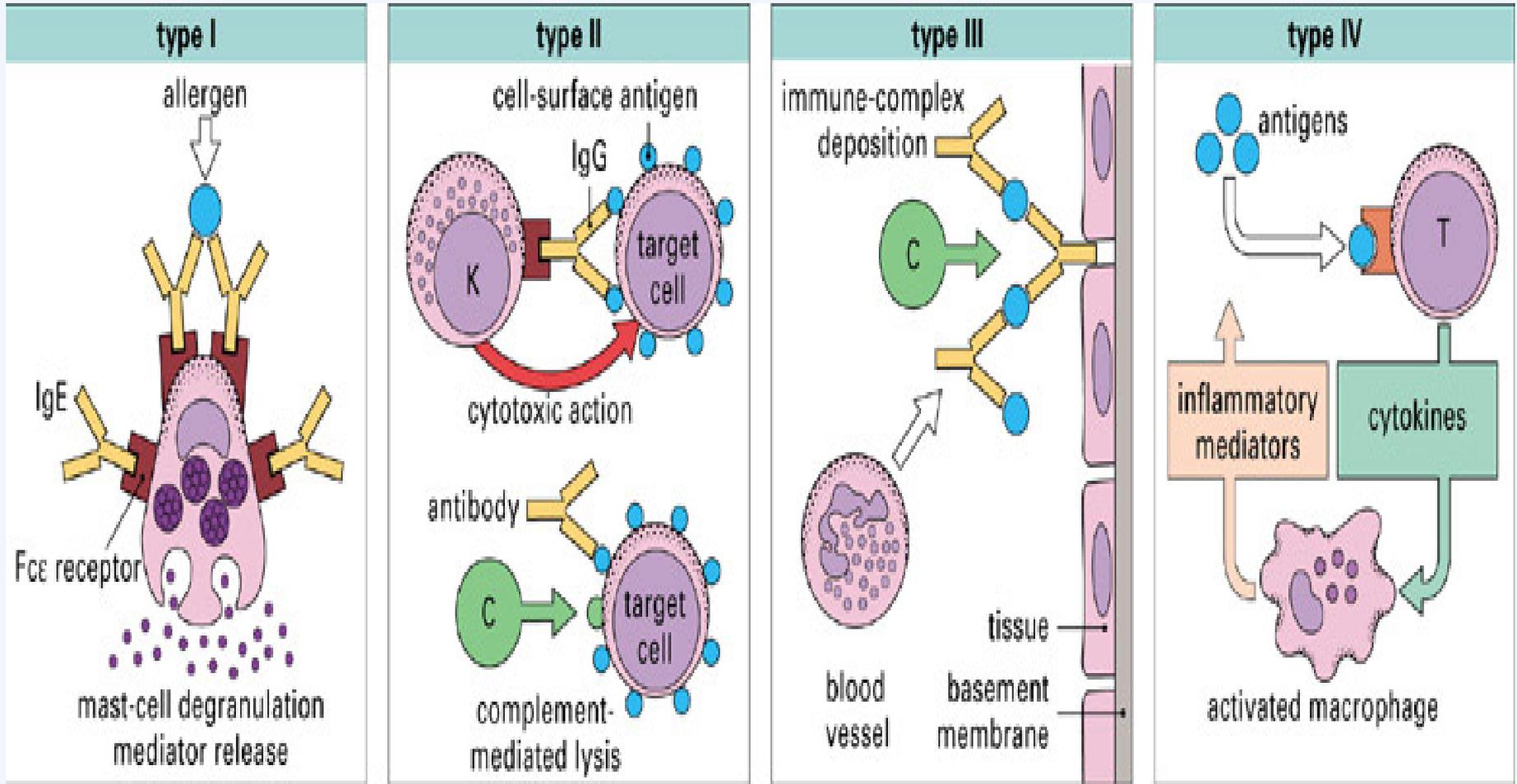
Antibiotics **considered safe** in penicillin allergy
(not complete list)

Azithromycin, Erythromycin, Roxithromycin
Aztreonam
Ciprofloxacin, Norfloxacin, Moxifloxacin
Clindamycin, Lincosamin
Doxycycline, Minocycline
Gentamicin, Tobramycin
Metronidazole
Trimethoprim/sulphamethoxazole (*Cotrimoxazole, Bactrim*)
Vancomycin

In **serious penicillin allergy** (e.g. anaphylaxis, bronchospasm, oedema of face, pharynx and larynx, hypotension) **ALL** penicillins, cephalosporins and other beta-lactams should be avoided. In cases of milder reactions such as rash to penicillins, cephalosporins can be used with caution.



Hypersensitivity reactions



© **Fleshandbones.com** Roitt et al: Immunology 6E

Type II reactions

- Antibody-mediated cell destruction
- Drugs bind to surfaces of certain cell types and act as antigens
- Complex targeted for clearance by macrophages
- May involve complement activation, but variable
- Presence of high titres of drug-specific IgG (or rarely IgM) antibodies
- In the context of high-dose, prolonged drug administration
- Haemolytic anaemia, thrombocytopenia, or neutropenia
- Symptoms usually appear 5-8 days after exposure, but may begin after much longer periods of treatment
- Symptoms can start within hours if the causative drug is stopped and then restarted



Specific presentations

- **Drug-induced haemolytic anaemia**
cephalosporins, penicillins (high dose IV), NSAIDs, quinine, quinidine
- **Drug-induced thrombocytopenia**
heparin, beta-lactam antibiotics, vancomycin, carbamazepine, abciximab, gold, quinidine, quinine
- **Drug-induced neutropenia**
propylthiouracil (PTU), amodiaquine, flecainide



Type III reactions

- Mediated by antigen-antibody complexes
- Usually present as serum sickness, vasculitis, or drug fever
- Uncommon
- In the context of high-dose, prolonged drug administration
- The drug is believed to act as a soluble antigen
- Binds drug-specific IgG, forming small immune complexes that can activate complement
- Precipitate in various tissues (blood vessels, joints, renal glomeruli)
- Immune complexes bind to Fc-IgG receptors of inflammatory cells and activate complement
- Takes ≥ 1 week to develop



Specific presentations

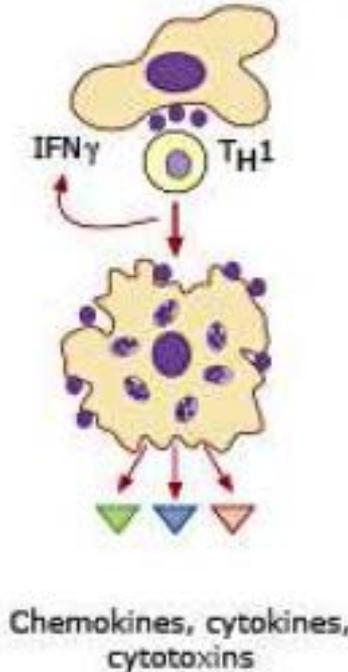
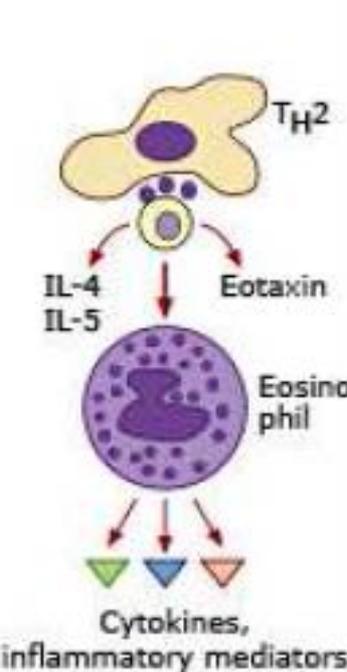
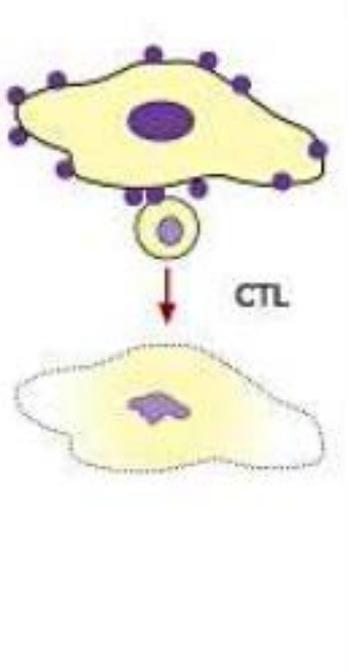
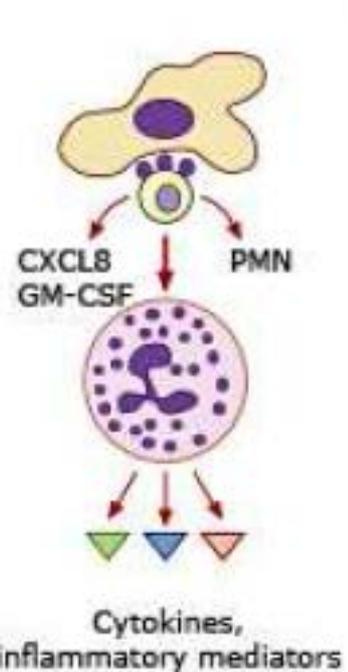
- **Serum sickness**
 - fever, urticarial or purpuric rash, arthralgias, acute glomerulonephritis
 - antitoxins, including those for rabies, botulism, and venoms
- **Arthus reaction**
 - antibody-antigen complexes deposited small vessel wall; skin necrosis
 - painful localised swelling within a few minutes; peak by 24 hrs
 - at site of booster injections (tetanus, diphtheria, hepatitis B vaccine)
- **Vasculitis**
 - palpable purpura, fever, urticaria, arthralgia, lymphadenopathy
 - ↑ESR, and ↓complement
 - beta lactam antibiotics, sulphomanides (loop, thiazide diuretics)



Type IV reactions

- Delayed hypersensitivity reaction
- Mediated by T cells, not antibody
- At least 48-72 hours; sometimes days to weeks following exposure to drug
- The time to symptom onset for reactions depends on the number of T cells activated by the drug.
- Illustrate different types of Type IV hypersensitivity but mechanisms often mixed; most severe reactions (e.g. bullous/exfoliative, hepatitis) usually involve cytotoxic T cells
- Stevens-Johnson syndrome (SJS); Toxic epidermal necrolysis (TEN)
- Drug rash with eosinophilia and systemic symptoms (DRESS)



Type	Type IVa	Type IVb	Type IVc	Type IVd
Cytokines	IFN γ , TNF α (T _H 1 cells)	IL-5, IL-4/IL-13 (T _H 2 cells)	Perforin/granzyme B (CTL)	CXCL8, GM-CSF (T cells)
Antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation
Cells	Macrophage activation	Eosinophils	T cells	Neutrophils
Pathomechanism	 <p>Chemokines, cytokines, cytotoxins</p>	 <p>Cytokines, inflammatory mediators</p>	 <p>Cytokines, inflammatory mediators</p>	 <p>Cytokines, inflammatory mediators</p>
Example	Tuberculin reaction, contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema hepatitis	AGEP Behçet disease

Contact dermatitis



Acute Generalised Exanthematous Pustulosis



Amoxicillin
Antimalarials
Ca channel blockers



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Stevens-Johnson syndrome



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For our patients and our population

Drug reaction with eosinophilia and systemic symptoms (DRESS)



Allopurinol
Antiepileptics
Sulfasalazine
Dapsone
Abacavir
Minocycline



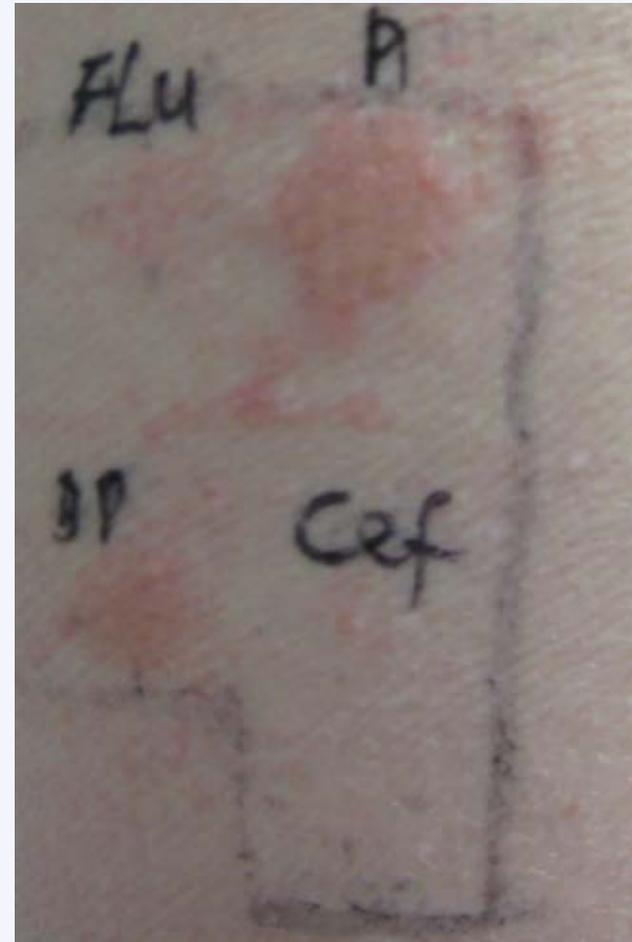
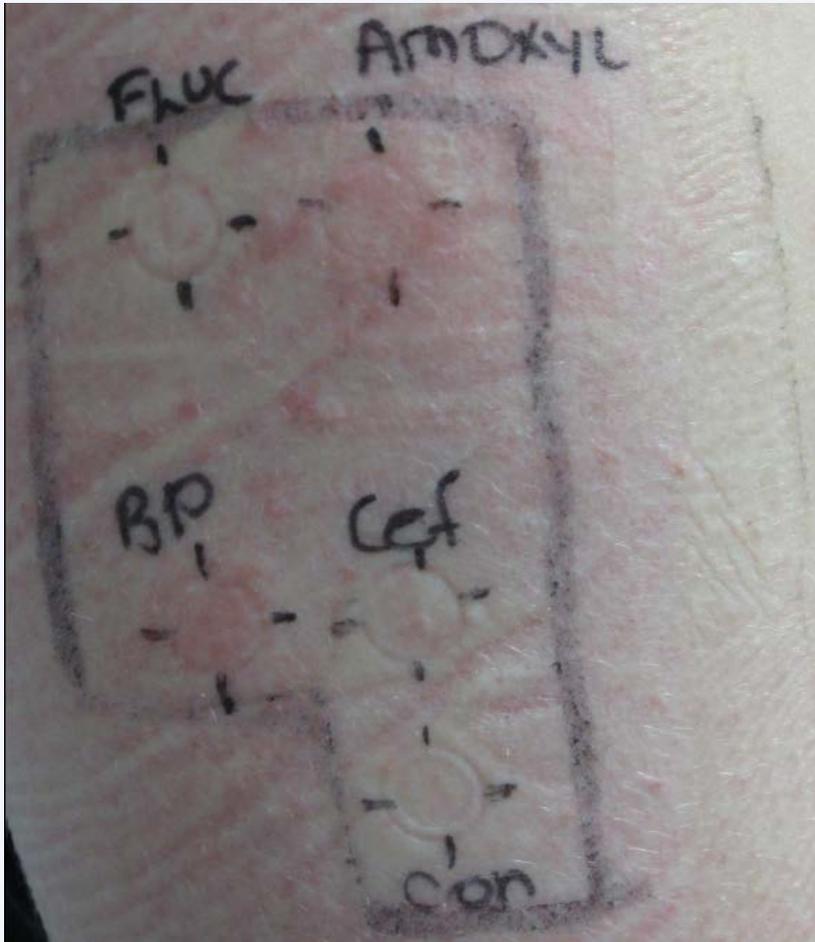
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Drug specific diagnosis in Type IV reactions

- T cell “read” is usually of narrower specificity than for B cells/antibody; cross reactivity is generally less but for many low frequency disorders poorly defined --> caution required if severe disorder e.g. TEN or DRESS
- Test means include skin patch testing, intradermal skin testing with 48-72 hour reading, in vitro tests involving subjects T cells
- All have limited sensitivity and are most useful when of several possible agents, only one is positive
- Skin tests most useful when original reaction involved rash but cannot be done in acute phase; in fixed drug eruptions patch test needs to be done on previously involved skin, usually impractical as that is often genital skin.



Patch testing



“Rule breakers”

Angioedema as a pharmacological idiosyncrasy

Inhibitors of drugs responsible for bradykinin breakdown; not mediated by adaptive immunity

- ACEI angioedema without rash or other anaphylaxis phenotypes OR cough (different syndrome); (less frequently with A2R inhibitors, mechanism not clear)
- gliptins, dipeptidyl peptidase 4 inhibitors- angioedema but less frequently than with ACEI



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“Rule breakers”

- Non Steroidal Anti-inflammatory Drugs (NSAID)
- 1) Aspirin NSAID exacerbated respiratory disease (AERD)
- 2) Aspirin/NSAID induced urticaria/angioedema
- 3) NSAID induced anaphylaxis (especially diclofenac)

- 1 and 2 likely pharmacological idiosyncrasy; natural history of “3” suggests specific sensitisation but direct evidence minimal



“Rule breakers”

- High osmolar radio-contrast agents (RCM)
 - Poor correlation with skin tests; likely direct mast cell activation, non-sequential complement activation
- Low osmolar RCM
 - Reactions far less frequent and many associated with positive skin testing for immediate allergy (IgE mediated?)
 - Sensitivity uncertain; test most useful when only one agent positive



“Rule breakers”

- Lack of prior exposure to specific drug
 - sensitization may have occurred from exposure to a cross-reactive compound, even though the patient showed no signs of allergy to the sensitizing product; e.g. pholcodine and neuromuscular blocking agents, cetuximab with mammalian meat and tick bites
 - Pharmacological interaction of drugs with antigen-specific receptors; the p-i concept; direct interaction of unmodified drug with T cell receptor reproducing various type-4 reactions without processing of drug or binding as hapten to host protein carriers.



“Rule breakers”

- Predictability of some reactions with modern genetics;
 - Anti-convulsant induced cutaneous ADR in Han Chinese
 - Allopurinol induced cutaneous ADR in Han Chinese
 - Anti-retroviral cutaneous ADR especially in Caucasians



Risk factors affecting probability of sensitisation

- Prior exposure, especially intermittent exposure
- Atopy for macro-molecules (e.g. latex) but not for haptens
- Age, systemic mast cell disorders, cardio-respiratory disease and possibly beta-blockers/ ACEI increase risk of severe or lethal reaction.

