Dr Khoshnevis

DRUG HYPERSENSITIVITY

ADVERSE DRUG REACTION

- Adverse drug reactions are classified as predictable (type A) or unpredictable (type B).
- A predictable drug reaction is related to the pharmacological actions of the drug.(toxicity, interaction, adverse effect) dose dependent
- An unpredictable reaction is related to immunological response (hypersensitivity reactions) or nonimmunological response.(idiosyncratic, pseudoallergic) dose independent and occur in genetically predisposed patients

DISTINCTIVE FEATURES OF ALLERGIC DRUG REACTIONS

- No correlation with known pharmacological properties of the drug
- No linear relationship with drug dosage
- Occur in a minority of persons receiving the drug
- Often include a rash, angioedema, the serum sickness syndrome, anaphylaxis and asthma which are reactions similar to those of classical protein allergy

CLASSIFICATION

- Coombs and Gell classification

1-Type I - immediate (atopic, or anaphylactic)

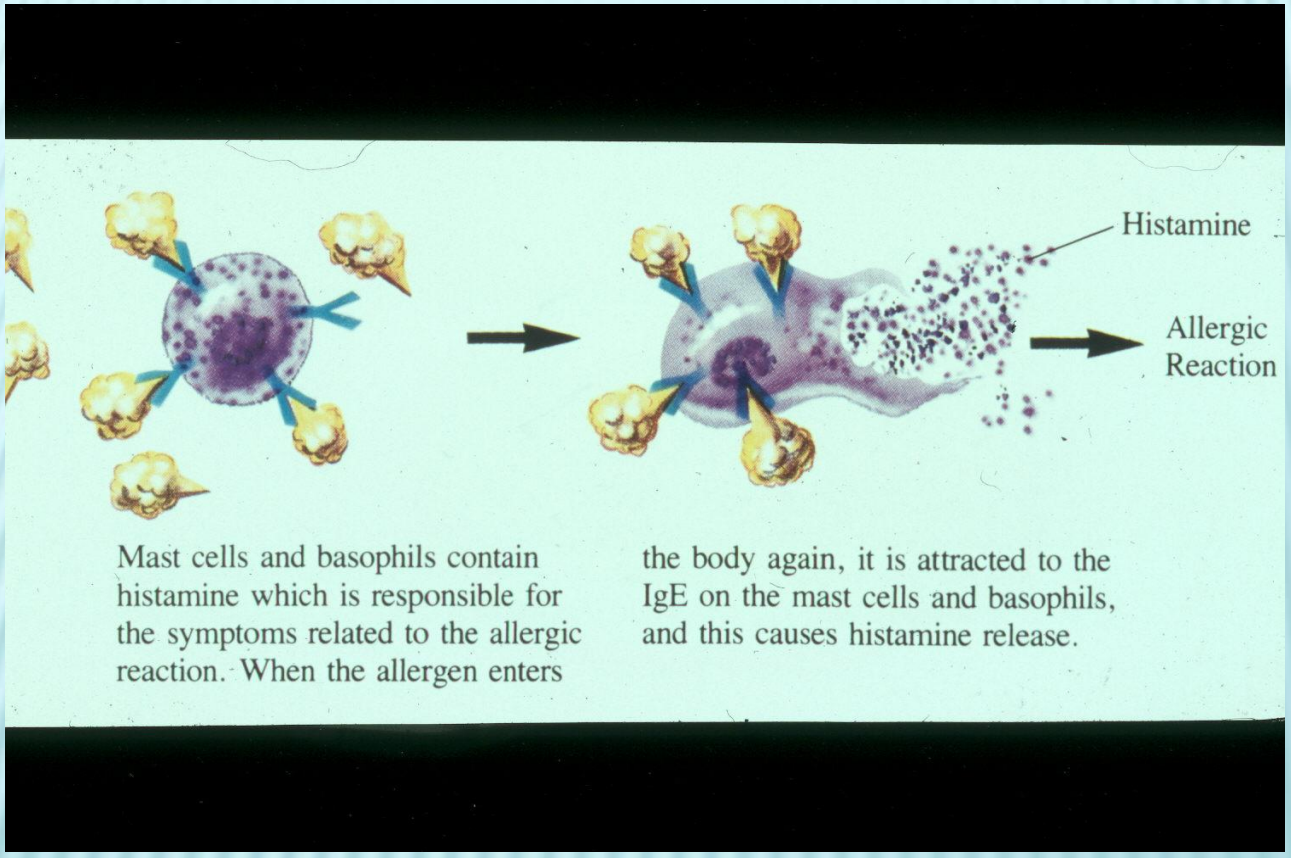
2-Type II - antibody-dependent

3-Type III - immune complex

4-Type IV - cell-mediated or delayed

THE CLASSIFICATION OF THE HYPERSENSITIVITY

- Type I
- Antigens combine with specific IgE antibodies that are bound to membrane receptors on tissue mast cells and blood basophils
- It causes the rapid release of histamine & leukoterienes and inflammatory mediators
- It produces vasodilatation, increased capillary permeability, glandular hypersecretion, smooth muscle spasm and tissue infiltration with eosinophils.
- It results to urticaria, bronchospasm,anaphylaxis.



Mast cells and basophils contain histamine which is responsible for the symptoms related to the allergic reaction. When the allergen enters the body again, it is attracted to the IgE on the mast cells and basophils, and this causes histamine release.

THE CLASSIFICATION OF THE HYPERSENSITIVITY

- Type II

  Cytotoxic reactions (activation of killer T cells or macrophages to produce cytotoxicity)resulting when antibody (IgG,IgM) reacts with antigenic components of a cell or tissue elements or with antigen or hapten that is coupled to a cell or tissue.

- Hemolytic anemia, thrombocytopenia

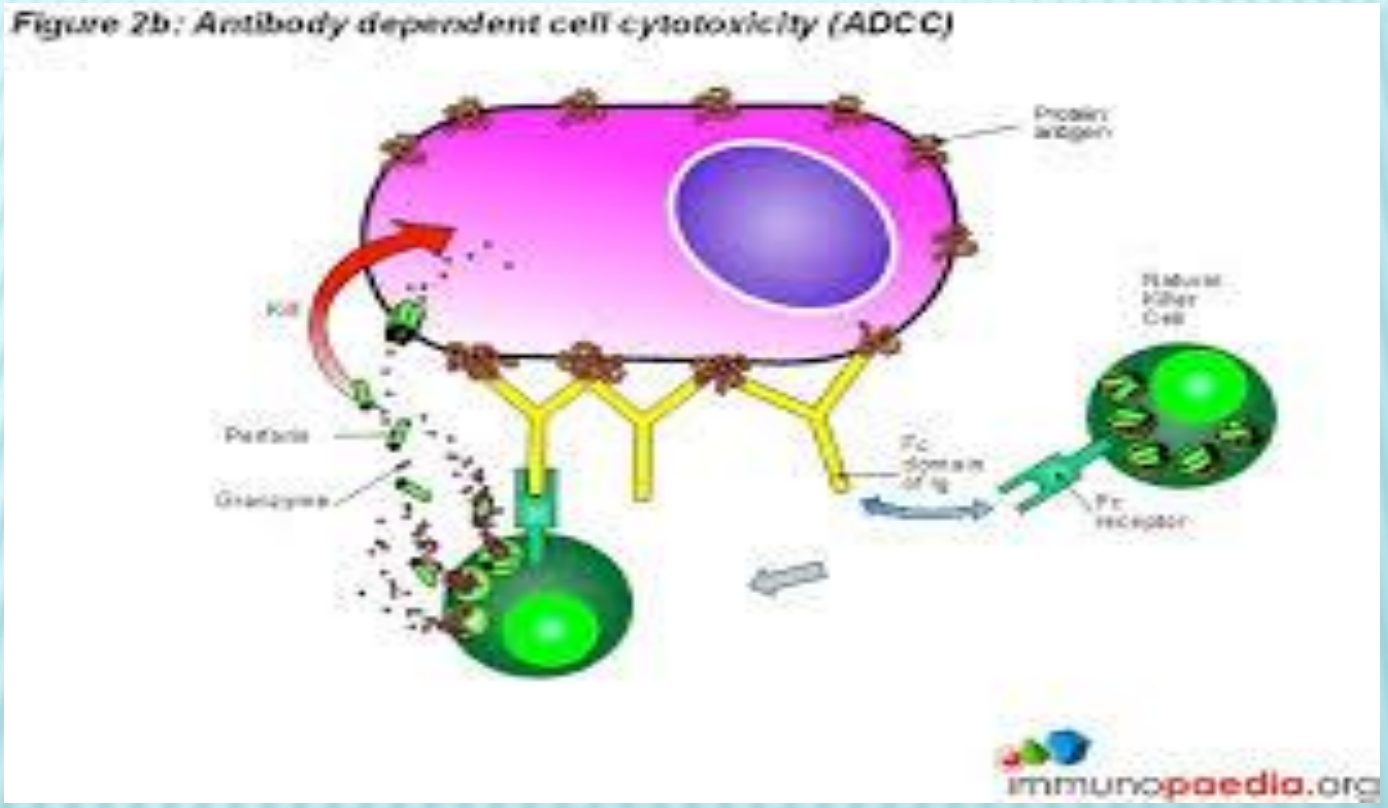


Figure 2b: Antibody dependent cell cytotoxicity (ADCC)
Target antigen
Kill
Perforin
Granzyme
Natural Killer Cell
Fc domain of Ig
Fc receptor
immunopaedia.org

THE CLASSIFICATION OF THE HYPERSENSITIITY

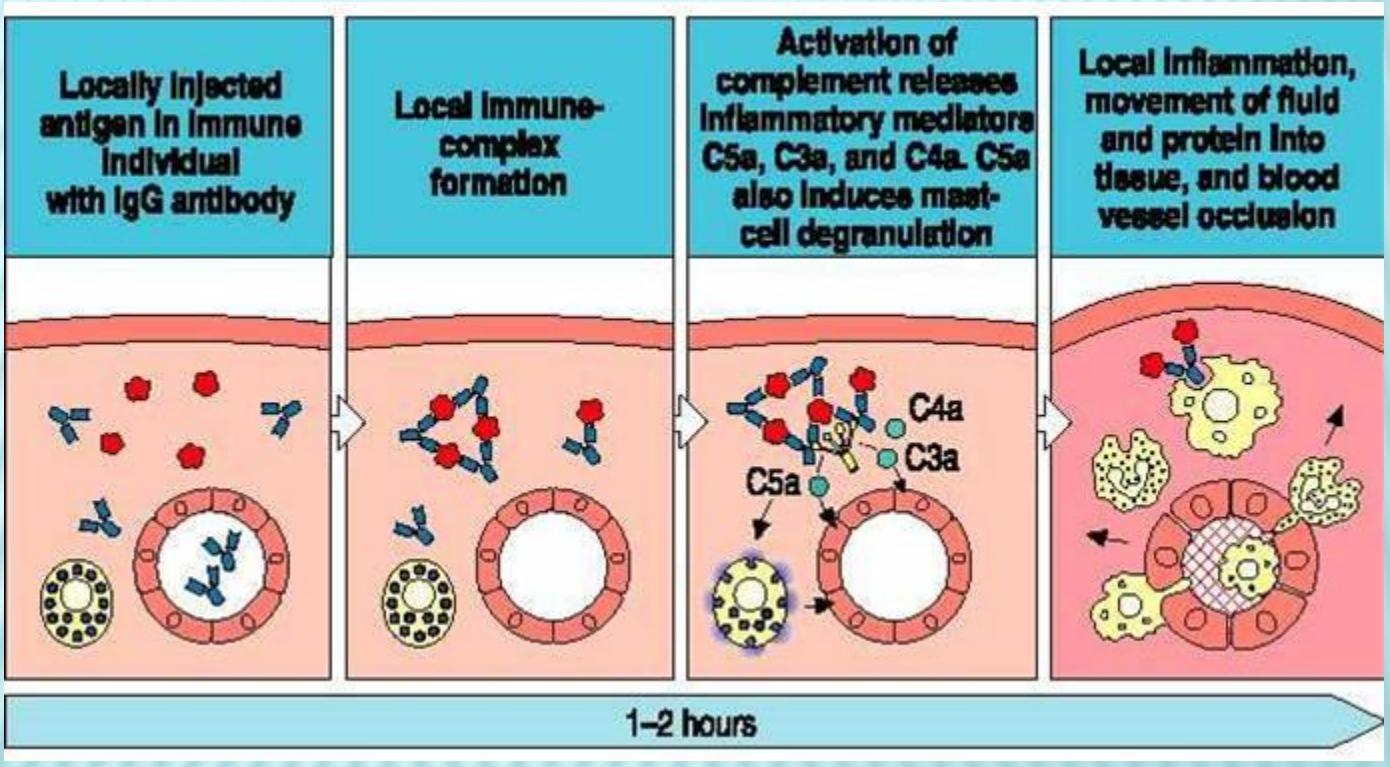
- Type III

  Immune complex (IC) reactions resulting from deposition of soluble circulating antigen-antibody ICs in vessels or tissue.

  It causes polymorphonuclear cell migration and release of lysosomal proteolytic enzymes and permeability factors in tissues, resulting in acute inflammation.

- Serum scikness: 1-3 weeks later: fever,wheal,rash,lymphadenopathy,arthralgia

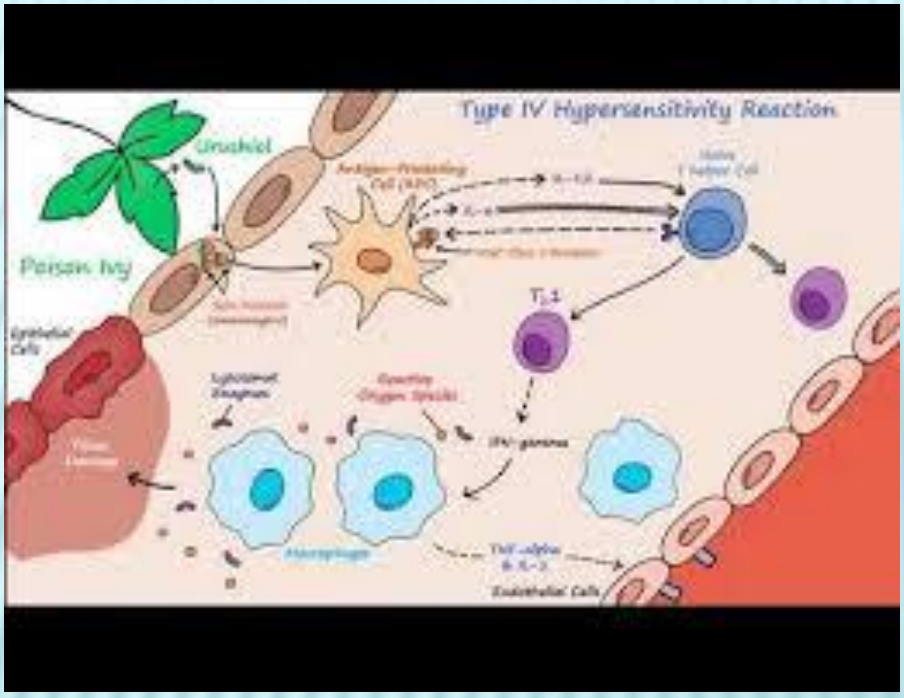
LOCALIZED DEPOSITIONS OF IMMUNE COMPLEXES WITHIN A TISSUE CAUSE TYPE III HYPERSENSITIVITY



THE CLASSIFICATION OF THE HYPERSENSITIVITY

- Type IV

  Cell mediated, delayed hypersensitivity reactions caused by sensitized T lymphocytes after contact with a specific antigen.
- Topical route(neomycin, local anesthetics): contact dermatitis


Type IV Hypersensitivity Reaction
Urushiol
Poison Ivy
Epithelial Cells
Macrophages
Endothelial Cells

RISK FACTORS FOR DRUG ALLERGY

- Frequent exposure to the drug
- Previous reactions
- Large or intermittent doses of the drug
- Drug given by injection rather than pill
- Family tendency to develop allergies and asthma.

DIAGNOSIS

- Accurate medical history
- Skin test (penicillin)
- Serum test for IgE to beta lactams
- Coombs test (anemia)
- Serum tryptase(mast cell)

PROPHYLAXIS OF PENICILLIN ALLERGY

- Skin test

  Skin tests for immediate-type (IgE-mediated) hypersensitivity are very useful in diagnosis of reactions to penicillin, enzymes, and some vaccines
- The drug, or one of its metabolites must be chemically reactive with protein can act as haptens and bond covalently to proteins.

PROPHYLAXIS OF PENICILLIN ALLERGY

- Skin test

  The major degradation product of penicillin, benzylpenicillenic acid, can combine with tissue proteins to form benzylpenicilloyl (BPO), the major antigenic determinant of penicillin.
- 20% don't react with Pre-Pen
- Penicillin G used as a substitute for minor determinant

PROPHYLAXIS OF PENICILLIN ALLERGY

- Skin Test

  A BPO-polylysine conjugate and penicillin G in a concentration of 1000U/ml are available for skin testing

  It is performed by prick technique-a drop of a dilute allergenic extract is placed on the skin, which is then pricked or punctured through the extract, usually by “tenting” up the skin with the tip of a stylet.

PROPHYLAXIS OF PENICILLIN ALLERGY

- Intradermal test

  A skin test is considered positive if it produces a wheal and flare reaction in 15 min with a wheal diameter at least 5 mm larger than the control.

INTRADERMAL TEST

Intradermal allergy test reactions

A.D.A.M.

PROPHYLAXIS OF PENICILLIN ALLERGY

- If skin tests are positive, the patient risks an anaphylactic reaction if treated with penicillin
- Negative skin tests minimize but do not exclude the risk of a serious reaction.(npv=97-99%)

TREATMENT

- Specific desensitization (IgE mediated)
- Graded challenge (Non IgE mediated) (cotrimoxazol, aspirin, NSAID)

EXAMPLE OF DRUG ALLERGY

PENICILLIN ALLERGY

- Symptoms

Fever

Rash

Urticaria

Angioedema

Nephritis

Lymphadenopathy

Arthralgias

RASH

URTICARIA

- What is urticaria?
- It is local wheals and erythema in the superficial dermis
- Urticaria induced by drug is generally acute and is limited to the skin and subcutaneous tissues.

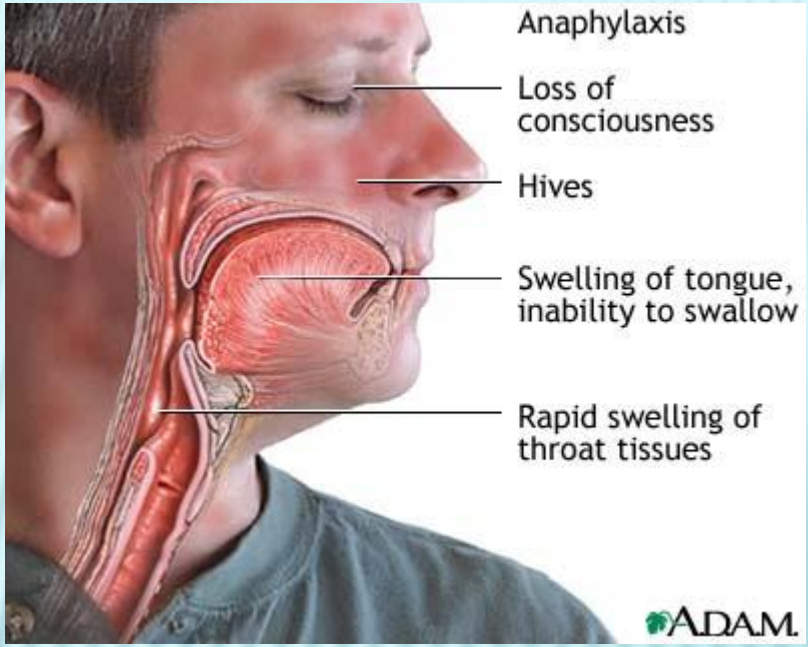
ANGIOEDEMA

- It is a deeper swelling due to edematous areas in the deep dermis and subcutaneous tissue and may also involve mucous membranes.
- Diffuse and painful swelling of loose subcutaneous tissue, dorsum of hands or feet, eyelids, lips, genitalia and mucous membranes.
- Edema of the upper airways may produce respiratory distress

ANAPHYLACTIC REACTION

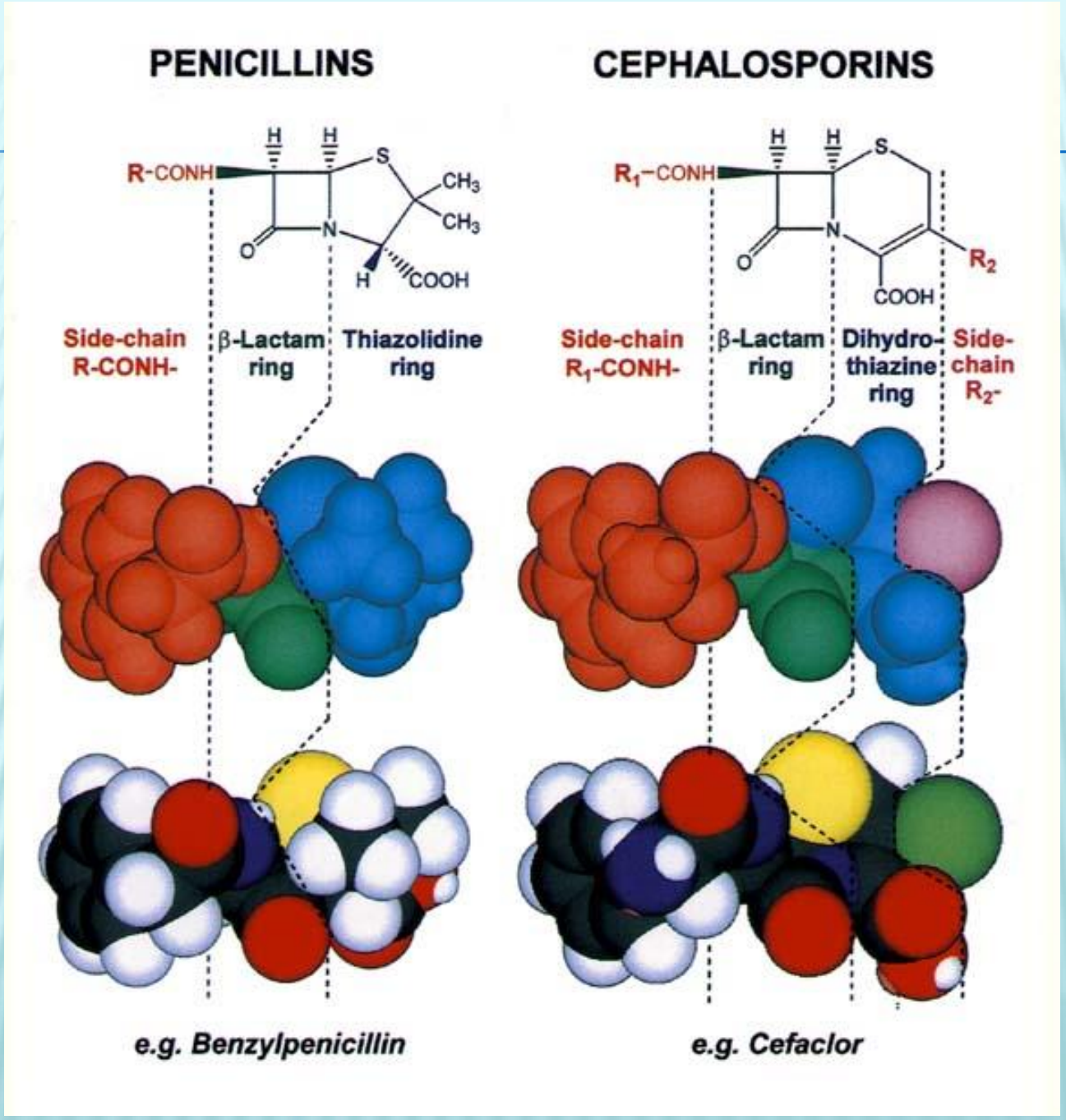
- penicillin allergy is Frequent cause of anaphylaxis (IV)
- Life threatening
- Almost all anaphylactic reactions occur within 4 hours of the first dose of the drug. Most occur within 1 hour of taking the drug, and many occur within minutes or even seconds.
- Skin reaction - Hives, redness/flushing,
- sense of warmth, itching
- Difficulty breathing - Chest tightness, wheezing, throat tightness
- Fainting - Light-headness or loss of consciousness due to drastic decrease in blood pressure ("shock")
- Rapid or irregular heart beat
- Swelling of face, tongue, lips, throat, joints, hands, or feet

ANAPHYLAXIS



CROSS-REACTIVITY

- Carbapenems have a bicyclic nucleus containing β-lactam ring and an adjacent five-membered ring.
- It was showed a cross-reactivity in allergy skin testing between penicillin major and minor determinants and the analogous imipenem reagents.
- Patients especially with positive penicillin skin test should withhold carbapenems
- Monobactams (azteronam) are safe in penicillin allergy but not in ceftazidime allergy


PENICILLINS
CEPHALOSPORINS
R-CONH
R1-CONH
CH3
CH3
COOH
R2
Side-chain R-CONH-
β-Lactam ring
Thiazolidine ring
Side-chain R1-CONH-
β-Lactam ring
Dihydro-thiazine ring
Side-chain R2-
e.g. Benzylpenicillin
e.g. Cefaclor

CROSS-REACTIVITY

- The structure of cephalosporin contains a β- lactam ring with a six-membered dihydrothiazine ring.
- Side chain antigens may be more significant and probably dominate in cephalosporin (patients with positive penicillin skin test results who were given cephalosporin had a cross reaction rate of 10%-20%)

SJS & TEN

- Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) develop 1-3 weeks after the culprit medication is initiated
- Sulfonamides, other antibiotics, NSAIDs, anticonvulsant and antiretroviral agents are the most common causative medications.

ALLERGIC REACTIONS ON SKIN

-A manifestation of acute graft versus host disease with blistering mucocutaneous lesions

- Epidermal detachment<10% (SJS) and>30% (TEN)
- Confluent purpuric macules of face, trunk, severe explosive mucosal erosions (>1mucosal surface),fever, constitutional symptoms.(eye, liver, kidney ,lung)
- Treatment: Admit to intensive care or burn unit
- Discontinue medication and IVIG

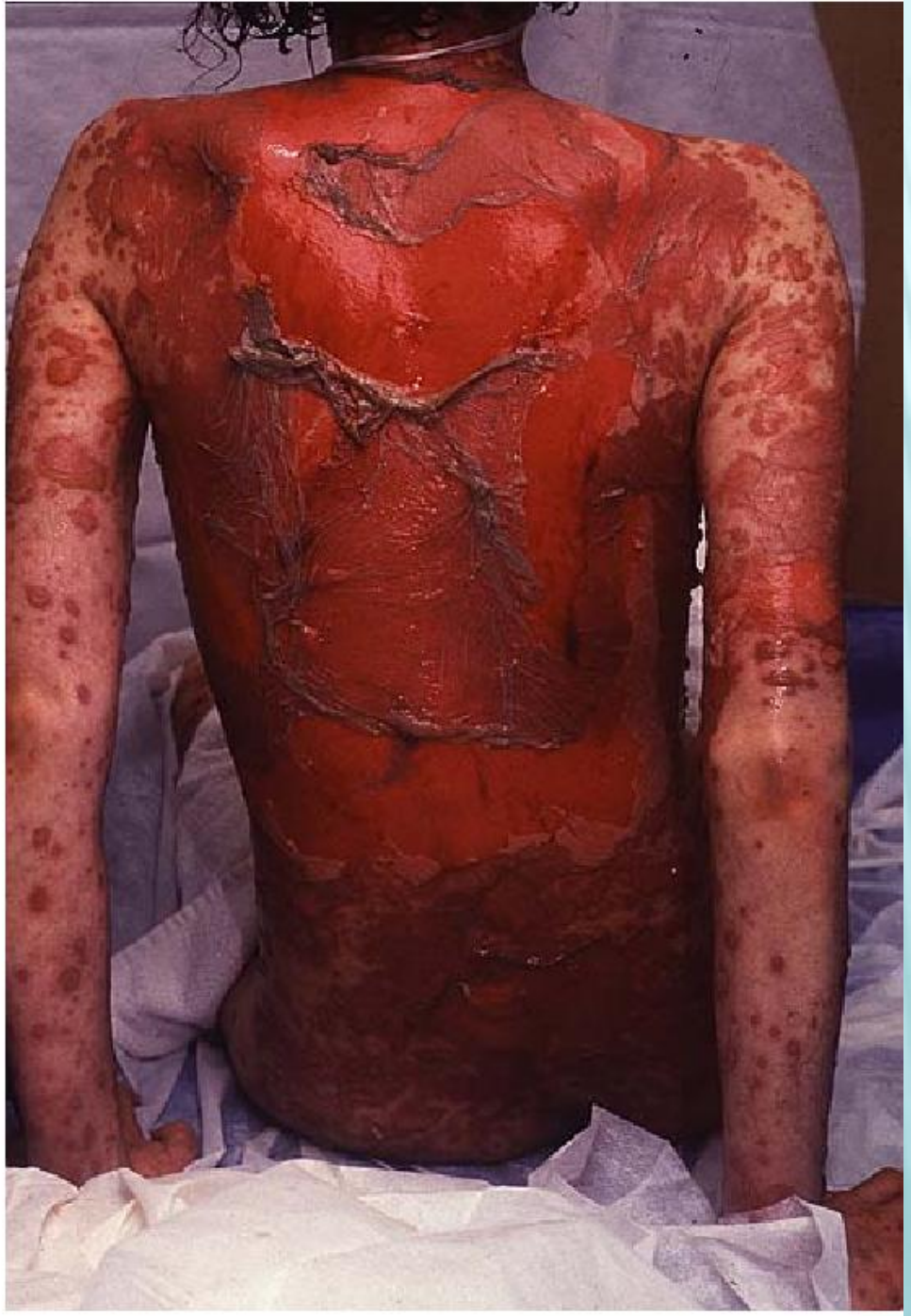


Fig. 1 Epithelial loss in a TEN patient

SERUM SICKNESS

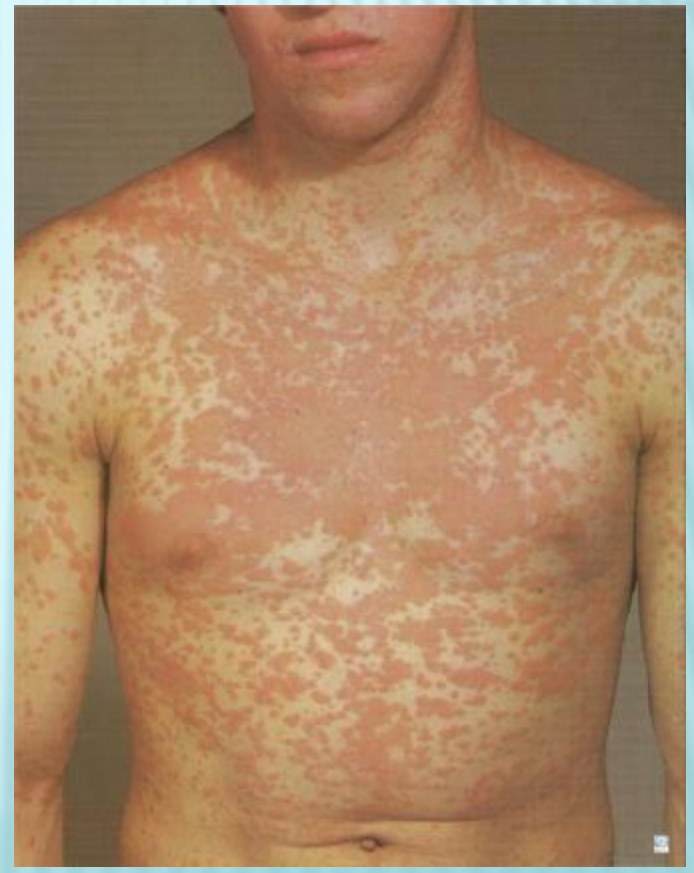
Route	Resulting disease	Site of immune-complex deposition
Intravenous (high dose)	Vasculitis	Blood vessel walls
	Nephritis	Renal glomeruli
	Arthritis	Joint spaces
Subcutaneous	Arthus reaction	Perivascular area
Inhaled	Farmer's lung	Alveolar/capillary interface

DRESS SYNDROME

- Anti convulsions(after 1-2 weeks)
- Fever, maculopapular rash, facial edema, eosinophilia, generalized adenopathy, organ injury(liver, kidney)
- Steroid, supportive care, drug withdrawal

SULFONAMIDES

- Maculopapular rash& fever (after 7-10 days)
- Immediate reactions, anaphylaxis
- Greater frequency in HIV infected
- Desensitization, graded challenge



RED MAN SYNDROME

- caused by the rapid infusion of Vancomycin
- RMS consists of a pruritic erythematous rash to the face, neck, and upper torso which may also involve the extremities to a lesser degree
- Non specific histamine release
- Prophylaxis with slow administration, early H1 blockers

CONCLUSION

As drug allergy can pose risk to patients' health,

Healthcare professions should…

- Be aware of patients' drug allergy history
- Record such information properly
- Double check patients' drug allergy history before drug administration

THANK YOU