

Drug allergy

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Lecture 9

Drug allergy

- Adverse reaction to a drug by a specific immune response either:
 - **Directly to the drug**
 - **One or more of its metabolites alone**
 - **Drug bound to a body protein such as albumin, (Hapten).**
- **No correlation** with known **pharmacological** properties of the drug
- **No linear** relationship with **drug dosage**

Drug allergy

- Drug allergy is an **uncommon and unwanted** side effect of medication.
- Reactions to drugs range:
 - Rasha (mild localized)
 - Angioedema
 - the serum sickness syndrome
 - anaphylaxis and asthma (serious effects on vital systems)
- The body's response can affect many organ systems, but **the skin** is the most frequently involved.

Classifications

- Adverse drug reactions are classified as
 - **A predictable drug reaction:**
 - related to the **pharmacological actions** of the drug.
 - **An unpredictable reaction:**
 - related to **immunological response** (hypersensitivity reactions) or **nonimmunological response**

Features of Allergic drug reactions

- Require an **induction period** on primary exposure
- **Disappear** on stop of therapy
- **Reappear** after re-administration of a small dose
- Occur in **a minority of persons** receiving the drug
- **De-sensitization** may be possible

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 **potent vasoactive and inflammatory mediators**
 - It produces **vasodilatation**, increased capillary permeability, glandular (غدي) hypersecretion and smooth muscle spasm.
- Type II
 - **Cytotoxic reactions** (activation of **killer T cells or macrophages** to produce cytotoxicity)resulting when antibody reacts with antigenic components of a cell or tissue elements or with antigen or hapten that is coupled to a cell or tissue.

The classification of the hypersensitivity

- **Type III (Immune complex (IC) reactions)**

- resulting from deposition of soluble circulating antigen-antibody ICs in vessels or tissue.
- It causes cell migration and release of lysosomal proteolytic enzymes and permeability factors in tissues, **resulting in acute inflammation**

- **Type IV**

- Cell mediated, **delayed hypersensitivity reactions** caused by sensitized T lymphocytes after contact with a specific antigen.

The most common drug to cause allergy

- **Analgesics:**

- Codeine
- Morphine
- NSAIDs, such as ibuprofen or indomethacin
- aspirin

- **Antibiotics** such as penicillin, sulfa drugs, and tetracycline

Risk factors for Drug Allergy

- Frequent exposure
- Large doses
- injection
- Family tendency

Most common allergic reactions

- Rash
- Fever
- Muscle and joint aches
- Lymph node swelling
- Inflammation of the kidney
- Anaphylactic shock

Anaphylactic Reaction

- **Life threatening**
- occur within 4 hours of the first dose of the drug
,or within 1 hour of taking the drug, and many occur within minutes or even seconds.

Complication of Anaphylactic shock

- Skin reaction - RASH, redness/flushing,
- sense of warmth, itching
- Difficulty breathing - Chest tightness, wheezing, throat tightness
- Fainting **أغماء** or loss of consciousness due to shock
- Rapid or irregular heart beat
- Swelling of face, tongue, lips, throat, joints, hands, or feet

The causative antigens causing anaphylaxis

- Blood products
- β -lactam antibiotics
- X-ray contrast agent
- Other drugs

Management

- **Immediate treatment** with adrenaline
 - **Adrenaline** is an antagonist to the effects of the chemical mediators on smooth muscle, blood vessels and other tissues.
- **For mild reactions** (e.g. angiodema, mild wheezing, nausea and vomiting)
 - 0.3-0.5 ml adrenaline 1:1000 should be given
 - After symptoms resolve, an oral antihistamine should be given for 24 hr.

Management

- For more severe reactions (massive angioedema but without evidence of cardiovascular involvement)
 - Diphenhydramine 50-100 mg IV
 - 0.005mL/kg of an aqueous suspension of long acting adrenaline 1:200 can be given for its 6-8hr effect
 - Oral antihistamine should be given for the next 24hr

Management

- For asthmatic reactions that do not respond to adrenaline
 - IV fluids should be started
 - Theophylline 5mg/kg IV can be given over 10-30 min
 - Endotracheal intubations or tracheotomy with oxygen administration if necessary
- Hypotension (caused mainly by hypovolemia):
 - fluid replacement/ vasopressor drugs e.g. dopamine, noradrenaline if necessary

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.



- Signs and symptoms

- Pruritus حكة (generally the first symptom)
- Crops of rash

- Treatment for acute urticaria

- Symptoms subside in 1 to 7 days, treatment is chiefly palliative ملطف.
- All nonessential drugs should be stopped until the reaction has subsided.
- Symptoms can be relieved by oral antihistamine and glucocorticoid.

Management for Chronic Urticaria

- Certain drugs e.g. aspirin may increase symptoms and should be avoided.
- Oral antihistamines
- H2 blockers

Angioedema



- Diffuse and painful swelling of:
 - loose subcutaneous tissue of hands or feet eyelids, lips and mucous membranes.
- Edema of the upper airways may produce respiratory distress

Management for Angioedema

- **Glucocorticoid** (e.g. prednisone 30-40mg/day)
- **Adrenaline** 1:1000, 0.3ml
- **IV antihistamine** (e.g. diphenhydramine 50-100mg) to prevent airway obstruction
- **Intubations or tracheotomy** and oxygen administration may be necessary

Penicillin Allergy

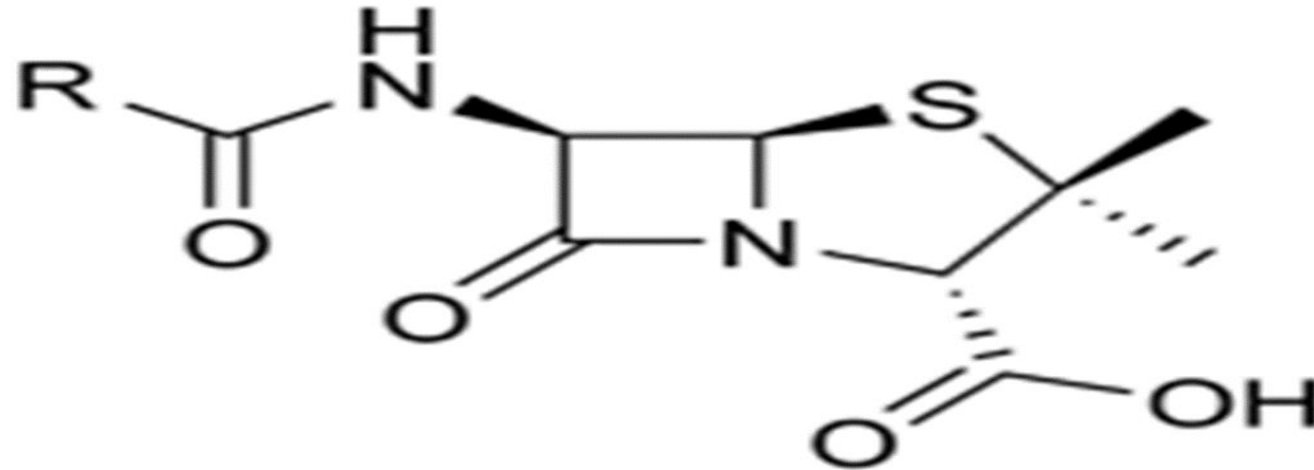
- Symptoms
 - Fever
 - Rash
 - Urticaria
 - Angioedema
 - Nephritis
 - Lymphadenopathy

Mechanism of Penicillin Allergy

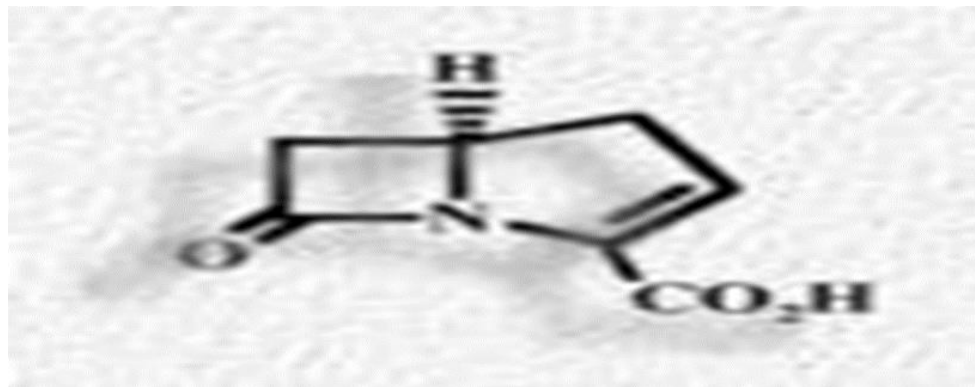
- The drug, or one of its metabolites must be chemically reactive with protein can act as haptens and **bond covalently to proteins.**
- The breakdown products can bond to **ϵ -amino groups of lysine residues, most importantly globulins.**
- This binding leads to a spectrum of potentially immunologically active moieties on serum proteins that can **cross-link with a variety of preformed anti-penicillin IgE bond to mast cells**

Cross-reactivity

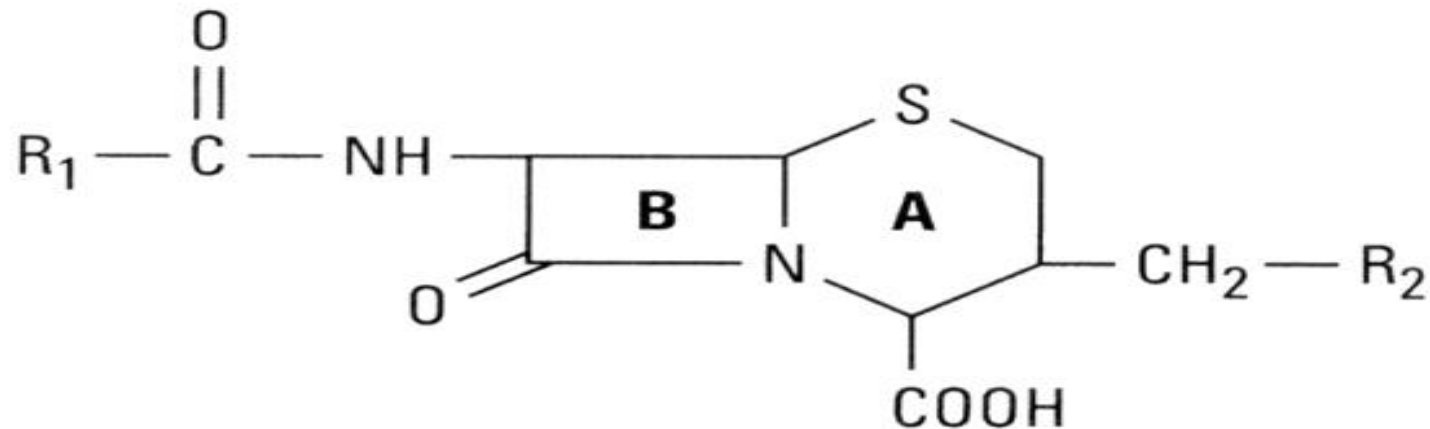
- The most important part of **penicillin antigen** appears to be the core structure
- The structure of the penicillin is a **β -lactam ring with the five-membered thiazolidine ring**



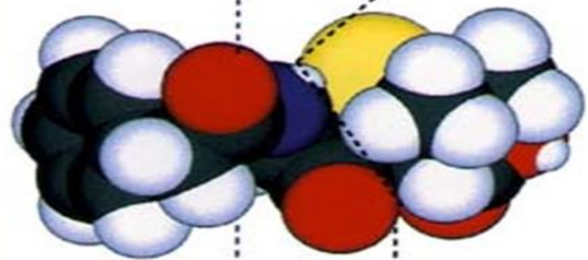
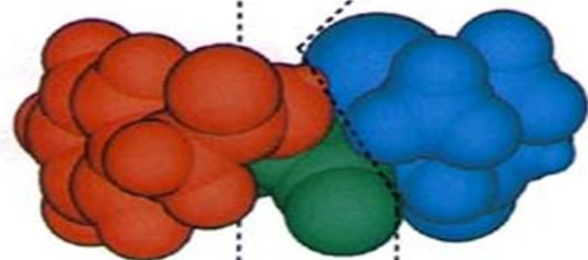
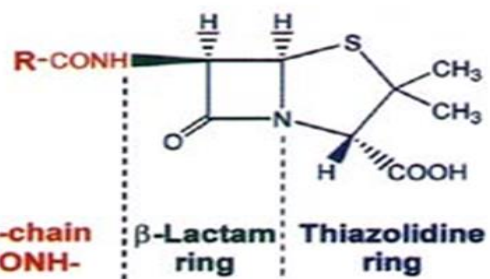
- **Carbapenems** have a bicyclic nucleus containing β -lactam ring and an adjacent five-membered ring.
- It showed **50% cross-reactivity in allergy skin testing between penicillin and the analogous Carbapenems reagents.**
- Patients especially with positive penicillin skin test should withhold carbapenems



- 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%**)

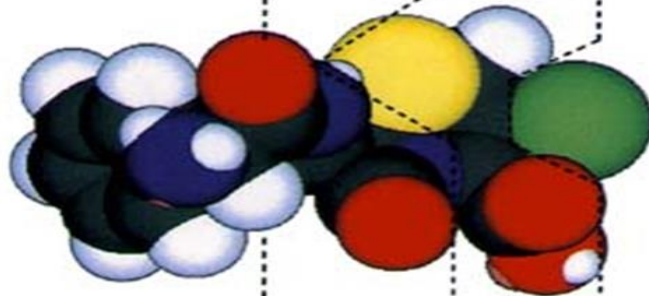
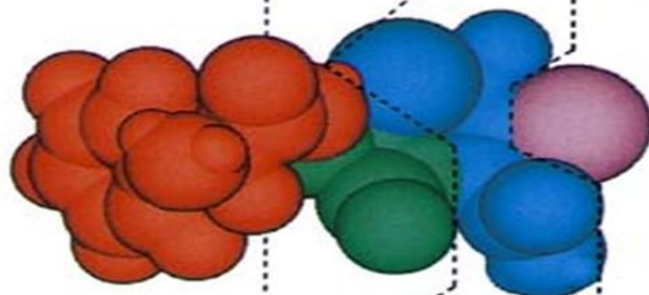
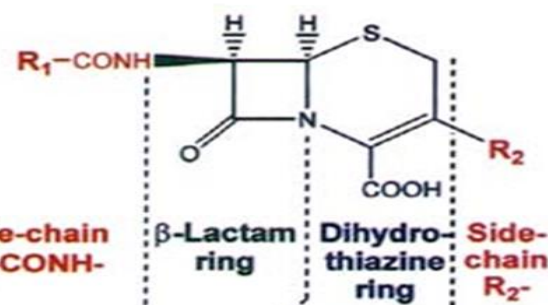


PENICILLINS



e.g. Benzylpenicillin

CEPHALOSPORINS



e.g. Cefaclor

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
- A BPO-polylysine conjugate and penicillin G in a concentration of 1000U/ml are available for skin testing
- performed by prick technique-a drop of a dilute allergenic extract

- If the patient has a history of a severe reaction, the reagents should be diluted **100-fold** for initial testing.
- Intradermal test
 - 0.5 or 1 ml dilute is injected
 - Each set of skin tests should include the diluents alone as a negative control and histamine as a positive control.
- 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.

Caution with the skin test

- **Antihistamines, tricyclic antidepressants and adrenergic drugs** can **inhibit** skin test results and should be discontinued before the testing procedure.
- **Patients using β -adrenergic blocking drugs or angiotensin-converting enzyme inhibitors** at the same time of skin testing **may not respond** to emergency treatment with adrenaline if a systemic reaction occurs.

Aspirin and NSAIDs allergy

- Signs and symptoms
 - Respiratory tract symptoms (bronchospasm)
 - urticaria/angioedema
 - GIT (nausea, vomiting, diarrhea)

How do NSAIDs cause allergy?

- NSAIDs inhibit the enzyme cyclo-oxygenase 1 (COX-1), which produces prostaglandins such as PGE2
- PGE2 are necessary to **protect against** excessive leukotriene release in susceptible individuals.
- The release of **leukotriene** from the affected target organs cause the clinical symptoms

Allergic reactions to vaccines

- Sensitivity reactions can occur when **egg-allergic patients** are vaccinated with vaccines containing egg protein.
- These vaccines include yellow fever, influenza and rubella
- Severe anaphylactic reactions to influenza vaccination have been reported to occur at a rate of 0.024 per 100,000 vaccinations
- Egg-sensitive individuals should not receive such vaccinations unless the need is great.
- Influenza vaccines can be contraindicated to patients who are allergic to the preservatives of the vaccine, e.g. neomycin

Latex allergy

- Latex is derived from natural rubber, composed of various polymers of isoprene.
- latex-allergic reactions could be mistakenly interpreted as medication allergies or allergic reactions to general anesthesia.
- Such reaction is IgE mediated
- Signs and symptoms
 - Urticaria
 - Flushing
 - Angioedema
 - Asthma (inhalation of the powder absorbed with latex protein allergens)
 - anaphylaxis

How to Distinguish Drug Allergy and Drug Toxicity

- Reduction in fever within 48h withdrawal of drug strongly suggests that suspected drug causing allergy.
- If fever is accompanied by Granulocytopenia, drug toxicity is more likely than allergy and is much more serious.