

Drug Allergy



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Definition

Allergic reaction to drugs get into the classification of intersection of drug (adverse drug reaction), which includes toxicity, side effects, idiosyncrasy, intolerance and medications allergy. Drug allergy is an abnormal response to the medicine or metabolites through immunological reactions are known as hypersensitivity reaction that occurs during or after use of the drug.

- Drug toxicity is associated with medicinal effects of a drug overdose.
- Drug side effects are the main effects of the drug in addition to properties that arise due to the pharmacological properties of the drug or interactions with other drugs.
- Idiosyncratic drug reactions arise is not related to the pharmacological properties of the drug, the proportion varies among populations with unknown causes.
- Intolerance is not a reaction to the drug because of the pharmacological properties, arising from non-immunological processes.

Pathophysiology

Type of drug allergens varies. In general, most common cause of drug allergy is penicillin group, sulfa, salicylates, and Pirazolon. Other drugs that mefenamic acid, luminal, phenothiazines, fenergan, dilantin, Tridion. However, the most common allergen is penicillin and sulfa.

Drug Allergy is usually not the case in the first exposure. Immunologic sensitization requires early exposure and a long grace period (latency period). Allergenicity of the drug depends on the molecular weight. Drugs with small molecular weight can not directly stimulate the immune system when it is not joined with other materials to be as allergen, called as hapten. Hapten can form covalent bonds with the protein network, is stable, and this bond will remain intact during processing in macrophages and presented at lymphocytes.

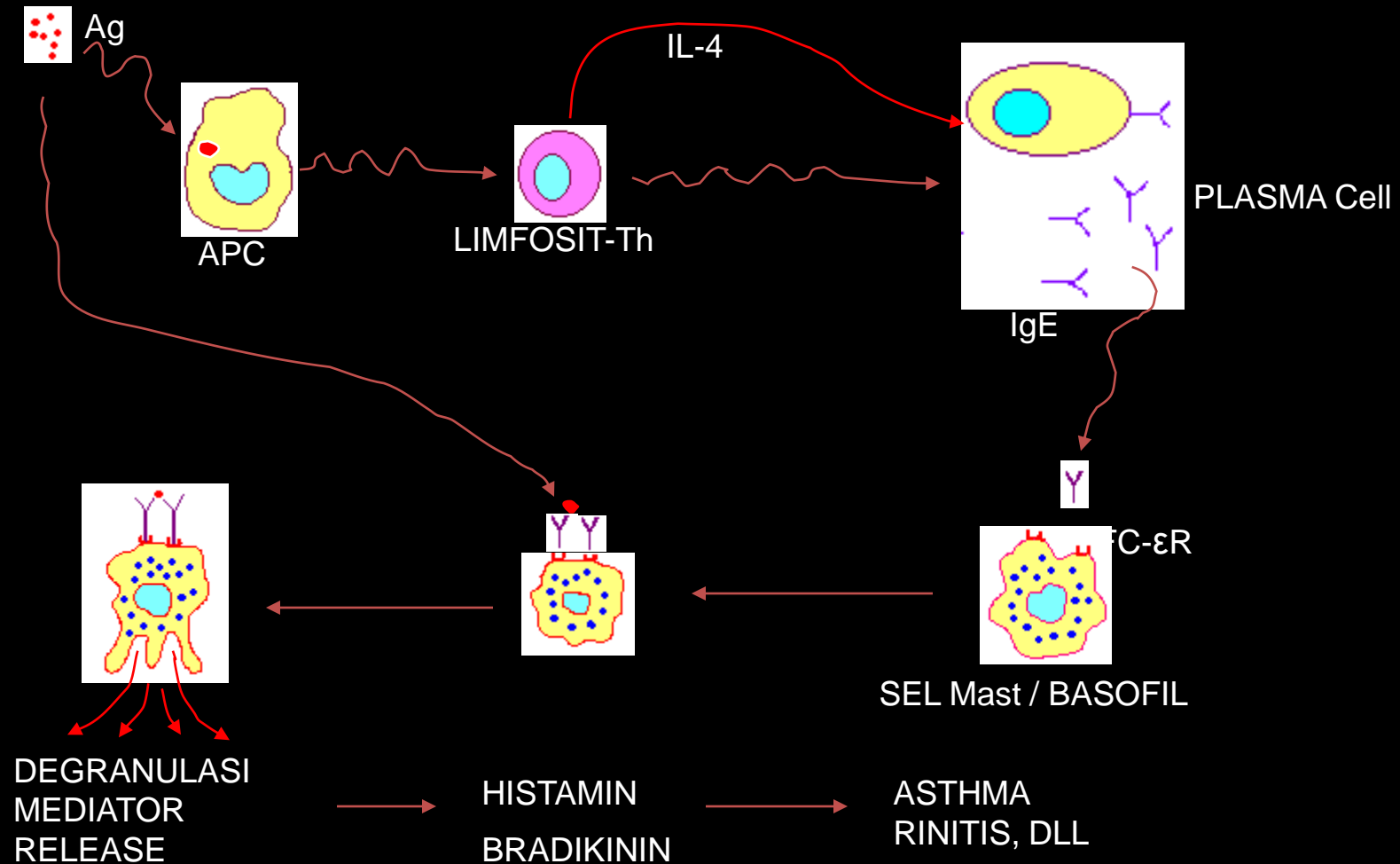
Fraction has a large molecular weight drugs such as insulin, antisera, is highly immunogenic organ extract can directly stimulate the body's immune system. There is a low molecular weight drugs are immunogenic without joining with other proteins. Mechanism is not clear, but it is thought the drug form long polymer chains. After the initial exposure to the drug stimulates production of antibodies and immune cell activation in the induction period (latent) which may take 10-20 days.

Drug allergies can occur through all four mechanisms of hypersensitivity Gell and Coomb.

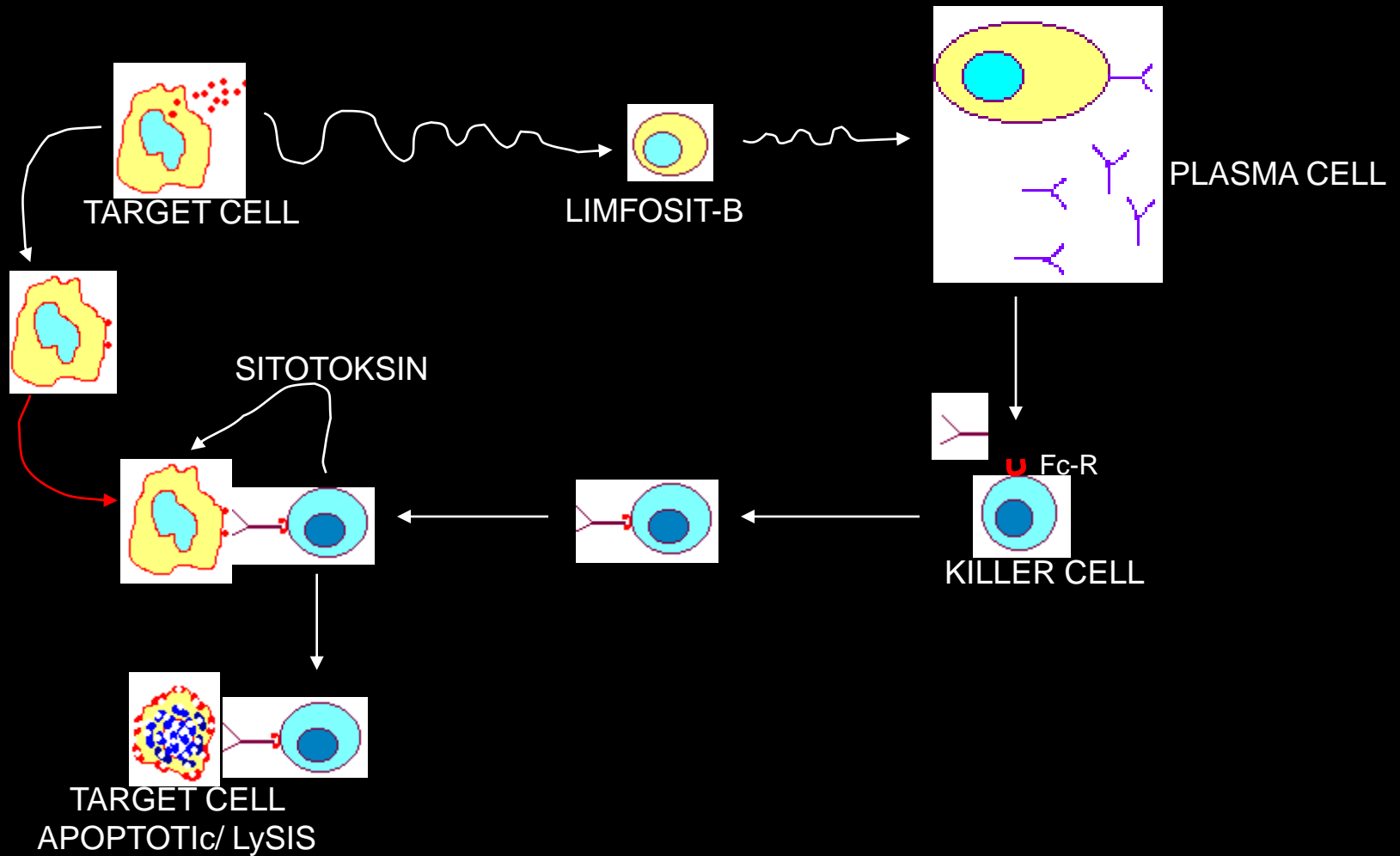
- ❖ If specific antibodies are formed IgE in patients with atopic then there is the reaction type I.
- ❖ If antibodies are formed IgG and/ or IgM, complement activation or ADCC followed then there is the reaction type II.
- ❖ Occurs when the immune complex then there is the reaction type III.
- ❖ When the cellular immune response arises then there is the reaction type IV.

Drug allergies can occur through the mechanism fourth to one drug, but the most common by type I and IV.

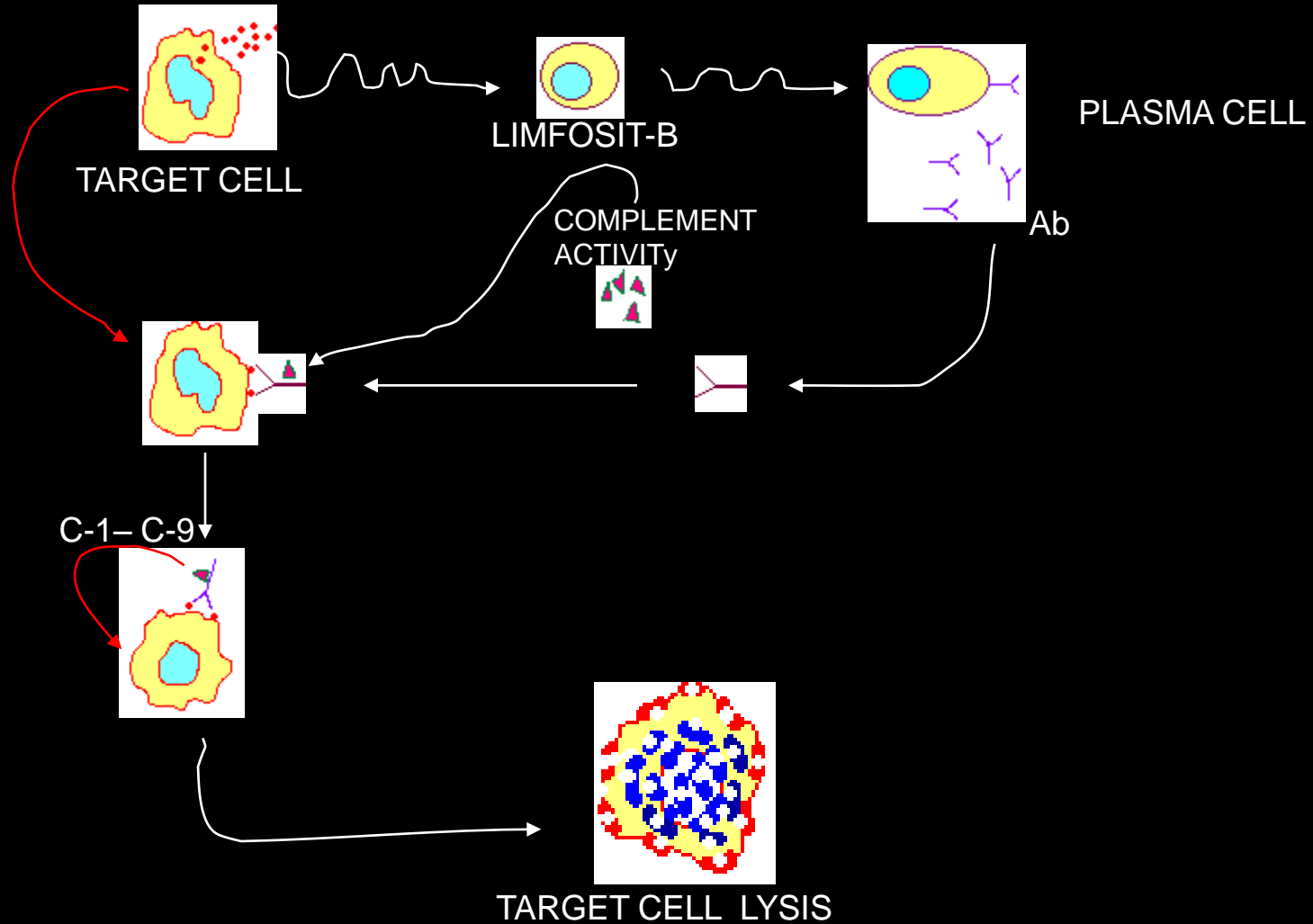
❖ HYPERSENSITIVITY TYPE-I (ALLERGY)



❖HYPERSENSITIVITY Type II through ANTIBODY DEPENDENT CELL CYTOTOXICITY



❖HYPERSENSITIVITY Type II through Complement activity



Symptoms

One drug can cause a variety of symptoms in a person, can be different from other people, the symptoms can be mild to severe. Skin eruptions are the most frequent clinical symptoms, can include itching, Urticaria, larynx edema, purpura, contact dermatitis, erythema multiforme, erythema nodosum, fixed drug eruption, serum sickness-like syndrome, photosensitivity reactions, exfoliative dermatitis, vesicobullous eruptions and Steven Johnson syndrome.

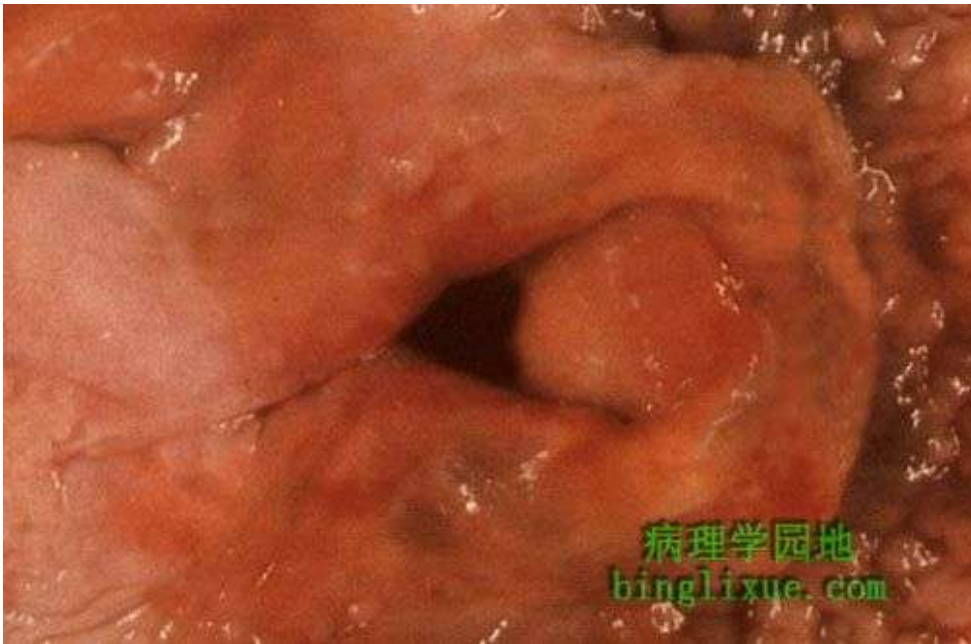
Epidermolysis bullosa



Vesico bullous Eruption



Larynx edema



Urticaria & Quinke's edema



Erythema nodosum



Purpura



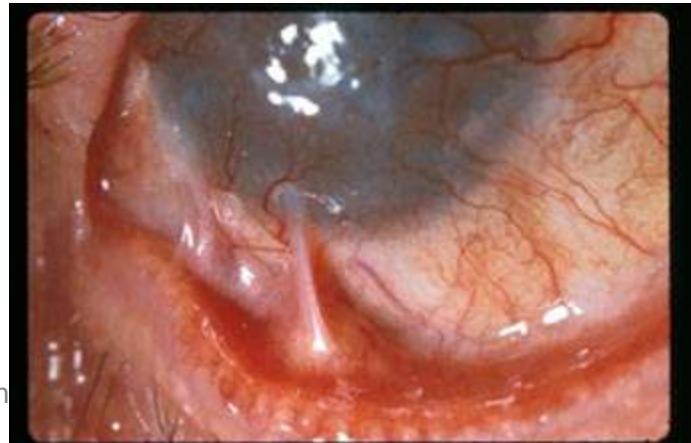
Contact Dermatitis



Erythema Exudativum Multiforme



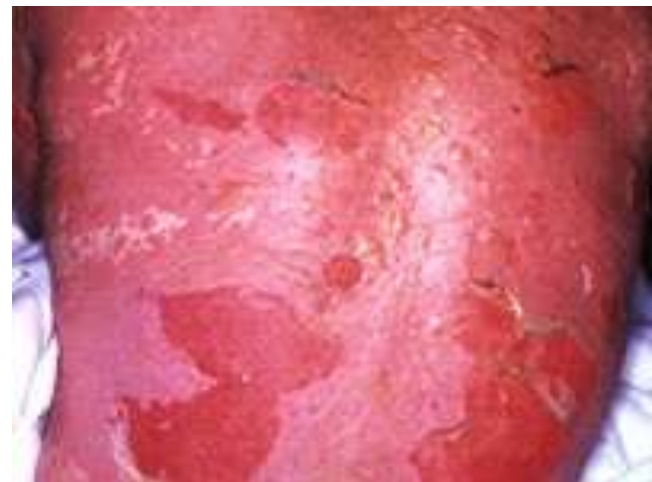
Steven Johnson Syndrome



Steven Johnson Syndrome.....



Toxic Epidermal Necrolysis



Patient with drug-induced
toxic epidermal necrolysis



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Fixed Drug Eruption



Dermatitis Exfoliativa



Morbiliform rash



Vasculitis



Acneiform eruption



Figure 2. Pustular acne lesion on back.



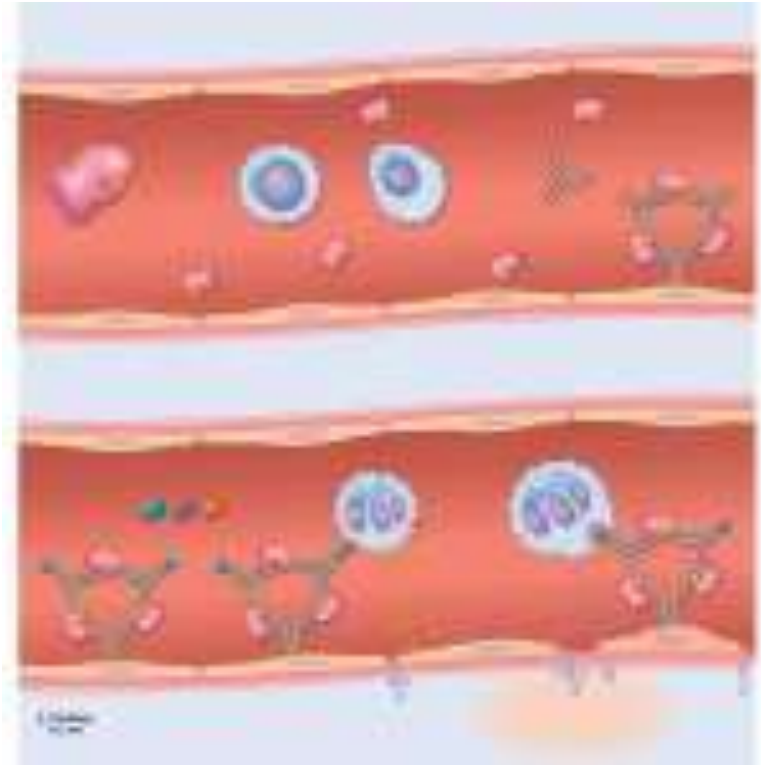
Figure 3. Closed comedonal acne with acne excoriee.

Maculo papular eruption



The diagrams illustrate the stages of a cell cycle:

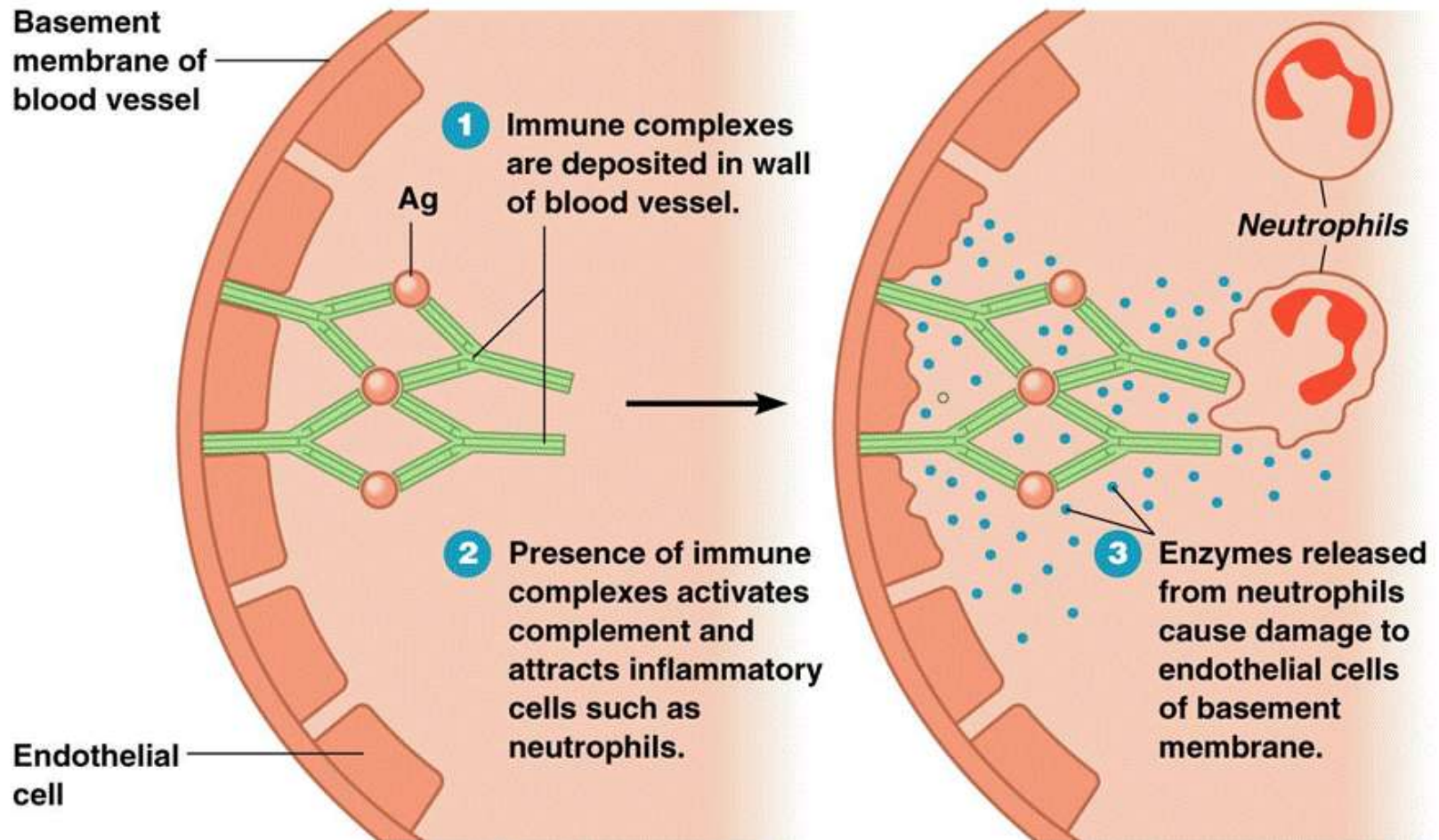
- Prophase:** The nucleus is visible, and the DNA is condensing. The spindle fibers are beginning to form.
- Metaphase:** The chromosomes are aligned at the metaphase plate (equator) of the cell.
- Anaphase:** The sister chromatids are separating and moving toward opposite poles of the cell.



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HYPERSENSITIVITY TYPE 3

the basic pathology of Serum Sickness



Symptoms

- The usual symptoms are severe skin reactions, often on the palms of the hands and soles of the feet. **Fever**, sometimes as high as 104o F, is always present and usually appears before the **skin rash**.
- Joint **pain** may be reported in up to 50% of cases. This is usually seen in the larger joints, but occasionally the finger and toe joints may also be involved.
- Swelling of lymph nodes, particularly around the site of the injection, is seen in 10-20% of cases. There may also be swelling of the head and neck.
- Urine analysis may show traces of blood and protein in the urine.
- Other symptoms may involve the heart and central nervous system. These may include changes in vision, and difficulty in movement. Breathing difficulty may occur.



Clinical symptoms that require immediate relief is appropriate and anaphylactic reactions, due to hypotension, bronchospasm, swollen larynx, angioedema or generalized urticaria. Fever can be a symptom of allergy medications or with a single other symptoms that occur several hours after administration of the drug, but usually in 7-10 days and disappeared within 48 hours after discontinuation of the drug or a few days later, waiting for drug excretion from the body.

Fever caused by the release of cytokines. Some drugs can be as direct pyrogen e.g. amphotericine B, cimetidine, dextran, calcium and iron dimercaprol.

Mechanism is not clear on the child, epinephrine can cause a fever because it is vasoconstrictor, thereby inhibiting the body heat expenditure. Similarly, administration of phenothiazines, atropine can cause fever by inhibiting the formation of sweat. Some medications such as allopurinol, azathioprine, barbiturates, blood products, cephalosporins, hydroxyurea, iodide, methyldopa, penicillamine, penicillin, phenytoin, procainamide and quinidine often cause fever without other symptoms of allergies.

Tabel 1. Classification of drug allergy

Renal disorder	Interstitial Nephritis, glomerulonephritis, nephrotic syndrome
Skin Eruption	Urtikaria/angiodema, pruritus , maculopapular rash, fixed drug eruption, contact dermatitis, vasculitis, erythema nodosum, erythema multiforme, Steven Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, photosensitive reaction.
Pulmonary disorder	Pneumonitis interstitialis/alveolaris, pulmonary edema /fibrosis, bronchospasm.
Hematologic disorder	Anaemia hemolytic, neutropenia, thrombocytopenia
Cardiovascular	Anaphylaxis, laryngeal edema, hypotension
Serum sickness Drug fever Systemic Vasculitis Lymphadenopathy	

Diagnosis

Diagnosis of drug allergy is often difficult to prove even if allegations are strong. The most important basic medicine diagnosis is a detailed history about the important things. Generally clinical symptoms are not typical, but some forms of skin eruptions such as generalized pruritus, urticaria, eruption fikstum, or anaphylactic reactions that meet the criteria above history. Several investigations can be done for completeness diagnosis, a test in vivo and in vitro are for drug or its metabolites. In Vivo test: a skin test and provocation test. Limited in vitro assays as a means of research and is not a routine procedure.

The greatest difficulty in making a diagnosis is to determine whether there was a relationship between the clinical manifestations of drug delivery and whether clinical symptoms are not part of his own history of the disease being treated. Diagnosis is based on clinical and drug allergy laboratory tests. Clinically the most important is a detailed anamnesis about important issues that arises that the reaction is not a pharmacological effect of the drug, usually occurs a few days after drug administration (unless they have been exposed to before).

Clinical symptoms will disappear some time after switching terganung drug clearance from the body, and the same phenomenon will occur with repeated administration of the same drug or drugs with similar structures (Table 2). Physical description, especially the skin eruption is no specific pattern for each picture each drug (Table 3).

Clinical Criteria for drug allergy

1. The observed manifestation do not resemble the pharmacological action of the drug
2. The reaction are generally similar to those which may, occur with other Antigen.
3. An induction period commonly 7-10 days is required following initial exposure to the drug
4. The reaction may be reproduced by cross reacting chemical structures.
5. The reaction may be reproduced by minute dose of the drug.
6. Blood and/or tissue eosinophilia may be present.
7. Discontinuation of the drug result in resolution of the reaction.
8. The reaction occurs in a minority of patients receiving the drug.

Clinical pattern of Drug Allergy

Exanthems:

Ampicillin, penicillin

Phenilbutazone

Sulphonamides

Phenitoin

Carbamazepine

Gold

Allopurinol

Lichenoid eruptions :

Anti maalarials

Beta blockers

Chlorpropamide

Gold

Methyl dopa

Penicillamine

Phenylbutazone

Sterptomycin.

Erythema multiforme and Steven Johnson Syndrome:

Trimetrprim, Smx

Penicillin

Griseofulvin

Tetracyclines

NSAIDs

Gold

Anticonvulsant

Toxic epidermal necrolysis

Allopurinol

Aspirin

Penicillin

Phenytoin

Sulfasalazine

Acneform eruptions :

Corticosteroids

Anabolic steroids

Androgens (in female)

Oral contraceptives

Iodides and bromides

Lithium

Isoniazid

Laboratory Examination

1. In vivo examination.

Proper skin test is done using materials that are immunogenic antigen that is the determinant of the drug or its metabolites. Skin test materials must be non-irritating to avoid false positives. This test is very limited due to the benefits of new antigenic determinants few drugs that have been known and available for skin testing. With the skin test can only be identified allergic to macro molecules: insulin, antisera, organ extracts, were to mikromolekul identified so far can only be allergic to penicillin.

Provocation test can confirm the diagnosis of drug allergy, but it is a diagnostic procedure that is limited because of the risk of anaphylaxis so dangerous that the only recommended to be done in place that has facilities and adequate manpower. Hence the counter-provocation test is an indication for severe drug allergies such as anaphylaxis, Steven Johnson syndrome, exfoliative dermatitis, hematologic abnormalities, vesico bullous erythema. Provocation test is done after a long elimination half-life depends on each drug.

In vitro examination

In Vitro tests for drug allergy is more commonly used in research. Examination undertaken include IgG and IgM specific agglutination test and lysis of red blood cells, RAST, histamine release assays, test sensitization network (basophils / leukocytes and cytokines essays and cell receptors), whereas routine screening such as total IgE and specific, Coombs' test, and complement not to confirm drug allergy.

Management

The main basis of the management of drug allergy is suspected of drug discontinuation and then address the clinical symptoms arise.

- Discontinuation of the drug.
- If perhaps all of the drug stopped, except for drugs that are unnecessary and not suspected as the cause of allergic reactions or replace with other drugs. When the drug is considered to be very important and can not be replaced, can continue to be provided with the approval of the family, and by way of desensitization.

Treatment

- Mild clinical manifestations generally do not require special treatment. For pruritus, urticaria or edema angioneurotic, antihistamines can be given, for example, diphenhydramin, loratadine or cetirizine and if abnormalities are given ample adrenaline anyway.
- When very severe clinical symptoms such as exfoliative dermatitis, toxic epidermal necrosis, Steven Johnson syndrome, vasculitis, pulmonary disorders, hematologic disorders should be given supportive treatment with corticosteroids and maintain fluid and electrolyte needs, transfusion, antibiotic prophylaxis, and treatment of skin as in burns to abnormalities exfoliative dermatitis, toxic epidermal necrosis and Steven Johnson syndrome.

Local treatment done immediately to prevent adhesions, scar or contracture. Anaphylactic reaction should receive treatment as soon as possible adequately. Topical corticosteroids are given for skin eruptions on the basis of the type IV reaction with respect to the rules that have been determined.

The selection and preparation of drugs depends on the extent of the lesion and place. The general principle is: start with a low potency corticosteroid. Cream has the advantage of more easily smeared, good for wet lesions but less protective skin to lose moisture. Ointment better protect the skin loses moisture, but often cause itching and folliculitis. Spray dosage used in the head and other hairy areas. In general, topical steroids given after a shower, not given more than 2 times a day. Should not be used for medium to high potential areas such thin skin face, neck, armpits and diaper area.

Prognosis

With good management, the prognosis is good even allergy medication for severe drug allergies though. Skin adhesions can occur, contractures, simblefaron, blindness if action is not appropriate and too late. 1 reported death rate of 10,000 events, the Steven Johnson syndrome mortality by 5-15%.



Thank you