# DRUG ALLERGY

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# DRUG ALLERGY

- Type-B ADR caused by drug involves immunological mechanism,

| Type-B ADR | Type-A ADR |
| --- | --- |
| - patient`s abnormality, | - related to pharmacological effect |
| - unpredictable, | - predictable, |
| - dose independent, | - dose dependent, |
| - low morbidity, | - high morbidity, |
| - high mortality. | - low mprtality. |

# TYPE – A ADR

## Primary pharmacology

- Augmentation of known action

- $\beta$-blockers induced bardycardia
  prazosin induces hypotension

## Secondary pharmacology

- Often involves different organ system but rationalizable from the known pharmacology

- $\beta$-blockers induced bronchospasm, $\alpha_1$-blockers induces tachycardia, NSAIDs induced bronchospasm,

# TYPE – B ADR → mechanism

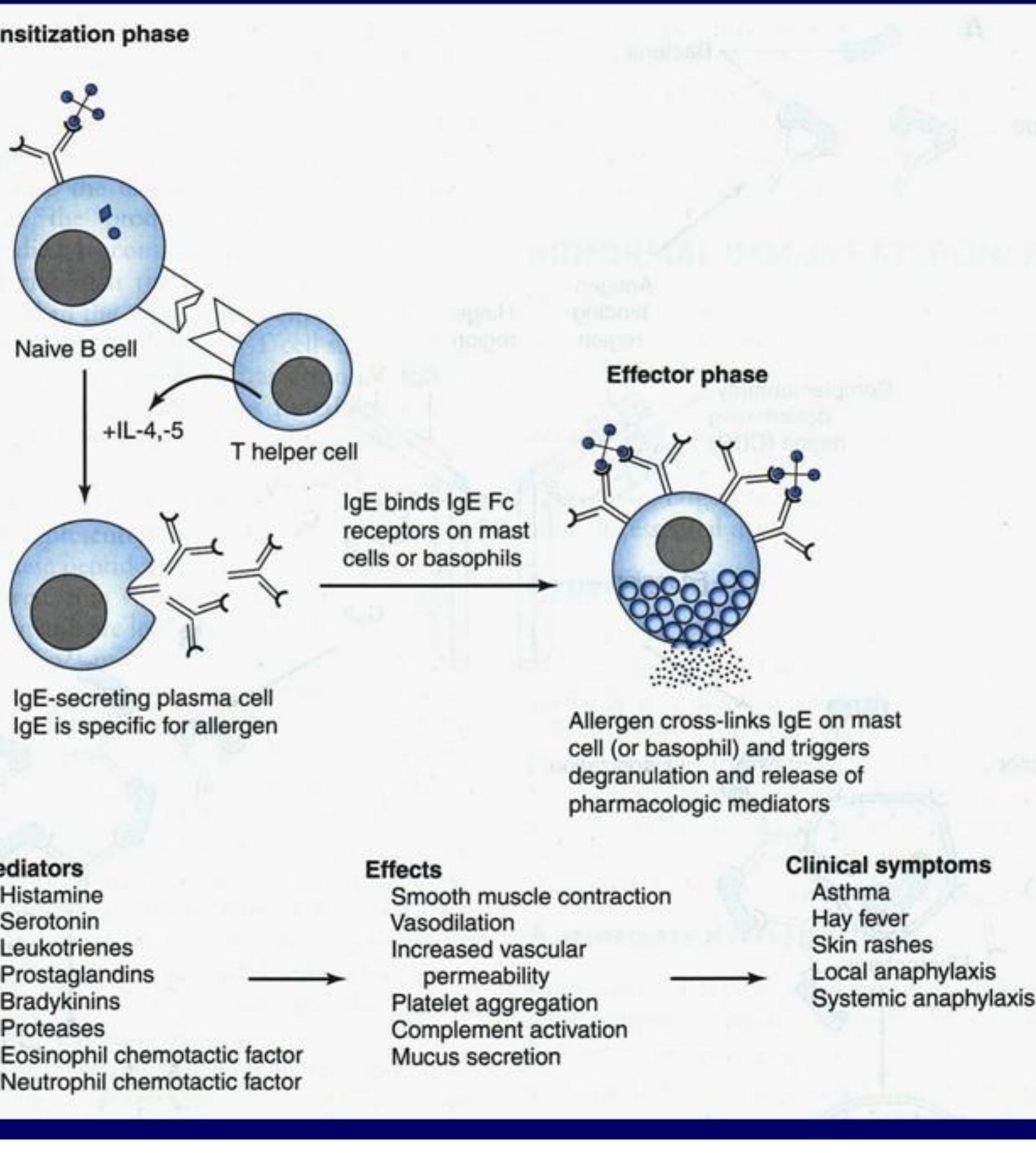
| Mechanism | Example |
|---|---|
| - Pharmaceutical variation | - eosinphilia-myalgia syndrome with L-tryptophan |
| - Receptor abnormality | - malignant hyperthermia with general aesthetics |
| - Abnormal biological system unmasked by drug | - primaquine induced haemolysis with G6PD deficiency |
| - Abnormal drug metabolism | - INH induced neuropathy in slow acetylators |
| ➢ **Immunological involvement** | - **penicillin induced anaphylactic shock.** |
| - Drug-drug interaction | - INH induced hepatitis in concomitan administration of rifampin, |
| - Multifactorial | - halothane hepatitis |

# TYPE – B ADR → organ system

| Organ system | Type of reaction | Drug example |
|---|---|---|
| - Generalized reaction | - Anaphylaxis<br>- Hypersensitivity | - Penicillins<br>- Temafloxacin |
| - Skin | - TEN<br>- SJS | - NSAIDs<br>- Sulfonamude |
| - Liver | - Hepatitis | - Halothane |
| - Haematological system | - Aplastic anemia<br>- Agranulocytosis<br>- Maemolysis | - Remoxipride<br>- Clozapine<br>- Nomifensine |
| - Central nervous system | - Guillain-Barre syndrome | - Zimeldine |
| - Kidney | - Interstitial nephritis | - penicillins |
| - Lung | - Pneuminitis | - Dapsone |
| - Heart | - Cardiomyopathy | - Tacrolimus |

# DRUG ALLERGY

- Lack of correlation with known pharmacological effects,
- Lack of linear relation with the dose,
  (very small dose may cause very severe effect)
- Rash, angioedema, serum sickness syndrome, asthama or anaphylactic shock – allergic reaction.
- There is induction period on primary exposure but not an re-exposure,
- Disappearance on cessation of administration and reappearance on re-exposure to the drug,
- Occures in a minority of patient receiving the drug (low morbidity),
- Possible response to desensitisation.


Sensitization phase
Naive B cell
+IL-4,-5
T helper cell
IgE-secreting plasma cell
IgE is specific for allergen
IgE binds IgE Fc receptors on mast cells or basophils
Effector phase
Allergen cross-links IgE on mast cell (or basophil) and triggers degranulation and release of pharmacologic mediators
Mediators
Histamine
Serotonin
Leukotrienes
Prostaglandins
Bradykinins
Proteases
Eosinophil chemotactic factor
Neutrophil chemotactic factor
Effects
Smooth muscle contraction
Vasodilation
Increased vascular permeability
Platelet aggregation
Complement activation
Mucus secretion
Clinical symptoms
Asthma
Hay fever
Skin rashes
Local anaphylaxis
Systemic anaphylaxis

# TYPE – I DRUG ALLERGY

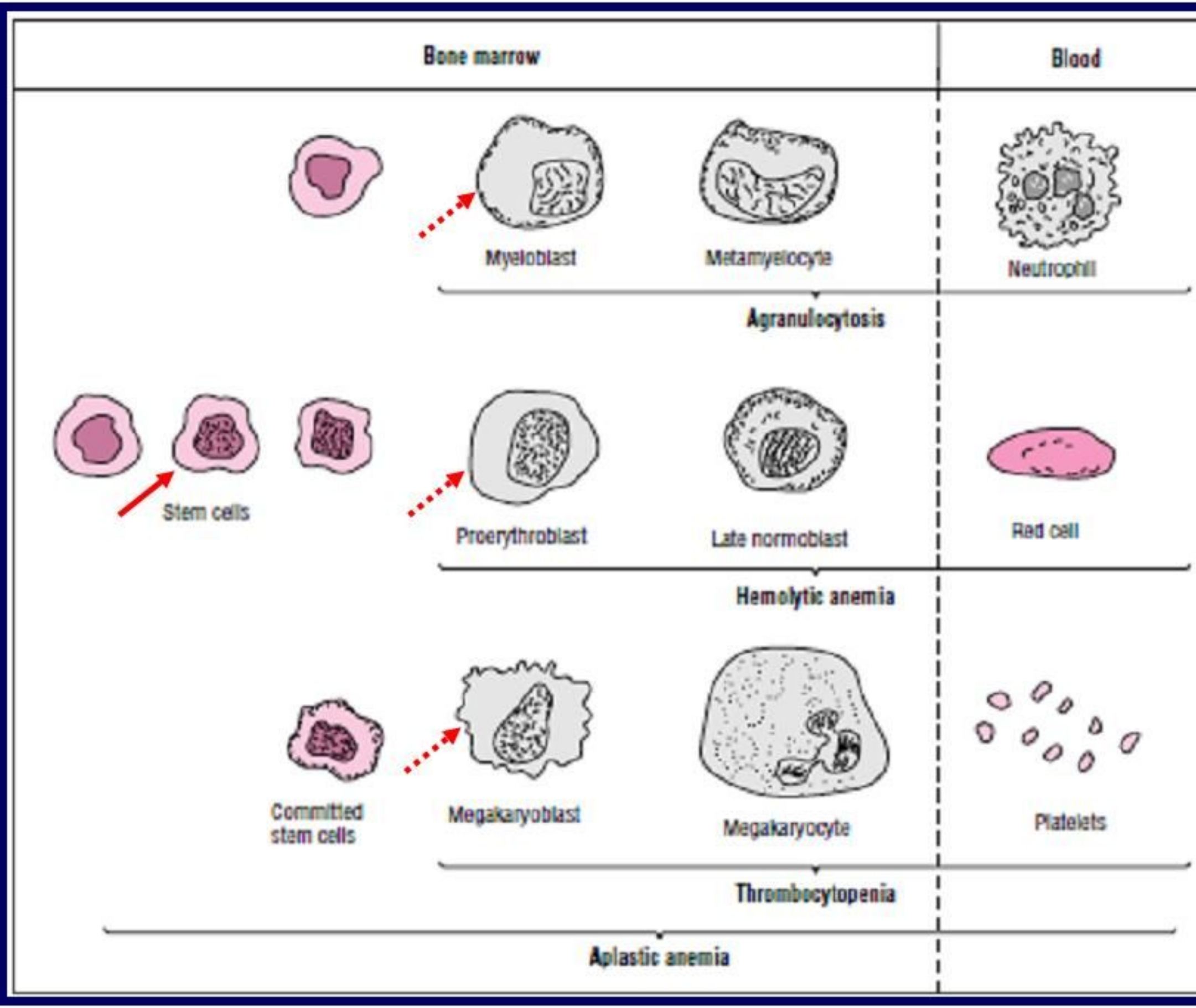
- Immediately → occurs in minutes and last in 1 – 2 hours,
- IgE mediated in response to a drug hapten conjugated to protein,
- IgE and antigen interaction cause mast and basophylic cells release histamine and other chemical mediators (PGs, LTs and PAF)
- Severe anaphylactic reaction (shock) occur in 1 among 200 patients,
- Atopic patients are at increased risk,
- Urticaria, pruritus, bronchospasm, hypotension, shock,
- Penicillins and cephalosporins.

# TYPE – II DRUG ALLERGY

- Antibody dependent cytotoxic type,
- IgG and IgM mediated,
- Reaction of drug as hapten and IgG or IgM activates complement → cells damage → ,
- Hemolytic anemia (methyldopa, penicillins, quinidine), aplastic anemia (sulfonamide – OAD, allopurinol), thrombocytopenia (rifampin, quinidine, thiazides) or neutropenia (clozapine, carbamazepine, sulfonamide – OAD etc.),
- Occurs in days, weeks or years after exposure,

# Drug induced aplastic anemia

- Immune or non-immunologic ADR,
- Most serious drug induced blood dyscrasia,
- Mortality rate > 50%,
- Aplastic anemia established if there are 2 signs of WBC < 3.500 / $mm^3$, thrombocytes < 55.000 / $mm^3$, Hb < 10 g%, reticulocytes < 30.000 / $mm^3$,
- Severe aplastic anemia established if there are 2 signs of : neutrophyl < 500 / $mm^3$, thrombocytes < 20.000 / $mm^3$, anemia corrected index < 1%,
- Onset vary but often 6 – 7 weeks after drug exposure
- Clinical symptoms palor, malaise, fever, chilling, pharyngitis sore throat, petechiae, bruisability and bleeding.


Bone marrow
Blood
Myeloblast
Metamyelocyte
Neutrophil
Agranulocytosis
Stem cells
Proerythroblast
Late normoblast
Red cell
Hemolytic anemia
Committed stem cells
Megakaryoblast
Megakaryocyte
Platelets
Thrombocytopenia
Aplastic anemia

# TYPE – III DRUG ALLERGY

- IgM or IgG mediated,
- Immune complexes activate complement system and cells, → cause release chemical mediators,
- Serum sickness, fever, rash, urticaria, arthralgia, vasculitis, lymphadenopathy, proteinuria,
- Occurs 1 – 3 weeks after drug exposure,
- Heterologous serum, monoclonal antibody etc.

# TYPE – III DRUG ALLERGY

IgM or IgG mediated,

↓

activate complement system, platelets,
macrophage and neutrophils.

↓

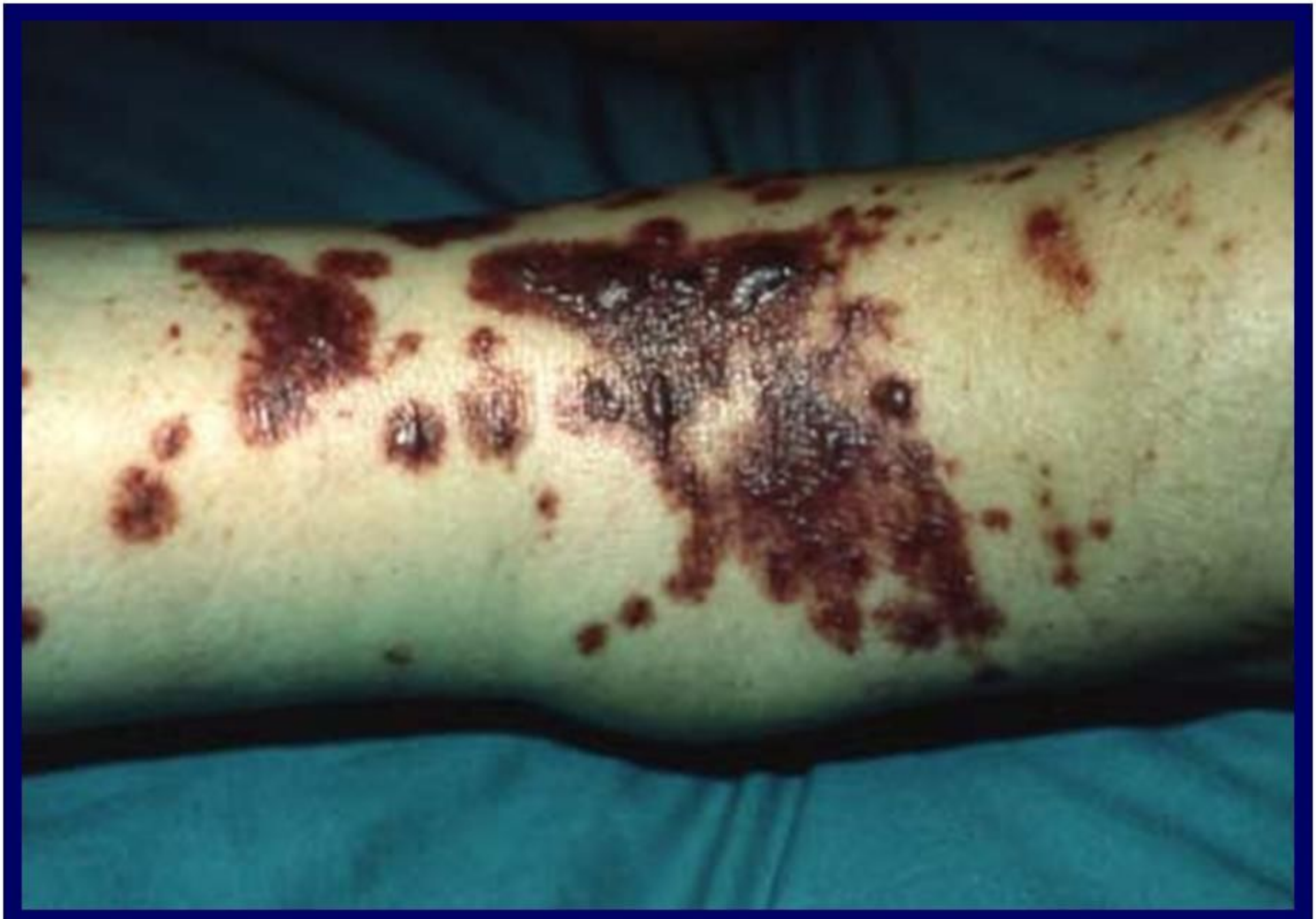
activated cells release a variety of chemical
mediators and free radicals

↓

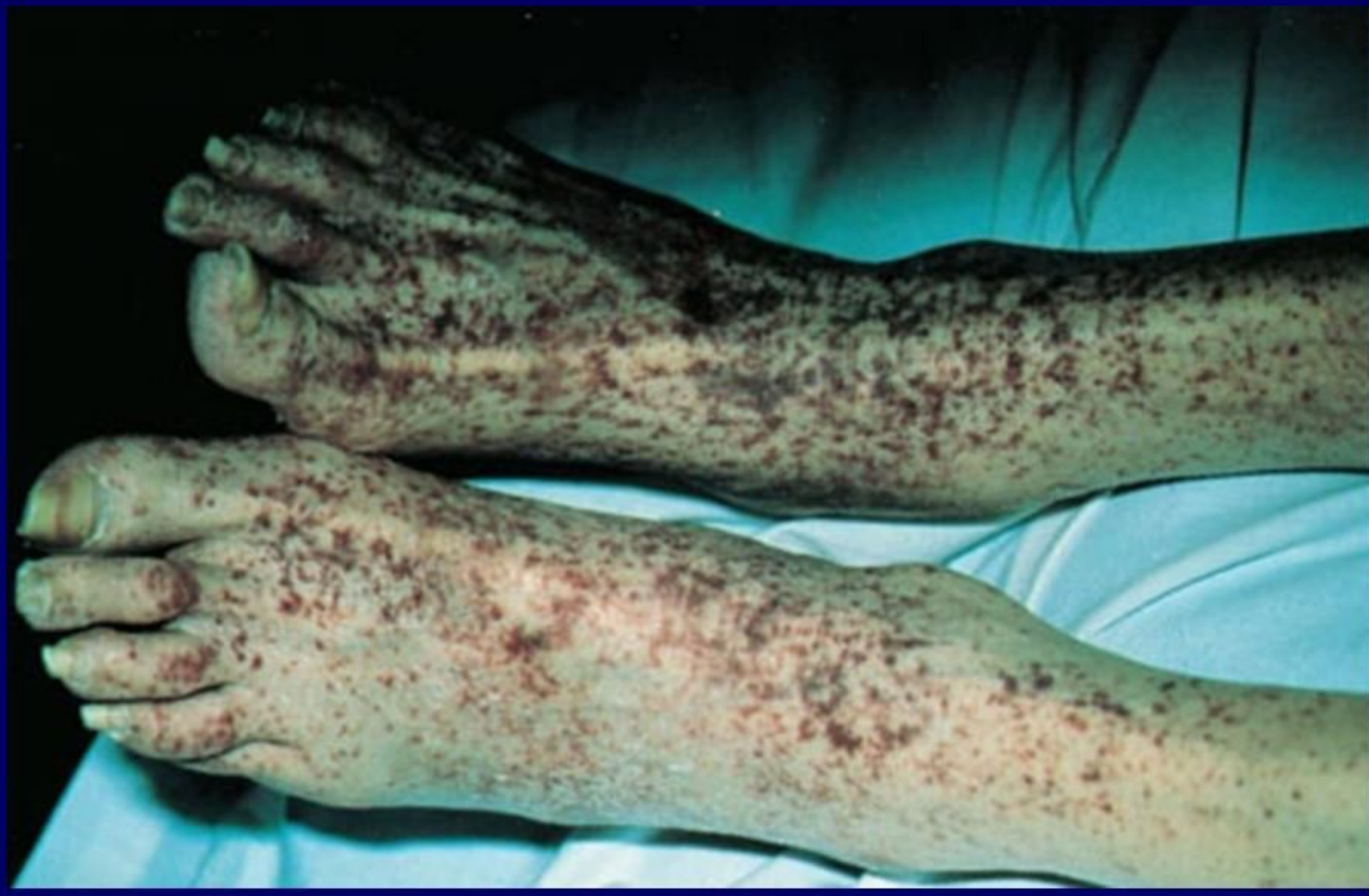
damage endothelial cells

↓

clinical manifestation



Vasculitis caused by furosemide (Lichtman *et al.*, 2007)



quinidine purpura (Lichtman *et al.*, 2007)

# TYPE – IV DRUG ALLERGY

- Delayed and cell mediated,
- Eczema, rashes, other contact dermatitis, SJS or TEN,
- Flu like symptoms → variable severity of mucous membrane and cutaneous involvement.
- SJS and TEN manifestation 0,5 – 2 per 1.000.000 patients per-year, mortality rate 5% (SJS) and 30% (TEN).
  (but some evidence are not immune mediated reactions)
- Occures 48 hrs – 7 days after drug exposure,
- Type-IVa reaction involves a $TH_1$ response, type-IVb involves a $TH_2$ response.

# DRUG ALLERGY (Gell & Coomb classification)

| Type-I | Type-II | Type-III | Type-IV |
|---|---|---|---|
| - IgE mediated,<br>- immediate type,<br>- urticaria, pruritus, vomiting, diarrhea, brnchospasm, hypotension, shock.<br>- minutes – hours, after drug expos.<br>- penicilline | - IgG and IgM<br>- cytotoxic,<br>- hemolytic anemia, neutropenia, thrombocytopenia,<br>- vary<br>- penicilline, methyldopa | - immune complex,<br>- serum sickness, rash, fever, lymphadenopathy, glomerulonephritis,<br>- 1 – 3 weeks after drug exposure,<br>- globuline | - cell mediated, CT.<br>- delayed,<br>- dermatitis, SJS, TEN<br>- 2 – 7 days after cutaneous expos.<br>- antihistamine top., sulfonamide*) |

# Management of Drug Allergy

- Consider desentisitization (IgE) graded challenger (non-IgE) before administration, as appropriate
- Prompt emergency treatment for anaphylactic reactions
- Avoid drug if possible,
- Consider prophylactic regimen before administration of drug,
- Prudent use of drugs in the future,
- Patient education,

# DIAGNOSTIC TEST

| Immune reaction | Laboratory tests |
| --- | --- |
| - Type-I (IgE mediated) | - skin testing, RAST (radioallergosorbent test), serum tryptase |
| - Type-II (cytotoxic) | - direct or indirect Coombs test |
| - Type III (immune complex) | - ESR (erythrocyte sedimentation rate), immune complex, complement studies, antinuclear antibody, tissue biopsy for IF etc. |
| - Type IV (delayed, cell mediated) | - patch test, lymphocyte proliferation assay |

# TREATMENT OF DRUG ALLERGY

| Immune reaction | Therapeutic considerations |
|---|---|
| - Type-I (IgE mediated) | - discontinue drug, adrenaline, antihistamines?, systemic corticosteroids, bronchodilators, inpatients. |
| - Type-II (cytotoxic) | - discontinue drug, consider systemic corticosteroids, transfusion. |
| - Type III (immune complex) | - discontinue drug, consider NSAIDs, antihistamines, or systemic corticosteroids, plasmapheresis. |
| - Type IV (delayed, cell mediated) | - discontinue drug, topical corticosteroids, antihistamines, systemic corticosteroids if necessary . |

# Therapy of drug induced aplastic anemia

- Remove suspected drug from exposure,
- Supportive care, including treat the infection, erythrocyte and platelet support transfusion,
- Antithymocyte globulin (polyclonal immunoglobulin,
- Corticosteroids, methylprednisolon,
- Cyclosporin to block lymphocyte-T prolifaration and fucntion may block IL-2 production

Medical history
Physical examination
Clinical laboratory data

is a drug reaction likely?

yes

Is there suspicion of
- drug induced hypersensitivty?
- immunologic reaction?

yes

immune mechanism
- IgE mediated
- cytotoxic
- immune complex
- delayed cell-mediated
- other immune mechanis

no

non-immune mechanism
- pharmacologic side effects
- drug toxicity
- drug interactions
- drug overdose
- pseudoallergy
- idiosyncratic

no

other etiology likely

evaluate and treat other causes of symptoms

immune mechanism
- IgE mediated
- cytotoxic
- immune complex
- delayed cell-mediated
- other immune mechanis

evaluate with appropriate confirmatory tests

are tests supportive of immune drug reaction?

yes

diagnosis of drug hypersensitivity / immunolgic reaction confirmed

no

dose test have high negative predictive value?

yes

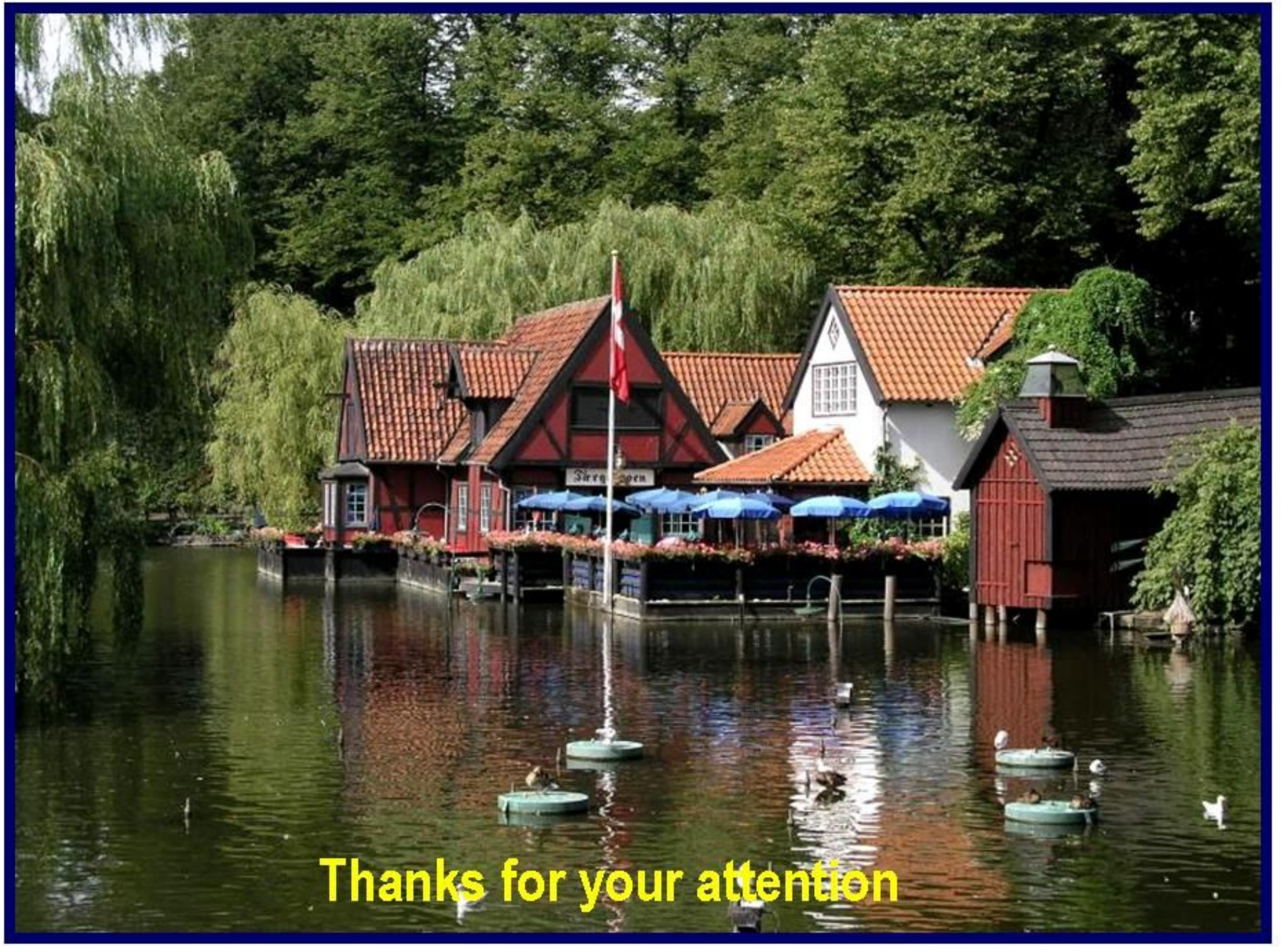
continue drug with closed observation

no

mamagement

non-immune mechanism
- pharmacologic side effects
- drug toxicity
- drug interactions
- drug overdose
- pseudoallergy
- idiosyncratic

management
- modify dose
- try drug substitusion
- treat side effects
- consider graded doses
- pasien educations


Thanks for your attention