CUTANEOUS DRUG ERUPTIONS

Definition

- An adverse cutaneous drug eruption is defined as an undesirable cutaneous manifestation resulting from the administration of a particular drug and may result from its overdose, predictable side effects or unanticipated adverse manifestations.

Mechanism of drug reactions

A – Immunological

- Are not normal pharmacological effects of the drug but are due to hypersensitivity following previous exposure or chemically related compound
- Less predictable, can develop even with low doses
- Appear after a latent period req. for immune reaction to develop

Hyper sensitivity	Immune effector mechanisms	Clinical manifestations
Type 1: immediate/ anaphylactic	IgE bound to mast cells or basophils causes mast cell degranulation, release of histamine and other mediators	Urticaria, asthma, anaphylaxis
Type 2: cytotoxic	Antigenic determinants on cell surfaces are targets for IgG /IgM. Damage cells by cytotoxic killing	Pemphigus haemolytic anaemia, neutropenia, thrombocytopenia

Hyper sensitivity	Immune effector mechanisms	Clinical manifestations
Type 3: immune complex	Circulating immune complexes deposited on tissue surfaces. Complement iactivated, neutrophils attracted damage tissues	Vasculitis – hypersensitivity vasculitis, Henoch–Schonlein purpura
Type 4: delayed type, T - cell mediated	Effector T lymphocytes (CD4+ or CD8+), produce cytokines and/or cytotoxic factors	

Type 4 subcategory	Immune mediators	Inflammation characterized by:	Clinical pattern
4a	Th1/Tc1 cells: IFN - γ, TNF - α	T cells, macrophages	Contact dermatitis, tuberculin reaction
4b	Th2 cells: IL - 4/ - 13, IL - 5	Eosinophils	Maculopapular rash, exanthemata with eosinophilia
4c	Cytotoxic T/NK/ NKT cells: granulysin, perforin, granzyme B	T cells Keratinocyte apoptosis	Contact dermatitis, maculopapular rash, drug - induced exanthemata, bullous eruptions (SJS/TEN)
4d	T cells: IL - 8, CXCL8, GM - CSF	Neutrophils	Acute generalized exanthematous pustulosis

Mechanism of drug reactions

B – Non immunological

- Usually predictable
- Affects all patients who take adequate amount
- Large amount of drug usually req. to initiate reaction
- May develop with first dose (no latent period req.)

Mechanism of drug reactions

Predictable

- Side effects
- Over dose
- Cumulative effect- defective metabolism or excretion
- Delayed toxicity
- Drug interactions
- Facultative effect
- Exacerbation of pre-existing skin conditions
- Teratogenacity
- Mutagenicity

Mechanism of drug reactions

B- Non immunological

Unpredictable

- Idiosyncratic reactions
- Intolerance

Mechanism of drug reactions

Special reactions

- Jarisch – Herxheimer reaction

  Syphillitic patients treated with penicillin develop exacerbation of existing lesions

- Infectious mononucleous – ampicillin reaction

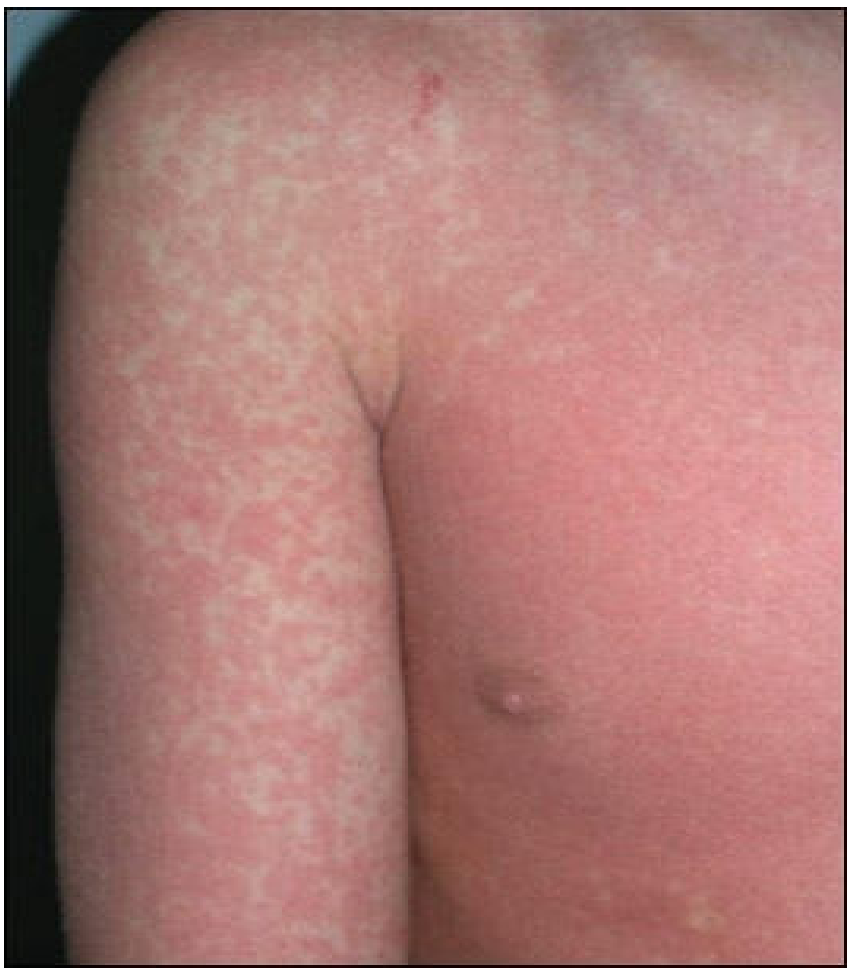
  patients with IM when treated with ampicillin develop an exanthematous rash

Pattern of drug reactions

EXANTHEMATOUS ERUPTIONS

- Symmetrical maculo-papular to papulo-squamous rash ; ± itchy
- Begin 1-2 wks of starting; subside in 1-2 wks of withdrawing the drug
- Immunological reaction 4b

EXANTHEMATOUS DRUG ERUPTIONS



- Penicillin & Ampicillin,
- Sulfonamides
- Phenytoin, Carbamazepine
- Allopurinol
- Nsaids
- Nevarapine

Viral rash

- **Itching** less
- **Pattern** – monomorphic with a pattern of evolution
- **Begin** – face, acral sites then spread to trunk
- **Systemic symptoms**: sore throat, cough, GIT, fever
- Asso. **enanthem**
- **Course** – usually self limiting

Exanthematous drug eruption

- **Itching** - often severe
- **Pattern** - polymorphic

No pattern of evolution

- **Begin** – trunk
- **Course -** May progress if drug continued

URTICARIA AND ANGIOEDEMA via

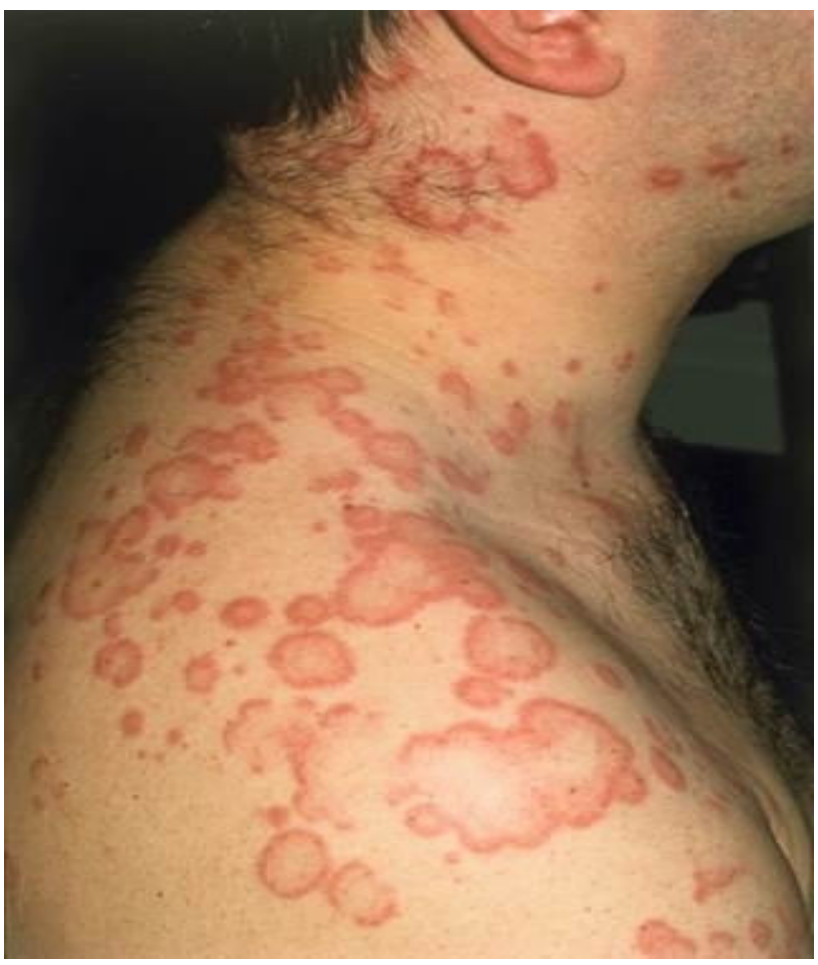
1. Direct degranulation of mast cells – aspirin, indomethacin
2. Interfering with arachadonic acid metabolism

   Morphine, codeine, sulfonamides, curare, radioactive contrasts
3. Ig –E mediated degranulation of mast cells

   Penicillin
4. Complement mediated mast cell degranulation

   Blood products

DRUG INDUCED URTICARIA

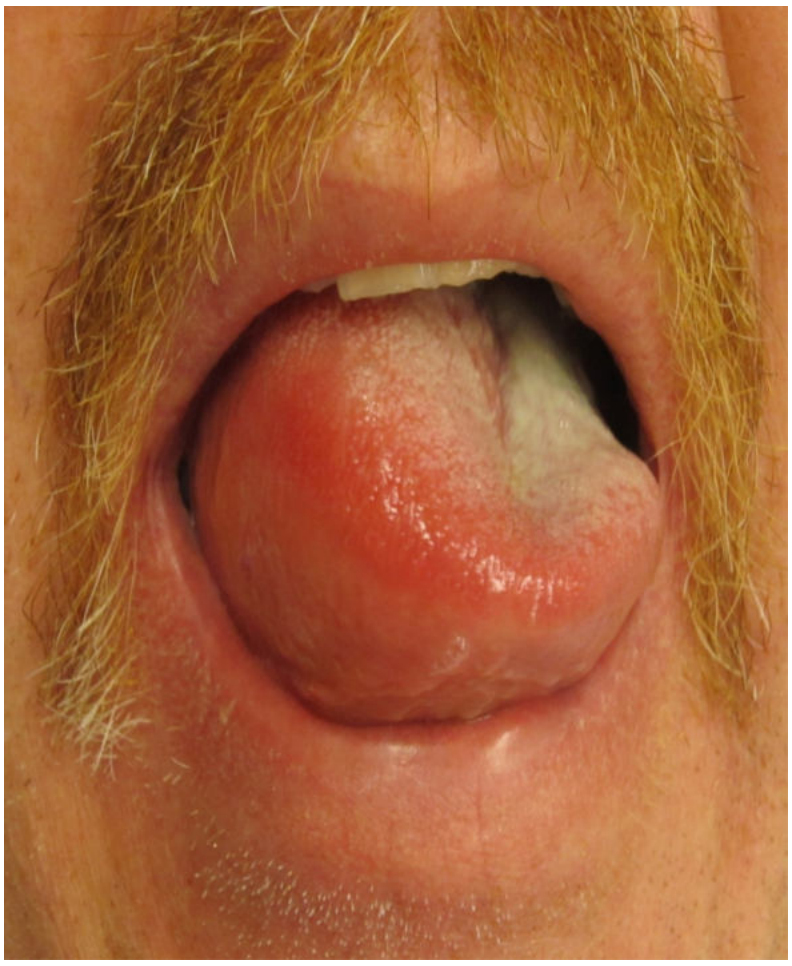


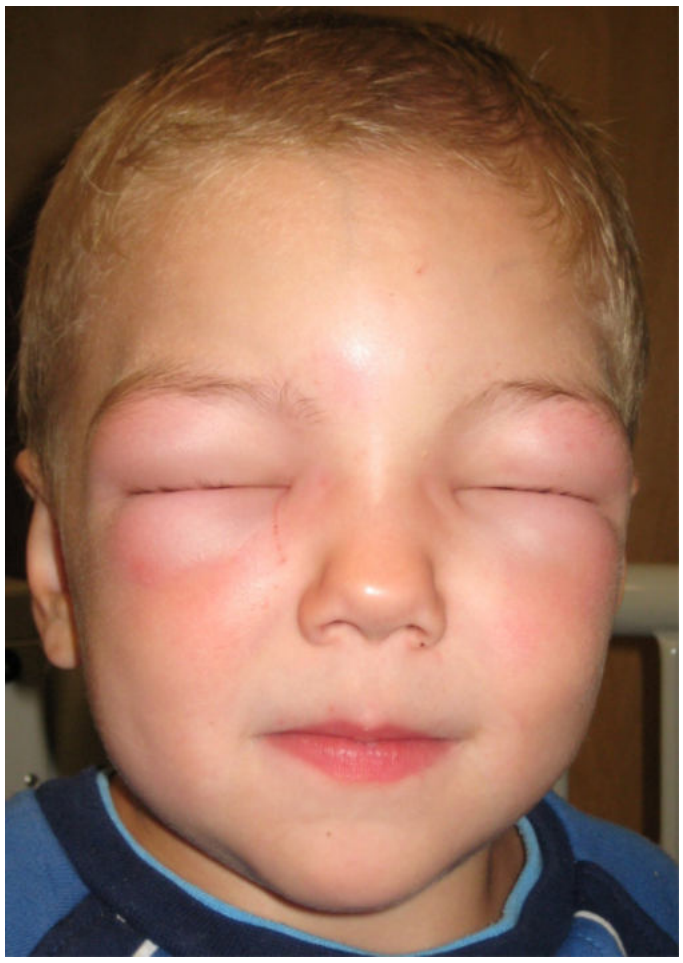
Common drugs

- Aspirin
- NSAIDs

Type I hypersensitivity

DRUG INDUCED ANGIO-EDEMA





ANAPHYLAXIS

- Common with parenteral administration than oral ingestion .
- Eg. Penicillin, Cephalosporins, NSAIDS, Thiopental, Neuromascular Blocking Agents, Opiods, Blood Transfusion (Pre, Intra-op) Vaccines, Toxoids, Lignocaine, Dextran, Radiocontrasts

ERYTHRODERMA

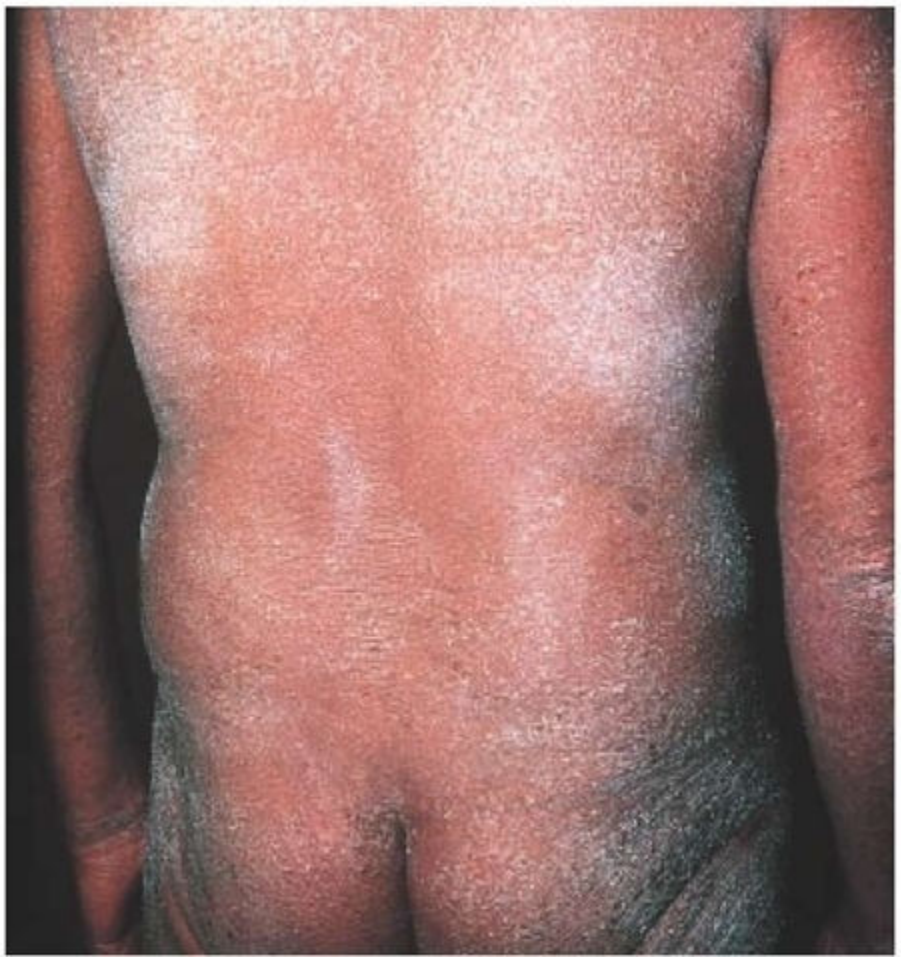
- generalized scaling and erythema associated with pruritus.
- malaise, hypothermia or fever, lymphadenopathy,
- Organomegaly, high - output cardiac failure

- resolve in 2-6 wks after stopping

- Carbamazepine,Phenytoin Phenobarbital
- Allopurinol
- Co - trimoxazole, Penicillins Cephalosporins, Vancomycin
- ATT
- ART
- NSAIDS
- Acitretin

- Omeprazole, Lansoprazole
- Calcium - channel blockers
- Lithium
- Chlorpromazine
- Imatinib
- Interferon - α
- Heavy metals

DRUG INDUCED ERYTHRODERMA



Stevens-Johnson syndrome – Toxic Epidermal Necrolysis(SJS-TEN) complex

Acute life threatening muco-cutaneous reactions characterized by extensive necrosis and detachment of epidermis and mucosa

- SJS - <10% BSA
- SJS- TEN overlap – (10%-30%)
- TEN - >30%

SJS-TEN complex

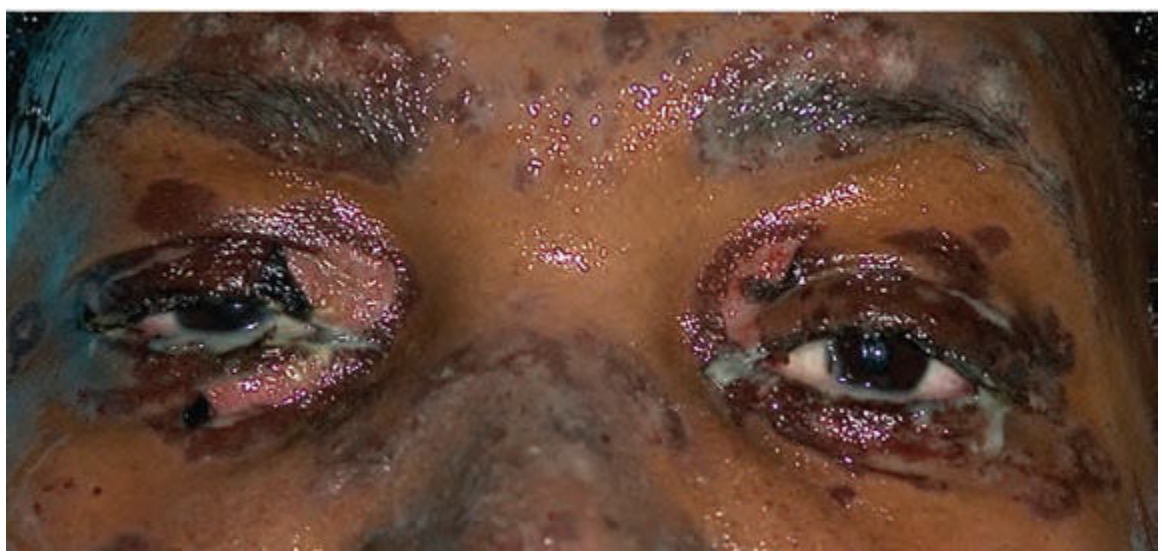
- H/o drugs 1-3 wks prior
- most recently added drug probable suspect
- Prodrome – fever, headache, rhinitis, myalgia
- Odynophagia, burning / stinging eyes
- Initial lesion – localized targetoid/ diffuse dusky erythema with crinkled surface, progressively coalesce. Start from face down to generalization

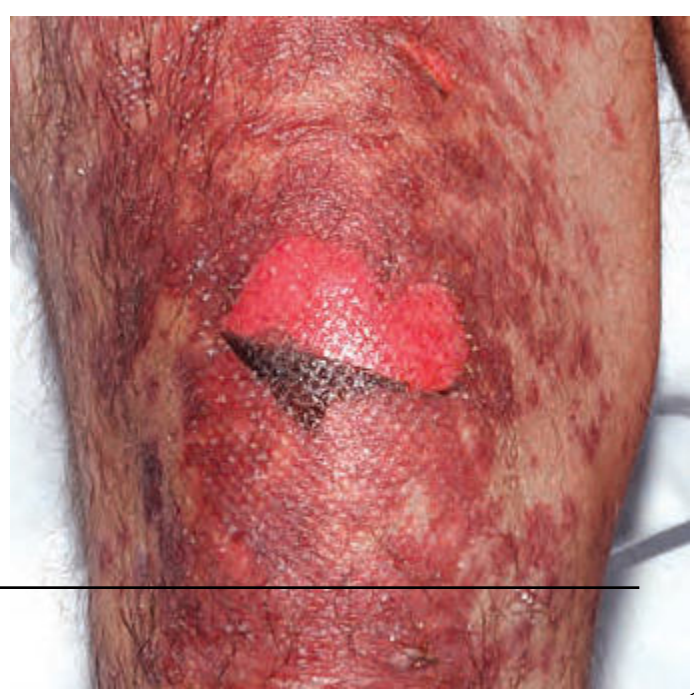
SJS-TEN complex

- Confluence of lesion extensive diffuse erythema, flaccid blisters develop
- Nikolsky's sign – lateral pressure over necrotic skin leads to epidermal detachment
- Eventually large areas of erosions develop
- Mucosa – oral(100%), eyes(90%), genital(50%)
- Complications – sepsis, electrolyte imbalance, multiorgan failure, death

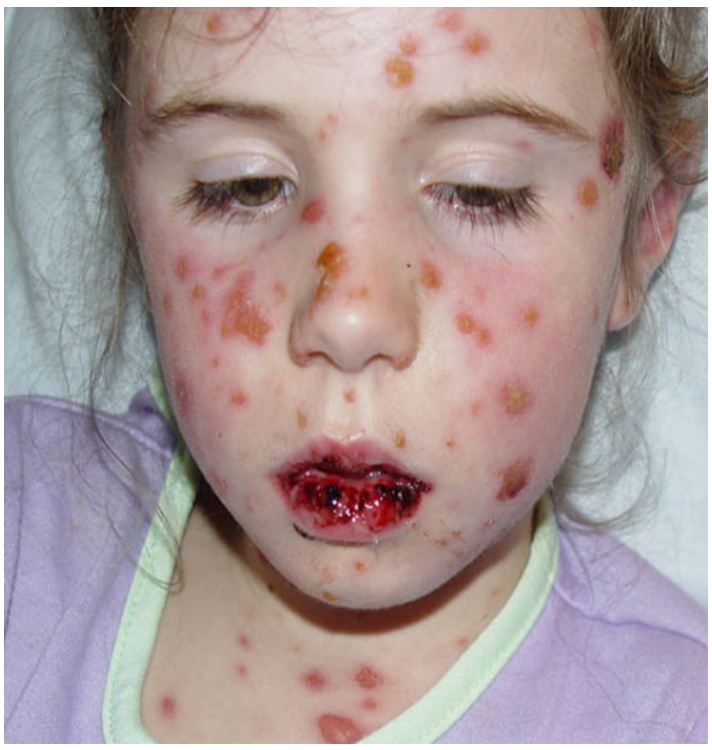
SJS-TEN complex

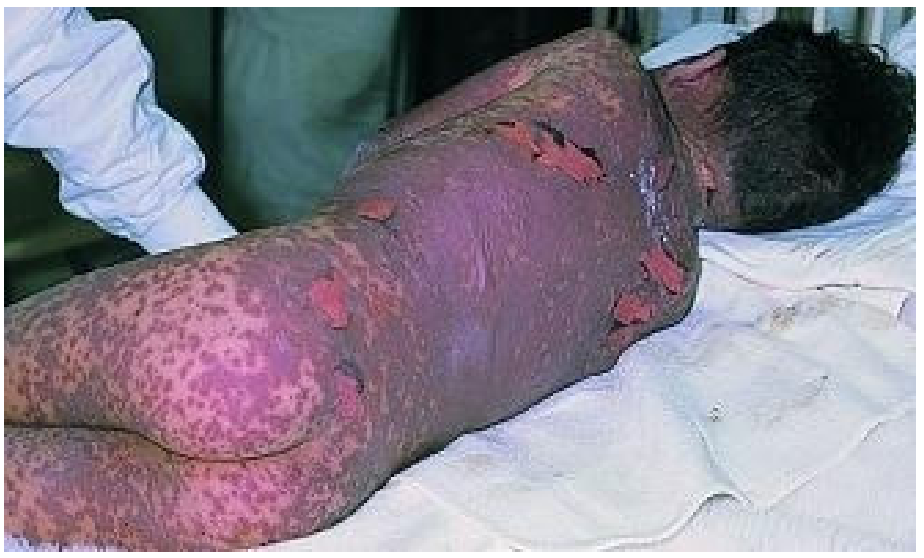
- Antibiotics – sulfonamides, quinolones, ampicillin and cephalosporins
- Anticonvulsants – barbiturates, phenytoin, carbamazepine, valproic acid, lamotrigine
- ATT
- NSAIDS – nimesulide, salicylates, ibuprofen, oxicams
- Cyclophosphamide, allopurinol, nevarapine





SJS-TEN complex





SCORTEN (SCORe of Toxic Epidermal Necrolysis)

- Age greater than 40 years
- Presence of malignancy
- Heart rate >120 beats/min
- Epidermal detachment >10% of BSA at admission
- Serum urea >10 mmol/L
- Serum glucose >14 mmol/L
- Bicarbonate level <20 mmol/L

- one point is attributed each of the parameters
- increasing scores predicting higher mortality rates

Investigations

- CBC,ESR
- Urea and electrolytes
- Amylase
- Bicarbonate
- Glucose
- LFT
- C - reactive protein
- CXR
- Blood C/S, Skin C/S
- Coagulation studies
- *Mycoplasma serology*
- Antinuclear antibody and extractable nuclear antigen
- Complement
- Indirect immunofluorescence

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)syndrome/ DHS

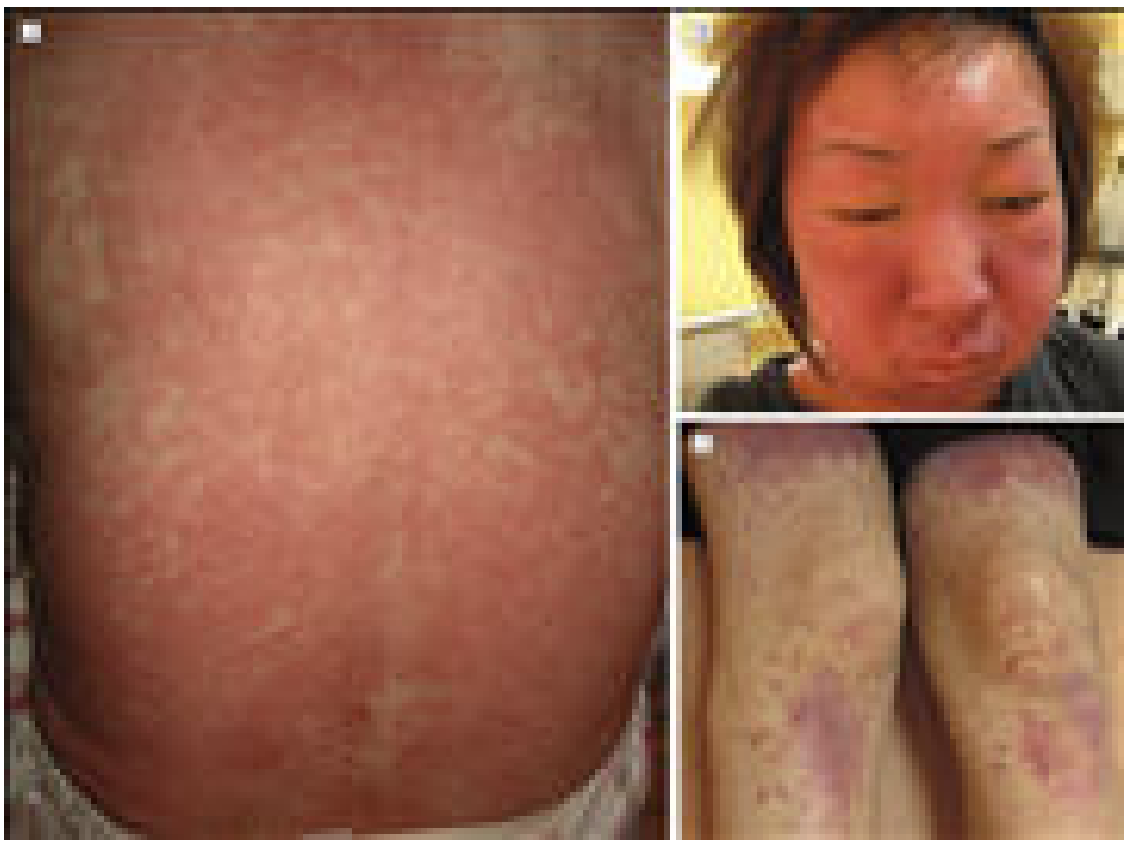
- starts 3 weeks after starting
- Drug Rash with facial edema
- Eosinophilia, atypical lymphocytes, mononucleosis
- Systemic sympyoms – hepatitis, nephritis, pneumonitis, myocarditis, encephalitis, hypothyroidism
- Lymphadenopathy – at least 2 diff. sites
- Fever

- Allopurinol
- Carbamazepine, Phenytoin, Lamotrigine
- Vancomycin, Amoxicillin, Minocycline, Piperacillin, Tazobactam
- Sulphasalazine, Dapsone, Sulphadiazine
- Furosemide
- Omeprazole
- Ibuprofen

Investigation

- Hepatic - LFT, LDH, Ferritin,Coagulation screen ,Hepatitis B, C, EBV, CMV, HHV - 6, HHV - 7 titres
- Cardiac-ECG, *Echo,*Cardiac enzymes (creatine kinase, troponin)
- Pulmonary- CXR, PFT*s*
- Autoimmune –ANA,Complement, ANCA
- Renal –Urea,creatinine,Calcium,Urinalysis,*Renal ultrasound*
- Neurological -Microscopy, C/S CSF, *CT/MRI head, EEG*
- Endocrine- Thyroid function test, Blood glucose
- Infection- Blood cultures, *Mycoplasma serology,PCR for HSV*
- Gastrointestinal –Amylase,*Lipase,Triglycerides,Colonoscopy*

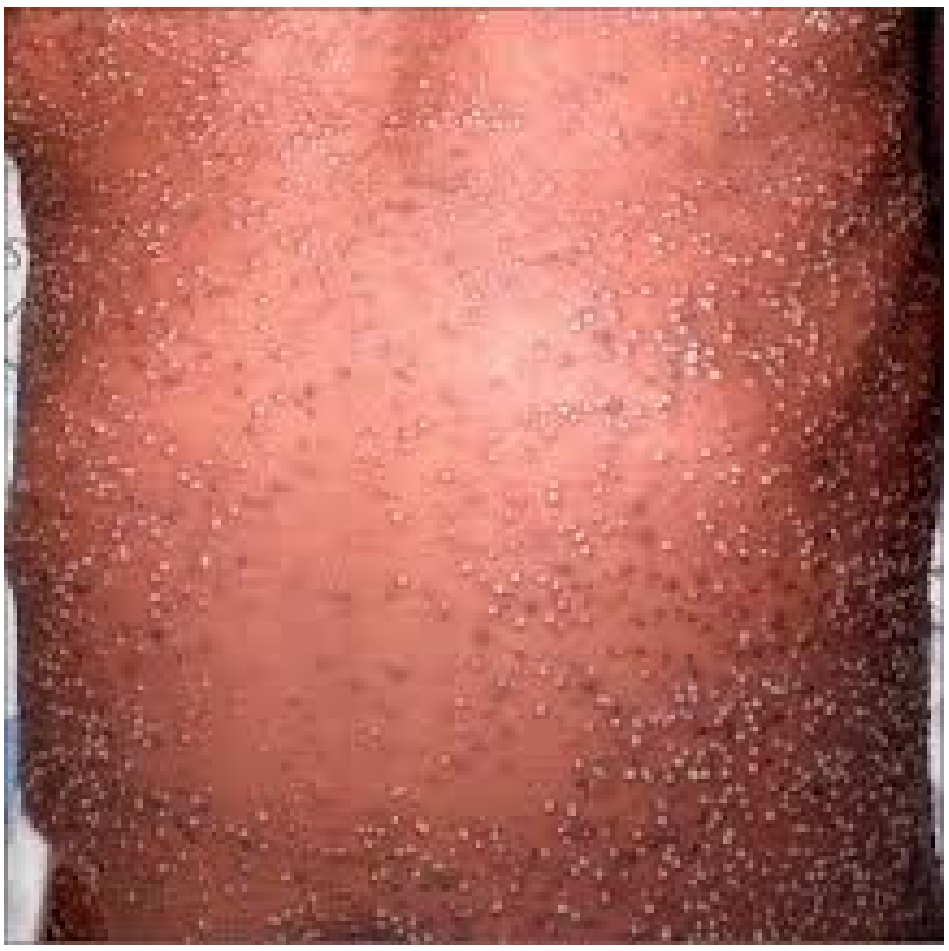
DRESS/DHS



ACUTE GENERALIZED EXATHEMATOUS PUSTULOSIS

- rapid appearance of sheets of non - follicular sterile pustules
- 1st in flexures (neck, axillae, inframammary, inguinal folds) → generalize
- Start within 1 day of drug, last 1-2 wks after stopping then subside with scaling
- Mild fever, malaise, neutrophilia,
- Transient hepatic, renal and pulmonary dysfunction

ACUTE GENERALIZED EXATHEMATOUS PUSTULOSIS



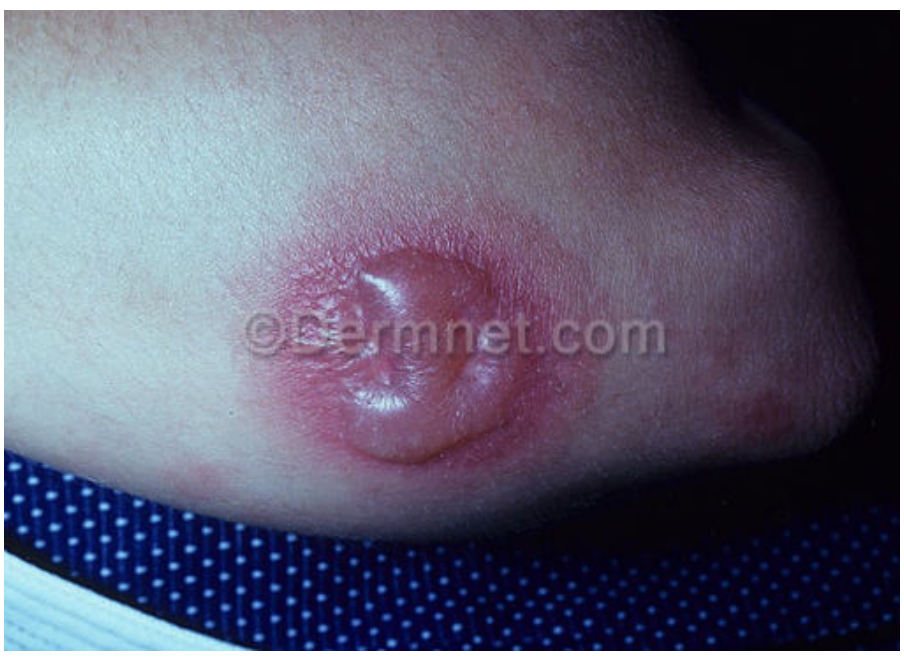
- Aminopenicillins
- Quinolones
- Chloroquine and hydroxychloroquine
- Sulphonamides
- Terbinafine
- Diltiazem

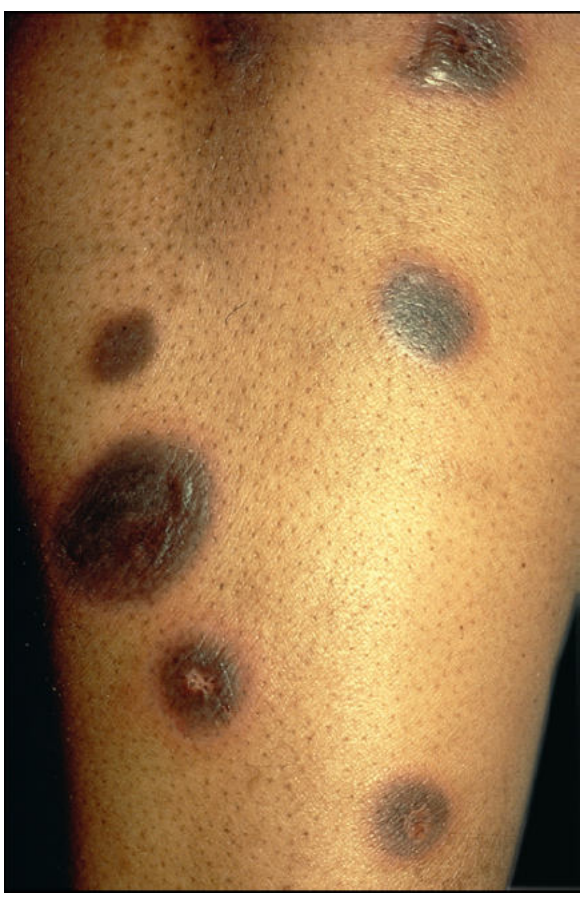
FIXED DRUG ERUPTIONS

- recurrent well - defined lesions occurring in the same sites each time the offending drug is taken
- well defined circular, deeply erythematous plaque, sometimes with central bullae; subside with slate grey hyperpigmentation
- sites- lips, glans, palms & soles: limbs, trunk
- Type IV hypersensitivity

- NSAIDS(lips genitals)
- Paracetamol
- Co - trimoxazole & Tetracyclines (genitals)
- Penicillins
- Metronidazole
- Rifampicin
- Erythromycin
- Pseudoephedrine
- Barbiturates
- Carbamazepine
- Sulphasalazine
- Calcium - channel blockers
- ACE inhibitors
- Omeprazole
- Iodinated contrast
- Azoles systemic
- Complementary medicines
- Food, e.g. cashew nuts, asparagus

FIXED DRUG ERUPTIONS





ERYTHEMA NODOSUM

- A septal panniculitis induced by a medication
- Symmetrical, erythematous, tender, subcutaneous nodules or plaques
- Typically over the anterior aspect of the limbs.
- Later become purplish before finally turning brown

- Oral contraceptives
- Hormonal replacement therapy
- Sulphonamides
- Penicillin
- Azathioprin
- Minocycline
- Ciprofloxacin
- NSAIDs
- Gold
- Benzodiazepines

- Barbiturates
- Isotretinoin
- Montelukast
- Vaccinations (hepatitis, HPV, rabies)
- GcSF
- Complementary medications

ERYTHEMA MULTIFORME

- acute self limiting lesion characterized by IRIS or TARGETOID lesions
- IRIS lesion - <3 cm, rounded lesion with 3 zones

central – dusky erythema or purpura

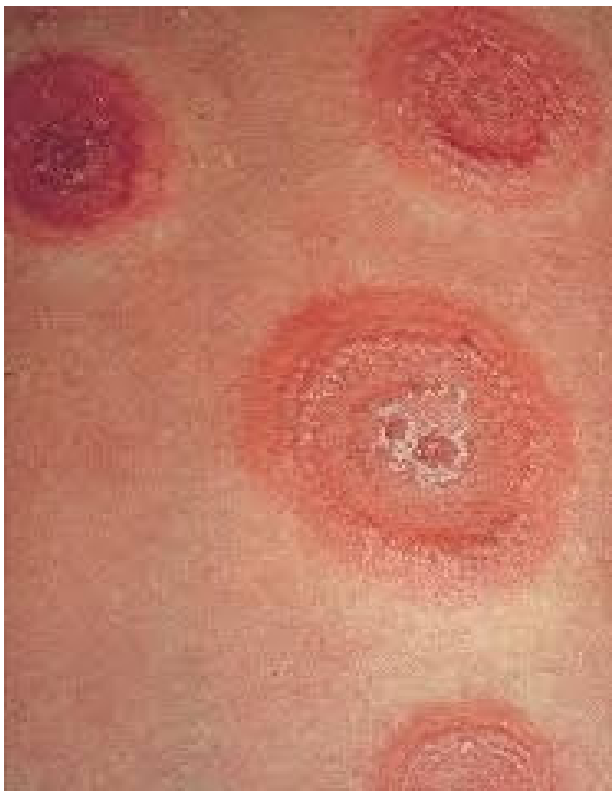
middle – pale edema

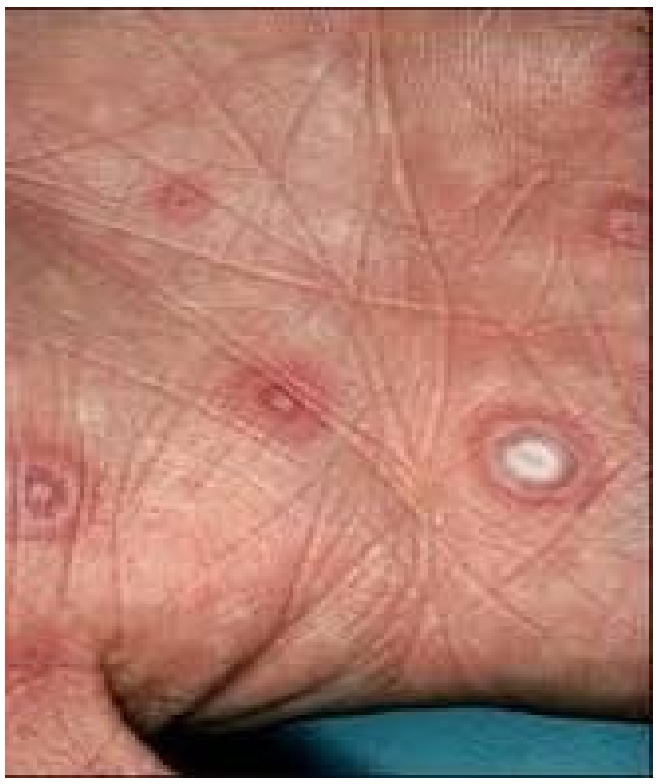
outer - erythema with well defined margin

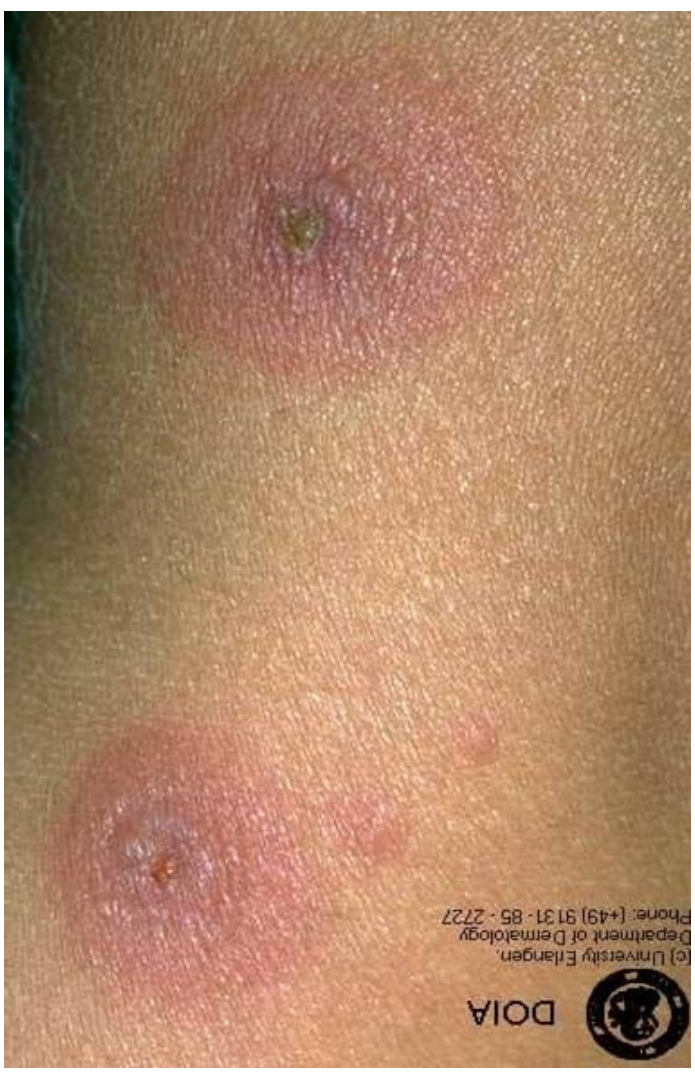
- Sulphonamides,
- Penicillin,
- Quinolones,
- Tetracyclins,
- Rifampicin,
- Anticonvulsants,
- NSAIDS,
- Thiazides,
- Nevarapin

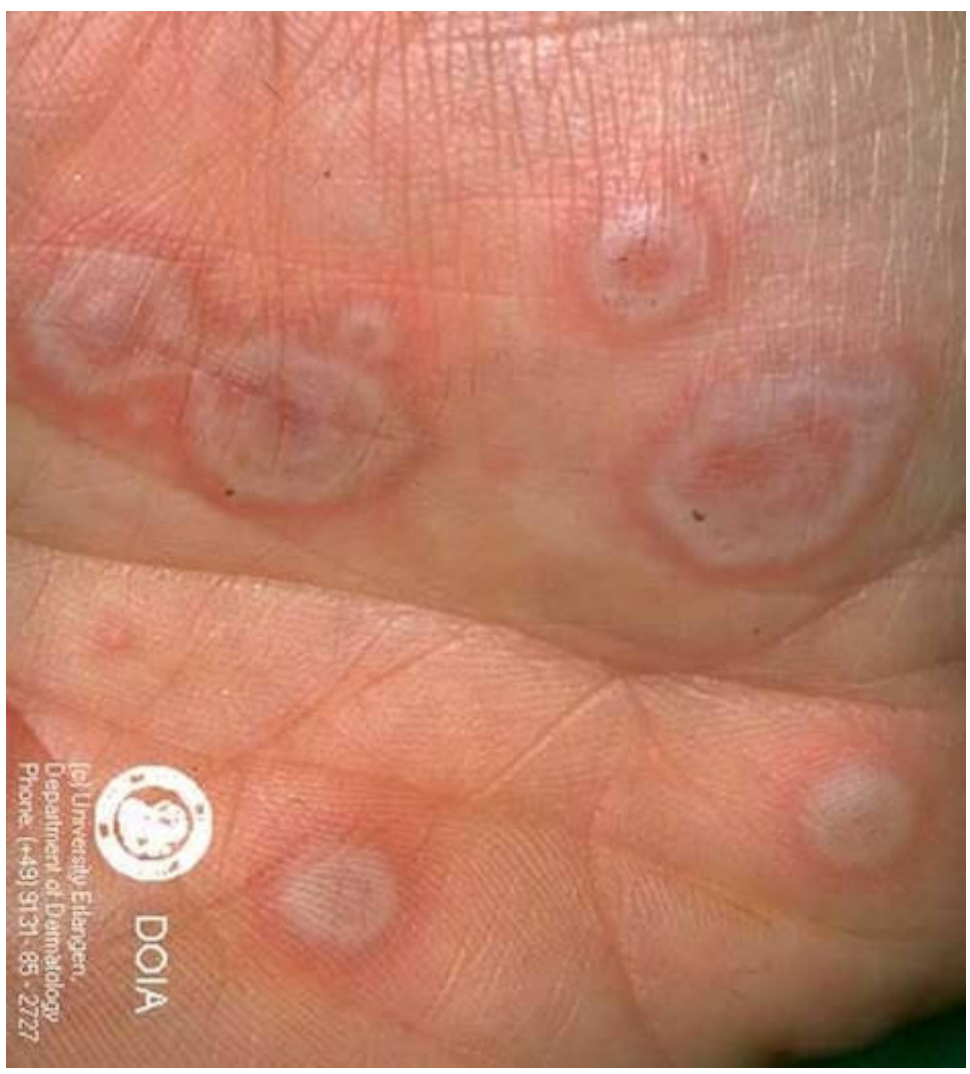
- Sites - face, extremities, oral, genital mucosa, trunk

ERYTHEMA MULTIFORME









DRUG INDUCED PRURITUS

- Primary, via neuronal/central nervous system interaction.
- Secondary pruritus

  (i) direct skin effects, e.g. induction of drug rash, xerosis;

  (ii) alteration of biochemical profiles (e.g. renal or hepatic dysfunction);

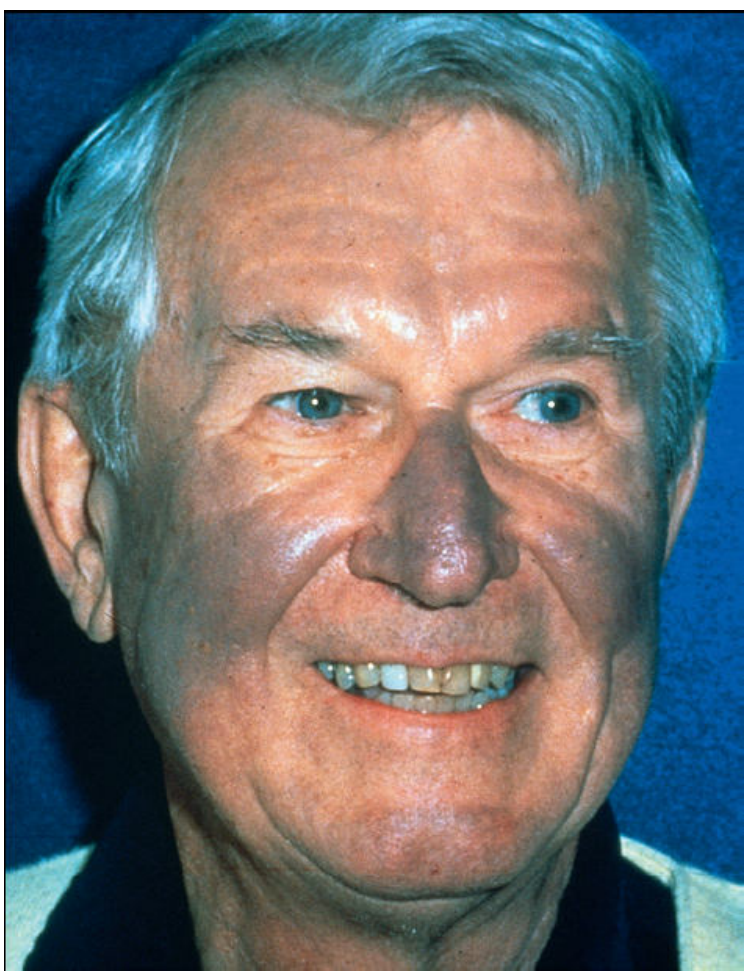
  (iii) other unexplained mechanisms

- Opioids
- Statins
- Paclitaxel
- Antimalarials
- Granulocyte–macrophage colony - stimulating factor
- Interleukin - 2
- Angiotensin - converting enzyme inhibitors
- Sulphonylurea derivates
- Non - steroidal anti - inflammatory drugs
- Hydroxyethyl starch (HES)

DRUG INDUCED PHOTOSENSITIVITY

- Itchy, erythematous papules, plaques on exposed areas;
- H/O photosensitivity
- drugs - quinolones, tetracyclins, sulphonamides, griseofulvin, phenothiazine, psoralens, ampicillin, amiodarone

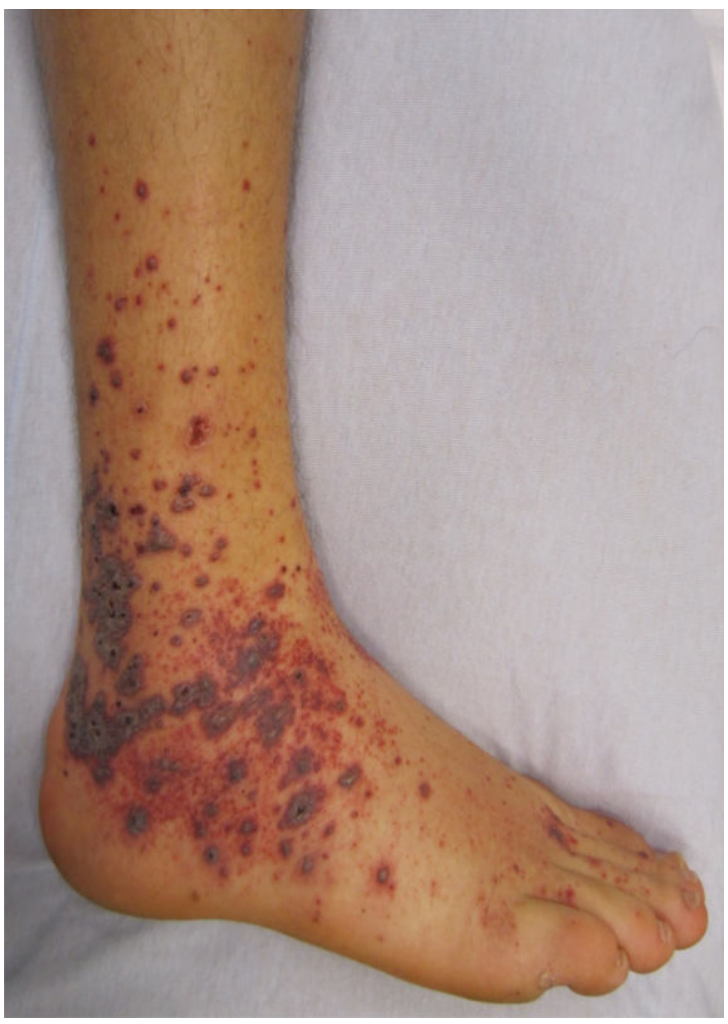
AMIODARONE INDUCED PHOTOSENSITIVITY



VASCULITIS

- urticarial vasculitis, palpable purpura, nodular vasculitis, necrotic ulcers

- drugs – aspirin, indomethacin, phenylbutazone sulphonamides, tetracyclin, ampicillin, erythromycin,diuretics, phenytoin, methatrexate



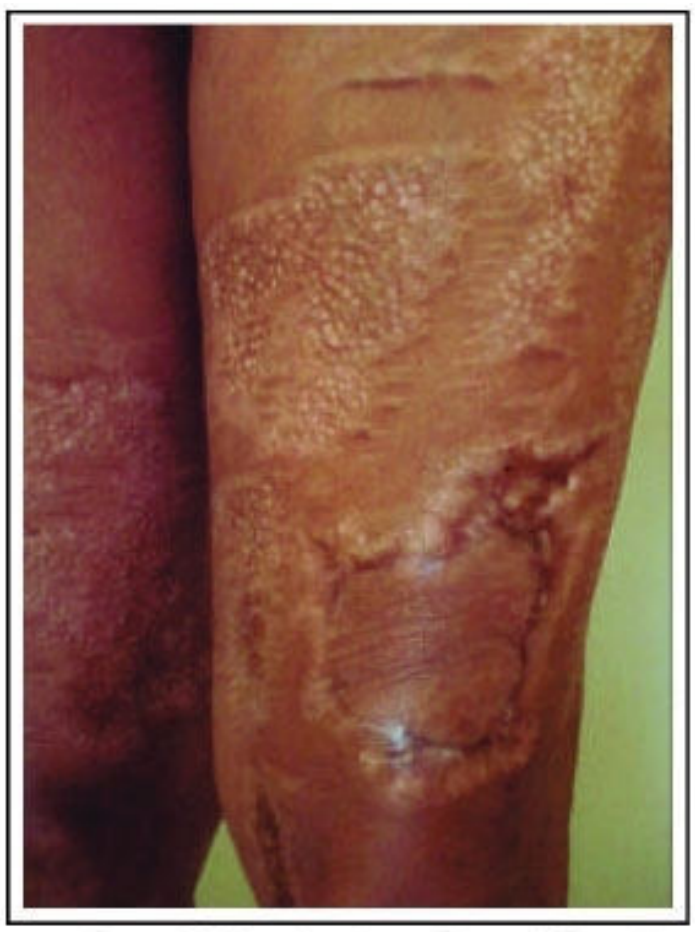


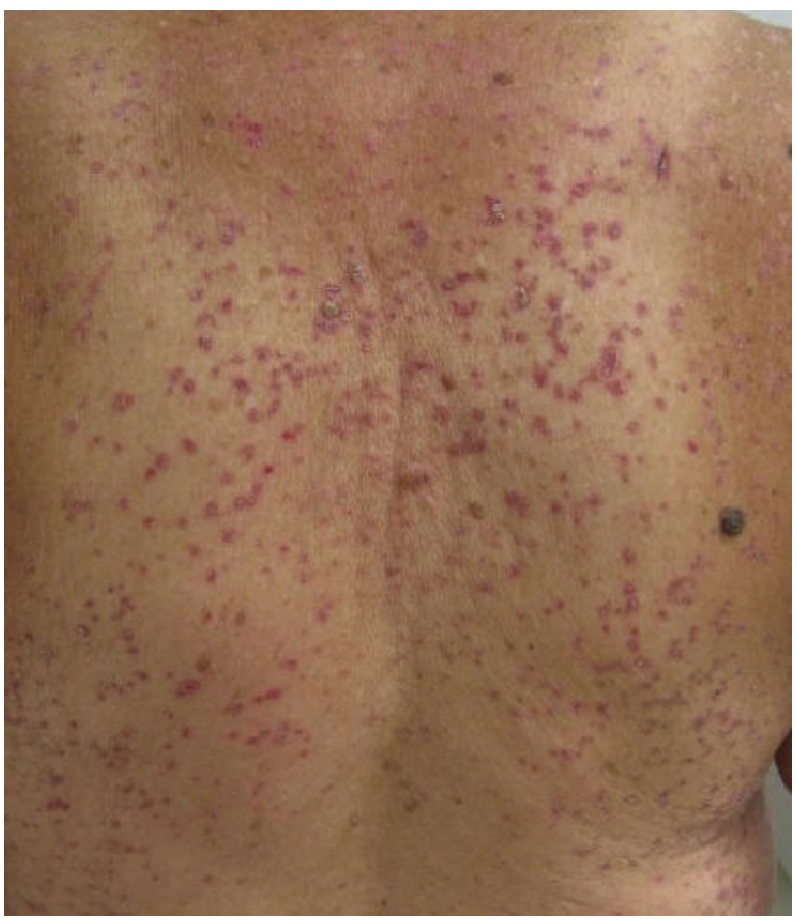
Figura 6: Vasculite de hipersensibilidade ao propiltiouracil. Lesões cicatriciais e áreas de pele provenientes de enxertia, após resolução do quadro.

Figure 6: Propylthiouracil hypersensitivity vasculitis. Cicatricial lesions and areas of skin grafts, after resolution of the picture.

LICHENOID ERUPTIONS

- Lichen planus like eruption, mostly trunk
- Generalized, eruptive, with prominent eczematous and scaling component
- Mucosa, nail involvement infrequent

LICHENOID DRUG ERUPTIONS



- Gold, Antimalarials,
- Mercury Amalgam,
- Thiazides,
- NSAIDS,
- Penicillamine
- Isoniazid,
- Tetracyclin,
- Dapsone,
- Beta Blockers
- Captopril

ACNEIFORM ERUPTIONS

- Extensive papulopustular monomorphic eruptions; absence of comedones
- Suspected : sudden, abrupt onset in the absence of past history of acne
- Trunk>face
- Any age

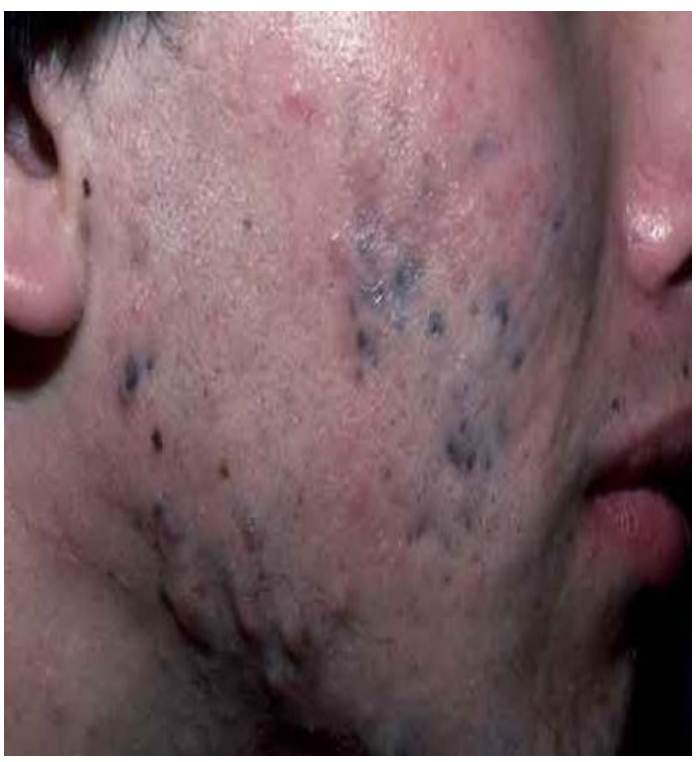
- Corticosteroids
- Androgens and anabolic steroids
- Hormonal contraceptives
- Danazol
- Tricyclic antidepressants, Lithium,Valproate,Phenytoin
- Vitamins B1, B6,
- Ciclosporin,Sirolimus Azathioprine
- Dactinomycin
- Thiourea, thiouracil
- Epidermal growth factor receptors inhibitors
- Imatinib
- Iodine,Bromine,Chlorine
- Isoniazid, Rifampicin Ethionamide

DRUG INDUCED PIGMENTATION

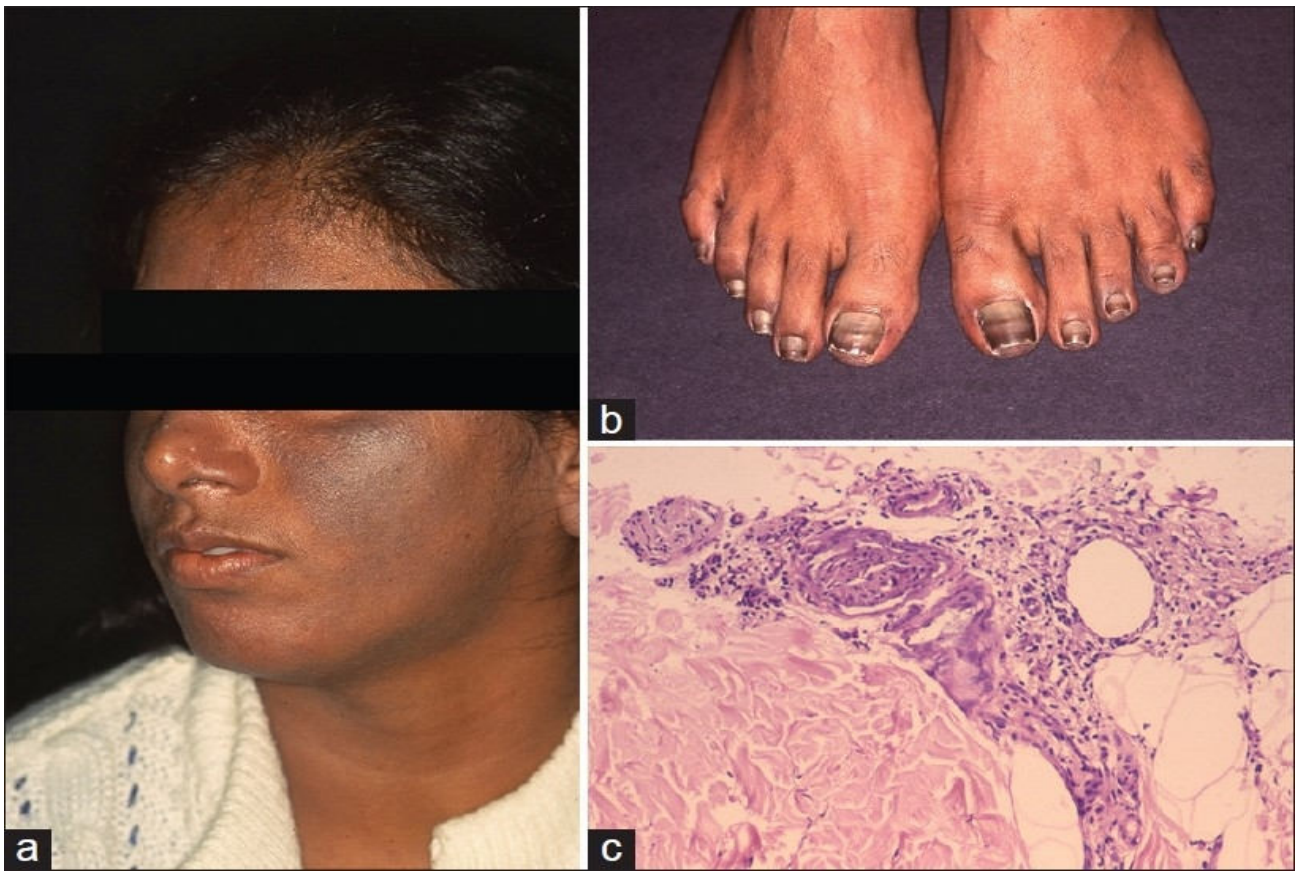
- Via - ↑melanin synthesis – psoralens
- Cutaneous deposition of drug/metabolite – minocyclin, heavy metals, clofazimine
- Hormonal effect – OCP causing melasma
- Post inflammatory hyperpigmentation

other drugs –bleomycin, cyclophosphamide, methotrexate, hydroxyurea, 5- fluorouracil

MINOCYCLIN INDUCED PIGMENTATION



CLOFAZIMINE INDUCED PIGMENTATION



ALOPECIA

Retinoids, cytotoxics, anticougulants, anti thyroids, danazol, OCP

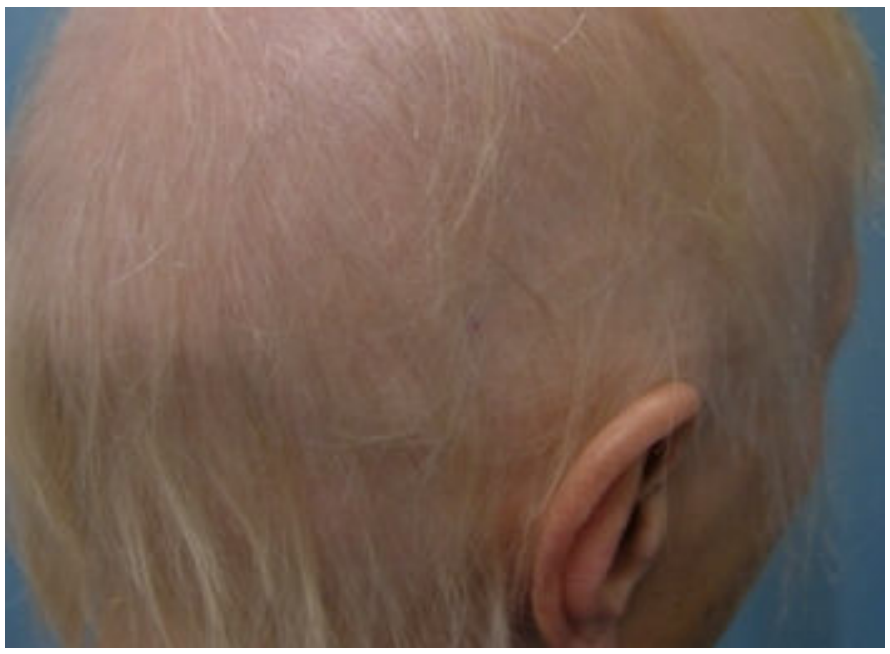
HYPERTRICOSIS

PUVA, phenytoin, minoxidil, penicillamine, cys A

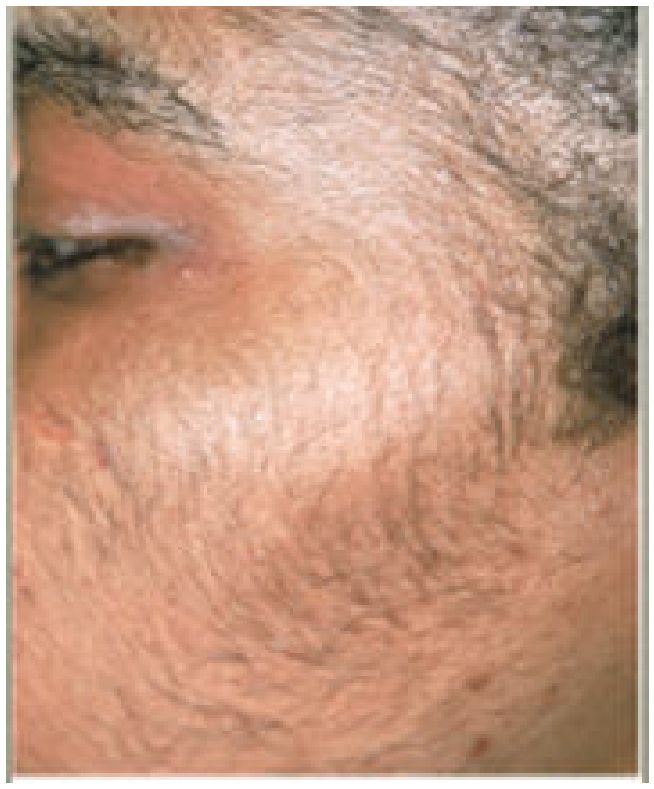
HIRSUITISM

Oral steroids, anabolic steroids, OCP

ALOPECIA



HYPERTRICOSIS



Management of drug reactions

- WITHDRAW and replace with chemically unrelated alternatives

- Mild/moderate cases

1. antihistamines,
2. local bland emollients,
3. Topical steroids

- Severe cases –

ANAPHYLAXIS -

- inj adrenaline (1:1000), 0.3- 0.5ml s.c/ i.m.
- inj chlorpheramine maleate (10-20mg), i.v.
- inj hydrocortisone 100mg i.v.
- observation for at least 6 hrs after stabilization

SJS-TEN Complex

- IVF replacement,
- Oral liquid diet,
- Nasogastric tube,
- Total parenteral nutrition
- Denuded skin – dressing
- Antacids/ H2 blockers
- pethidine/ tramadol,

- Emperical broad spectrum antibiotics
- Eye care – 2 hr NS/antibiotics, break synechia

SPECIFIC – steroids,
IV Ig,
cyclosporin,
cycloposphamide,
thaladomide,
plasmapheresis

THE END