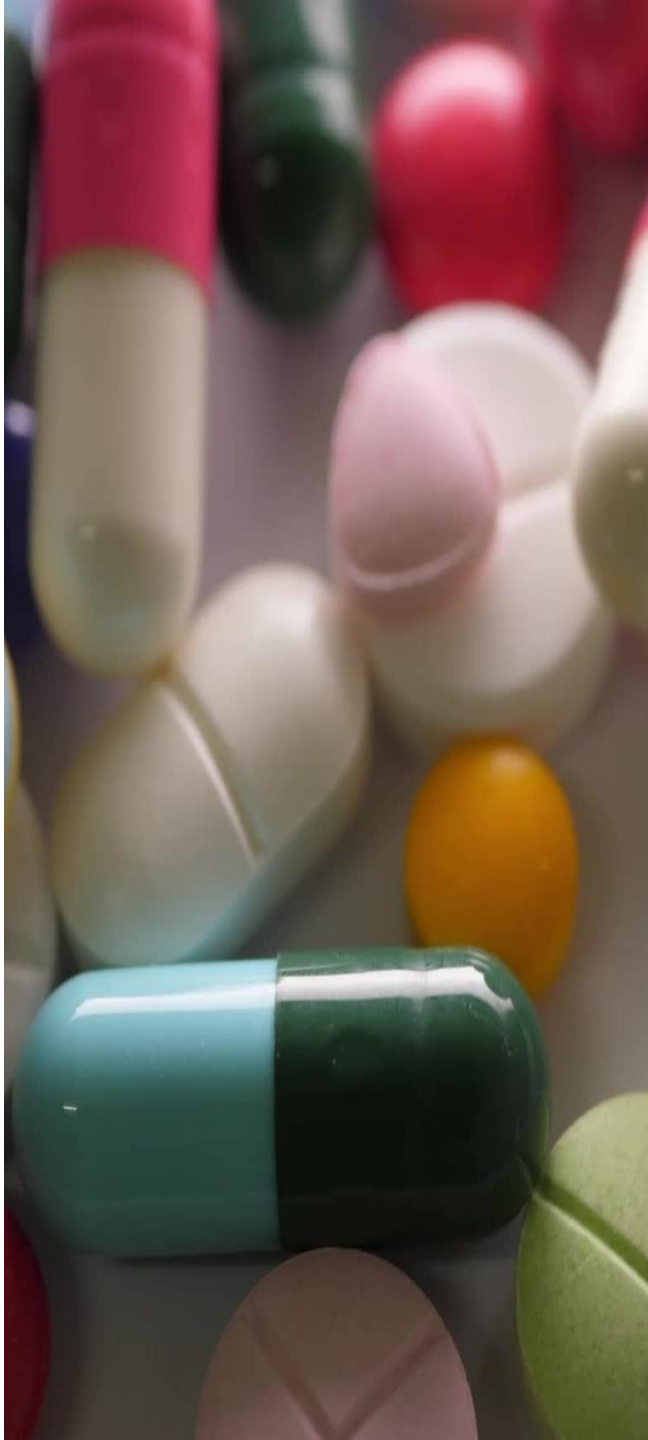
Drug Eruptions

By Bayan Al- Aoran & Rand Farhat

- Cutaneous adverse reactions account for a third of all adverse reactions to drugs. (common)
- Drugs can cause adverse reactions in several ways:

1. *changing normal skin function*
2. *exacerbating an existing dermatosis*
3. *causing an idiopathic dermatosis such as urticaria*
4. *causing a specific drug eruption (lichenoid drug rashes)*
5. *precipitating a severe drug reaction (toxic epidermal necrolysis).*



- Identifying the culprit drug requires careful history-taking and skin examination

- The most important step is **identification and withdrawal** of the culprit medication.

- Ranges from mild reactions that resolve quickly (maculopapular exanthems); to more severe ones that carry considerable morbidity and mortality (Stevens–Johnson syndrome and toxic epidermal necrolysis).

- Diagnosis of drug-induced skin disease may be difficult for a number of reasons:

1. Almost any drug can cause any rash.
2. Unrelated drugs can cause similar reactions.
3. The same medication can cause a different rash in different individuals.
4. Patients may not volunteer information about medicines that they have taken, which they deem not to be relevant (over-the-counter (OTC) preparations and complementary medicines).

History

It is imperative to take a thorough history from patients in whom a drug reaction is suspected.

Eliciting the temporal association of the ingestion of the drug and the onset of the eruption is key.

- ✓ Apart from noting any medications taken for the first time in the 3months prior to the appearance of the rash, patients should be specifically asked about any recent changes to brand, dosing or preparation of long-term medications.

- ✓ Patients may not volunteer information about drugs they have taken that they assume are not relevant, such as paracetamol taken for a headache, or an antihistamine taken for hay fever.

- ✓ Both generic and brand names of all drugs should be recorded, and the patient should be asked about any history of sensitivity to medications.

- ✓ Knowledge of whether the patient has been previously exposed to suspected culprit drugs is also relevant.

Examination

The patient should be exposed fully to allow complete examination of the skin.

The morphology of the rash should be described, in addition to the distribution of the eruption

Special attention should be paid to **the mucosal sites** – eyes, mouth, genitalia – as involvement at these sites can indicate one of the **severe cutaneous adverse reaction (SCAR) syndromes.**

Careful examination of the appendageal structures such as hair, nails and teeth should also be carried out as these can be affected by certain medications.

Investigation

Careful history and examination will provide all the necessary clues to make a confident diagnosis of a drug rash.

A skin biopsy **can be** helpful to confirm the diagnosis, but the result of this is likely to be delayed following an acute presentation, and so action based on clinical assessment will usually precede this.

- ✓ Exclusion of differential diagnoses such as infection may require other investigations such as blood tests (WBCs & CRP).

- ✓ There are no consistently reproducible diagnostic tests which confirm specific drug allergy in the convalescent period; however
    - certain investigations such as measurement of specific IgE, patch testing, intradermal testing and in vitro tests such as lymphocyte transformation tests and cytokine release assays may be helpful.

❖ Patch testing

- ✓ amount of the medication is applied to the skin in a suitable vehicle such as **petrolatum**.
- ✓ best performed **at least six weeks post-resolution of the eruption.**
- ✓ The best positive predictive value has been observed when testing for allergy to **abacavir, anticonvulsants, and beta-lactam antibiotics.** However, the sensitivity of patch testing alone is not great enough to conclusively exclude reactions.

❖ Intradermal testing

- ✓ Injection of the suspected agent into the dermis in the convalescent period is sometimes performed as an adjunct to patch testing.
- ✓ Using both modalities may **improve sensitivity in confirming a causative agent**.

❖ In vitro testing

In ***experimental settings***, a blood sample may be taken from a patient who is experiencing a drug reaction – the patient's lymphocytes are incubated with a series of suspected culprit drugs.

- ✓ Markers of activation of those lymphocytes are then measured, and this has been used as a testing modality in the investigation of drug reactions (lymphocyte transformation test).
- ✓ Measurement of cytokines such **as IFN-γ, IL4, TNF, and granulysin released by patient lymphocytes** in response to in vitro exposure to suspected culprit drugs have also been used to confirm causality (cytokine release assays).
- ✓ Blood samples are best taken as early as possible in the course of the illness.

Classification of drug reactions in the skin

- **Pathogenetically**, drug reactions in the skin may be classified as *immune-mediated or non-immune-mediated.*
- *Non-immune-mediated rashes include accumulation of medications* in the skin (causing pigment changes), instability of mast cells (causing histamine release), slow acetylators (metabolism of drugs affected) and photosensitivity reactions (increased susceptibility to UV light).
- *Immune-mediated rashes are the most common and include* hypersensitivity reactions from types I to IV.

Type I immediate reactions	usually mediated by IgE or drug-specific receptors bound to mast cells and other immune cell membranes, tend to manifest in the skin as urticaria or angio-oedema.
Type II reactions cytotoxic reactions	result in cutaneous purpura.
Type III (immune complex-mediated)	lead to cutaneous vasculitis.
Type IV delayed hypersensitivity reactions	the most common group of drug rashes resulting in generalized exanthems, phototoxic rashes and severe drug reactions such as toxic epidermal necrolysis (TEN).

- However, drug reactions in the skin may also be **classified clinically :**

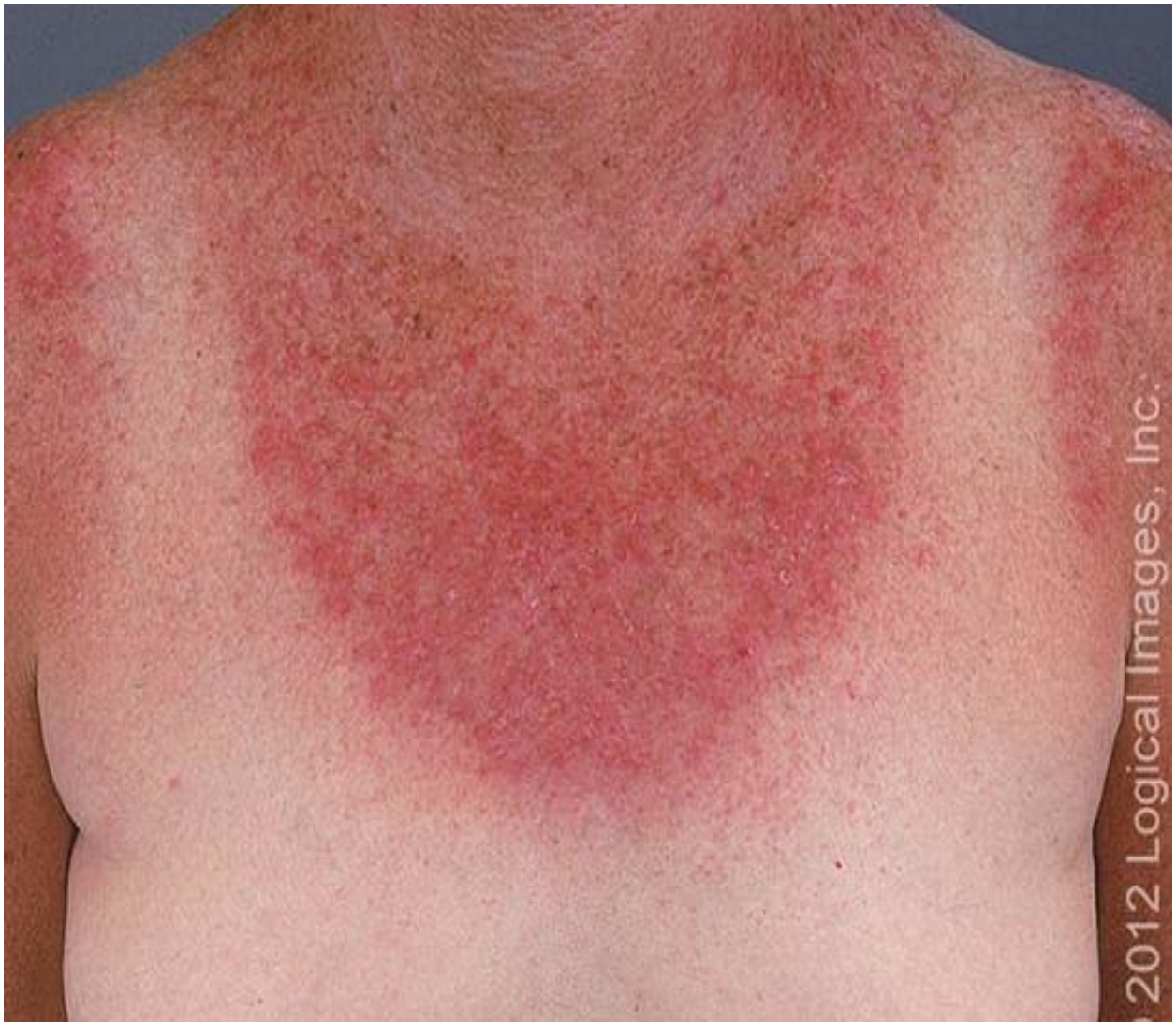
1. **Drugs which alter normal skin function.**
2. **Drugs which exacerbate an existing dermatosis.**
3. **Common drug-induced rashes**
4. **Severe drug-induced rashes**

Drugs which alter normal skin function

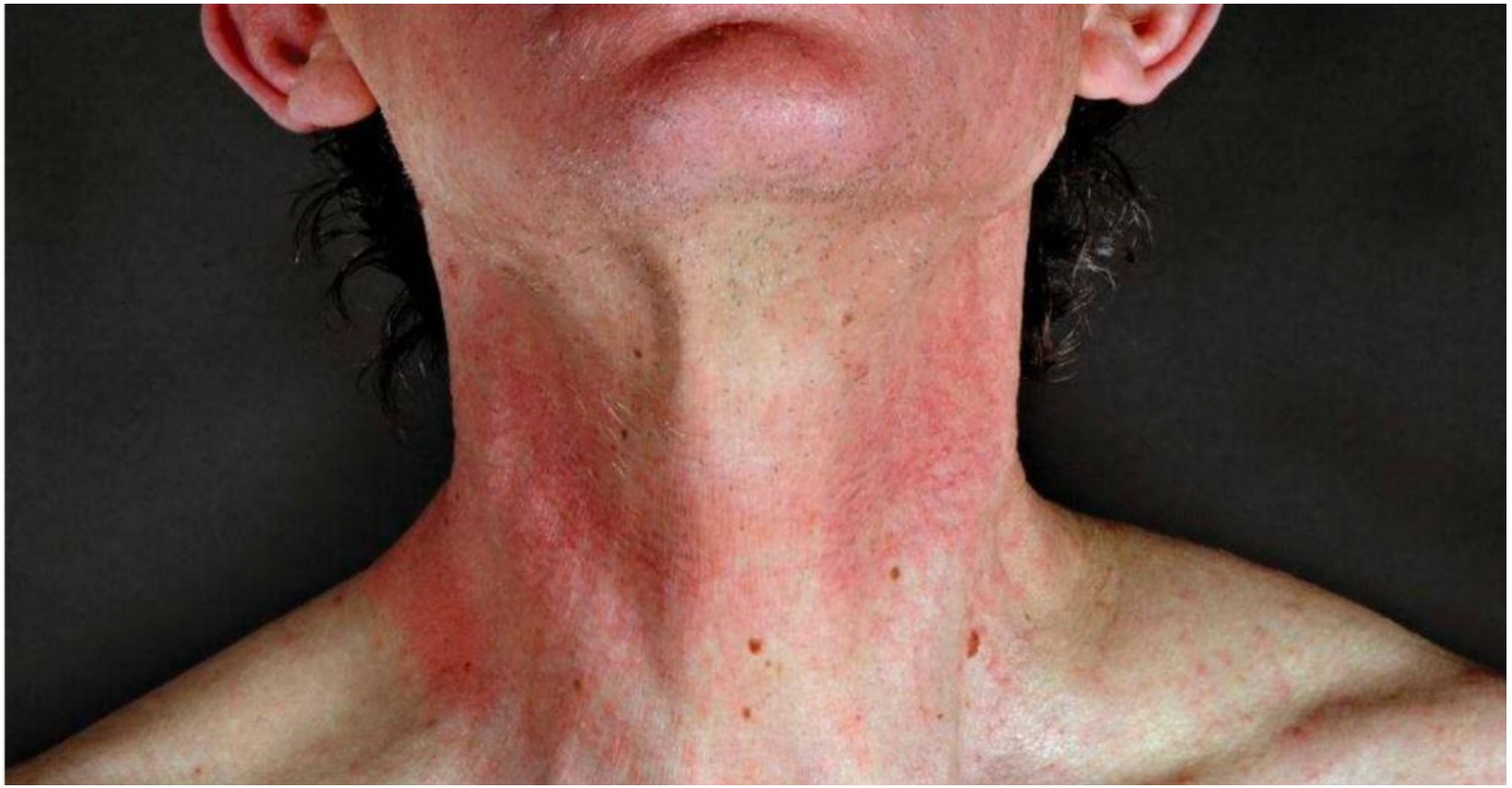
A-Photosensitivity

- Drugs may cause excessive sensitivity to light in two ways: phototoxic reactions and photoallergic reactions.
- Phototoxic reactions are the more common and resemble sunburn and maybe blister.
  - ❑ The onset will be fast (within 5–15 h of taking the drug and exposure to light) and recovery is quick on withdrawal of the medication.
- Photoallergic reactions are usually eczematous, but may be lichenoid, uriticarial, purpuric or bullous.
  - ❑ The onset may be delayed by weeks or months following introduction of the medication, and similarly, recovery may be slow on withdrawal.

Phototoxic eruption

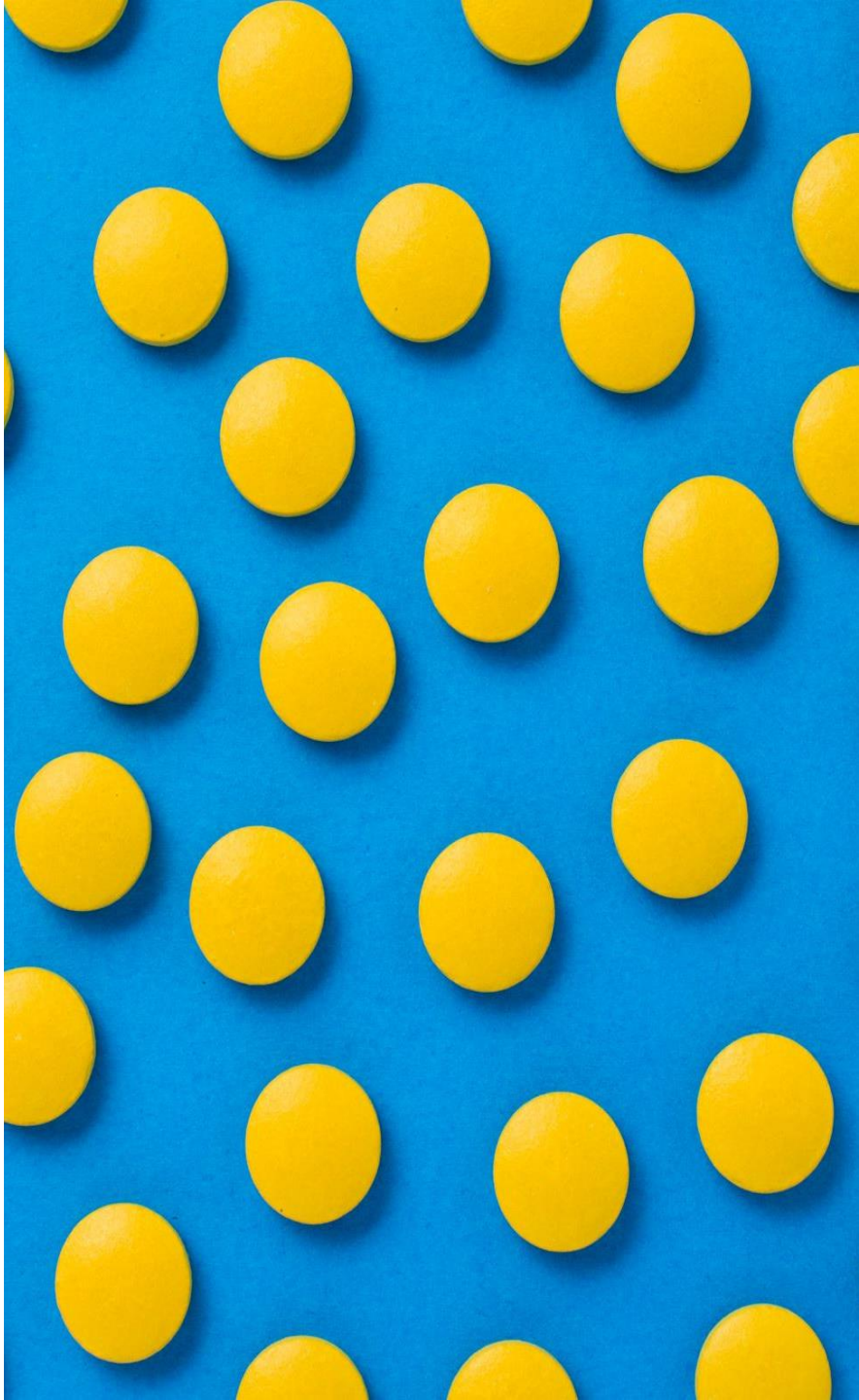


Photoallergic (photosensitive) eruption



- Drugs causing photosensitivity are:

  - Amiodarone
  - tetracyclines
  - calcium channel blocker
  - diuretics
  - voriconazole, itraconazole
  - terbinafine, ritonavir, saquinavir.



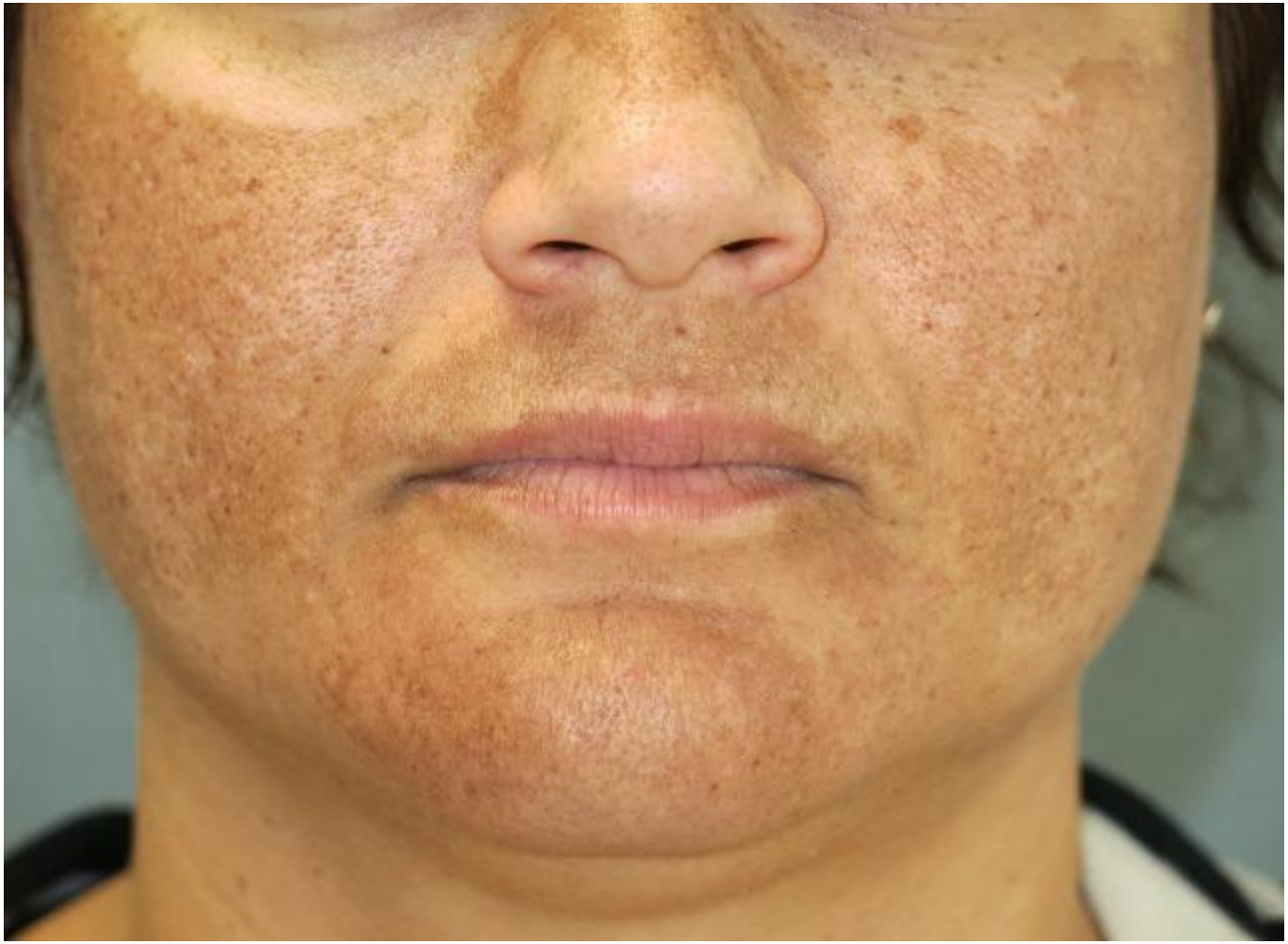
B-Pigmentation

- **Hyperpigmentation, hypopigmentation and discolouration** are all associated with certain drugs : Chlorpromazine, phenytoin, hydroxychloroquine, cyclofosphamide, bleomycin, amiodarone, clofazimine, minocycline, mepacrine

- The pigmentary change may require light exposure to manifest.

- Common examples would include
  - ✓ the development of melasma in female patients taking the oral contraceptive pill
  - ✓ the facial blue-black pigmentation which may be caused by amiodarone
  - ✓ Tetracycline antibiotics may also cause a slate-grey pigmentation

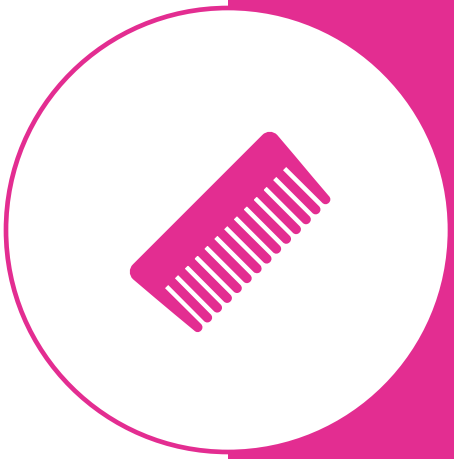
Melasma



Amidarone

C-Hair (Excessive hair / hair loss)

1-*Excessive hair*



- *Hypertrichosis is the growth of hair at sites which* are not normally hair-bearing
- *Hirsutism* is excessive growth of hair in the male pattern of hair growth, especially in women.

➢ Both hormonal and non-hormonal treatments may bring about this effect; the most commonly implicated would include ciclosporin and phenytoin.

Hypertrichosis

hirsutism

2- Hair loss

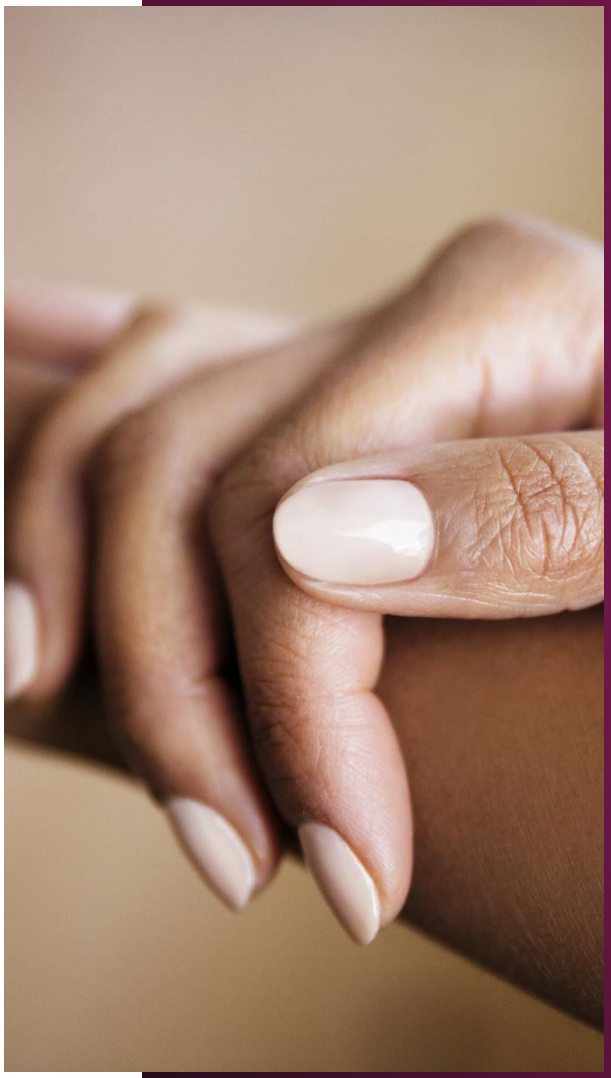
- Loss of hair may be dramatic or insidious in onset, and if the latter, may not be immediately noticed by the patient. The **temporal relationship** between the onset of the hair loss and the introduction of the medication **depends on the part of the hair cycle which the drug is interfering with**.

  - Cytotoxic agents interrupt the anagen ('growth') phase of the hair cycle, and so **loss is rapid** and complete
  - delayed, **insidious hair loss** generally results from interference with the telogen ('shedding') phase of the hair cycle.

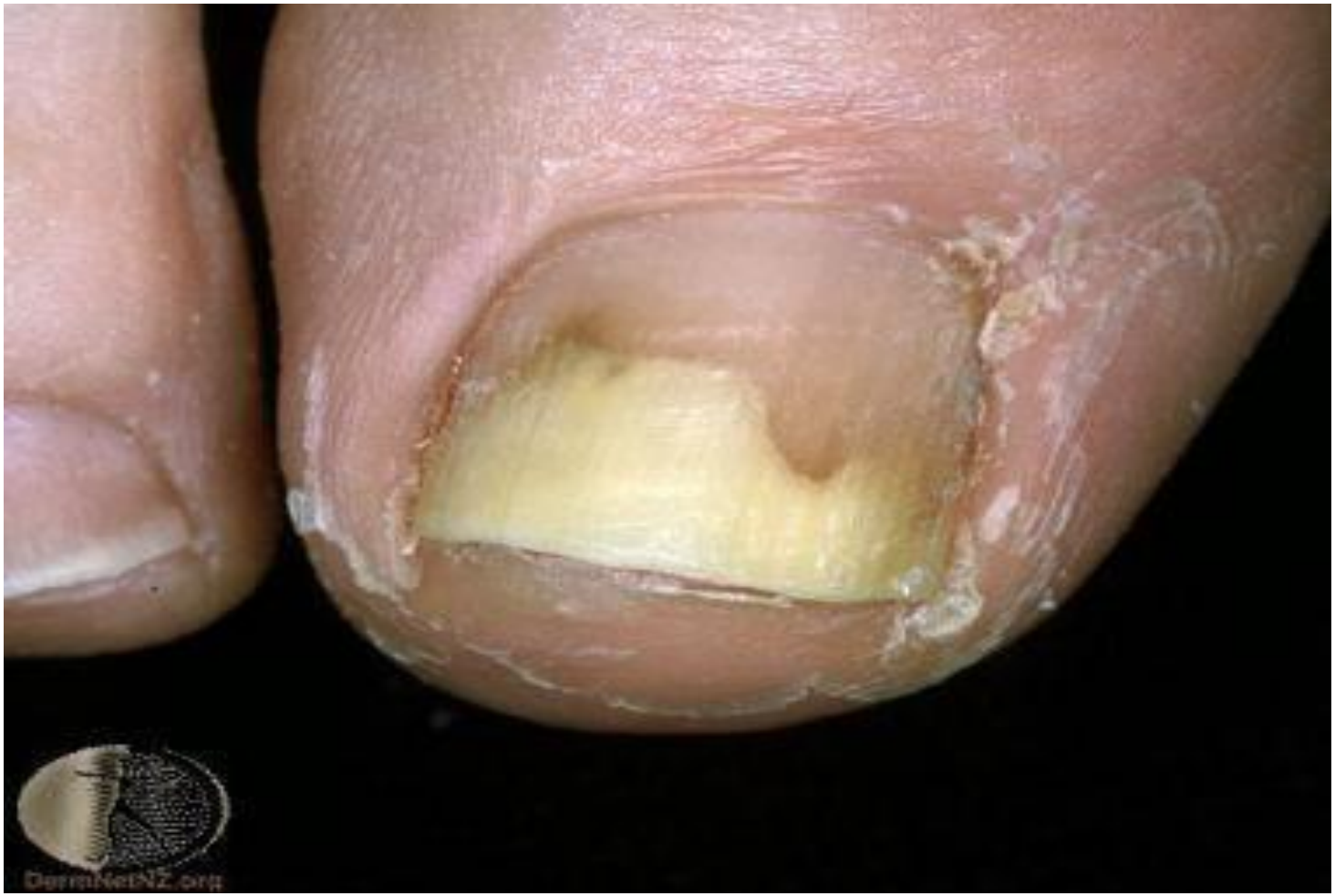
- Drugs such as acitretin, statins and anti-thyroid drugs may have this effect
  - Androgenic drugs promote shrinkage of the hair follicles and shortening of anagen (hair growth phase) , and so can cause hair loss. An example would be exogenously administered testosterone used to treat hypogonadism in male patients.

D-Nail

- Nails may become discoloured with use of mepacrine or hydroxyurea.
- Onycholysis, which is separation of the nail plate from the nail bed, may be caused by cytotoxic agents.



Onycholysis



Hydroxyurea treatment

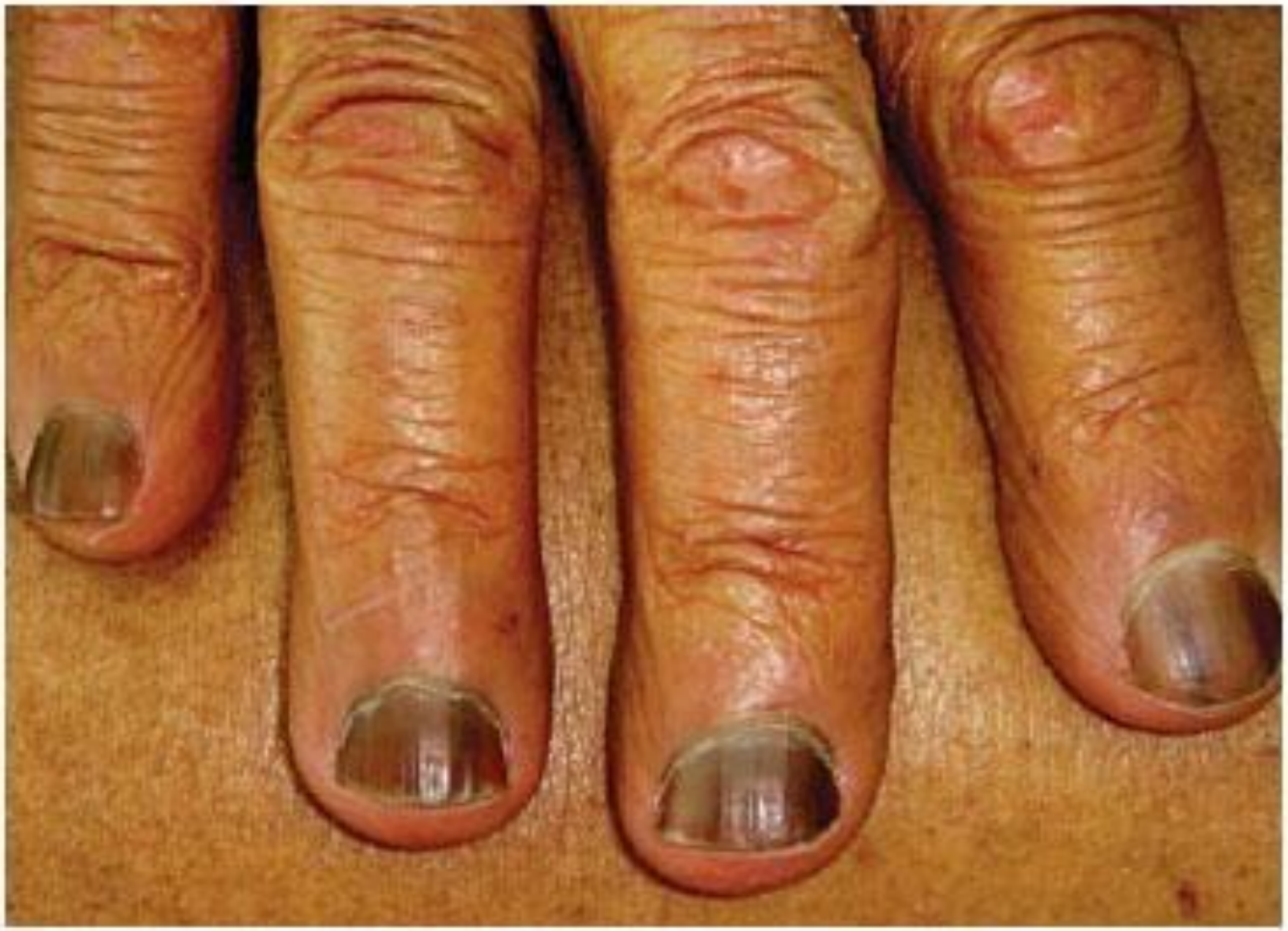


FIGURE 2: Melanonychia on right hand

2- Drugs which exacerbate pre-existing dermatoses

- exacerbate skin conditions which the patient already has

1. **Eczema** – statins and diuretics (hydrochlorothiazide)

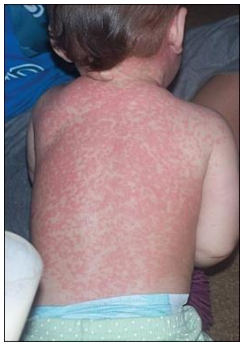
2. **Acne** – OCP(progesterone-only pills) ,Corticosteroids, ciclosporin and anti-epileptics.

3. **Psoriasis** – beta blockers, lithium and antimalarial medications, newer drugs such as ACEi, alcohol.

4. **Urticaria** – NSAIDs and opiate analgesics in a susceptible individual*
   - ✓ ACE inhibitors and angiotensin receptor blockers may exacerbate angio-oedema, this is non-allergic urticaria/angio-oedema.

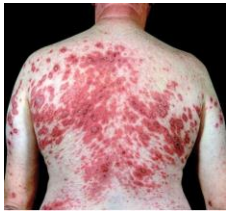
*by lowering the threshold for mast cell degranulation.

3-Common drug-induced rashes

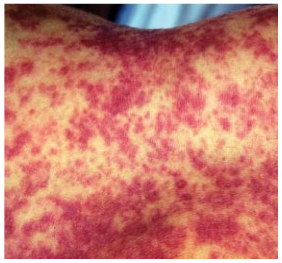


Drug-induced exanthems

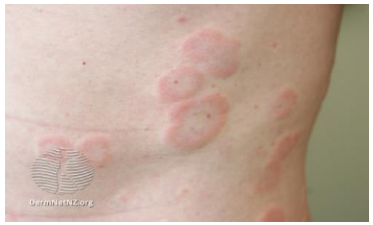
Drug-induced lupus



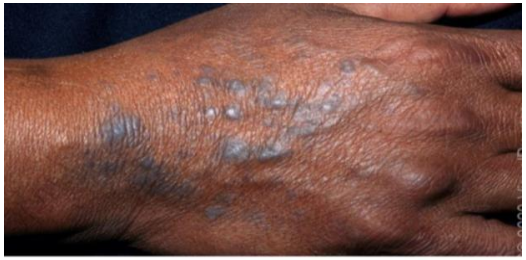
Drug-induced vasculitis



Urticaria/angio-oedema

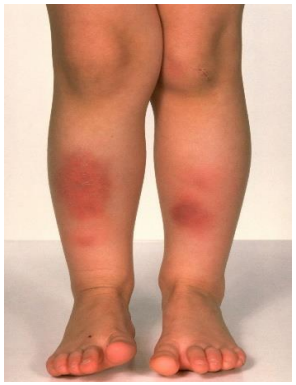


Lichenoid drug eruptions

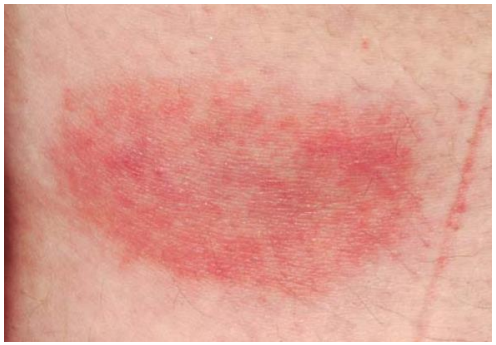


icaly, flat-topped, violaceous papules and plaques on the dorsal hand secondary to a drug.

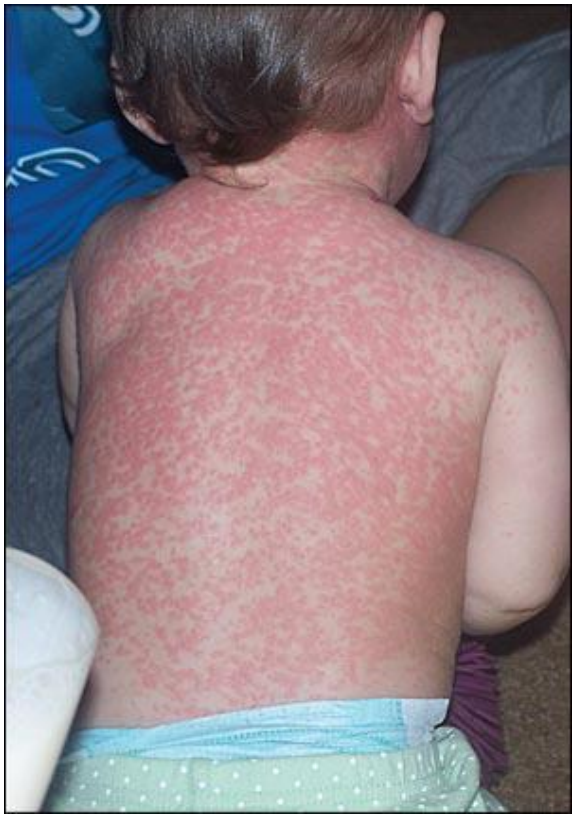
Erythema Nodosum



Fixed Drug Eruption

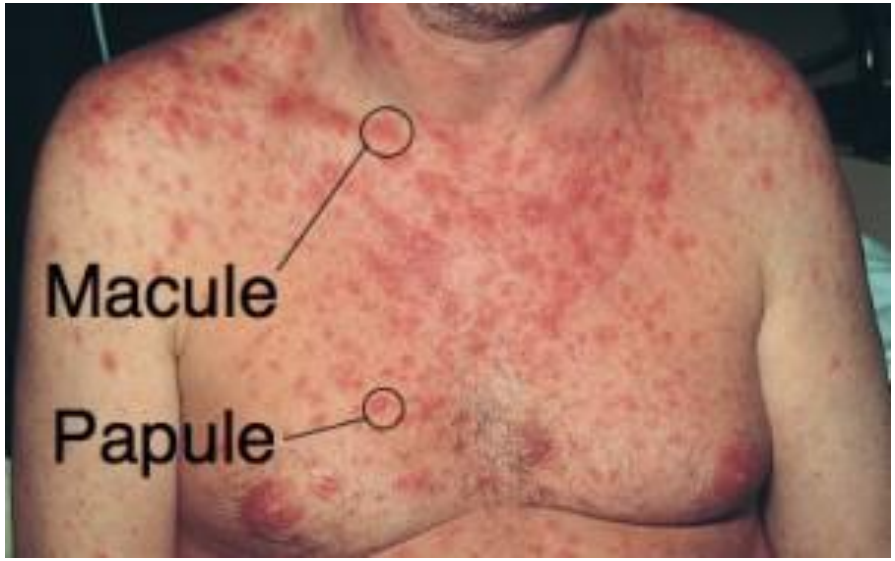


A- **Drug-induced exanthems**



- M/C cutaneous reaction to a drug >> exanthem (meaning a widespread rash)
- M/C drugs >> Antibiotics , anti-hypertensive agents and cholesterol-lowering drugs.
- Rashes may be ***morbilliform*** (resembling measles) *or* ***maculopapular*** (consisting of a mixture of raised and flat areas).

- ✓ Any drug may cause a drug-induced exanthem
- ✓ Onset — within **7–10 days** of starting the drug.
- ✓ delayed-type hypersensitivity reaction



- May be symptomatic with burning, itch or discomfort arising from the skin.
- Re-exposure to a culprit drug may provoke a reaction in the skin more quickly, because of the presence of **memory T cells** in the lymph nodes.
- The proportion of the body surface area (BSA) involved may vary, and in cases where it exceeds 90%, the patient may be described as erythrodermic.
- Trx following drug withdrawal >> potent topical corticosteroid and emollient will help alleviate discomfort and itch.

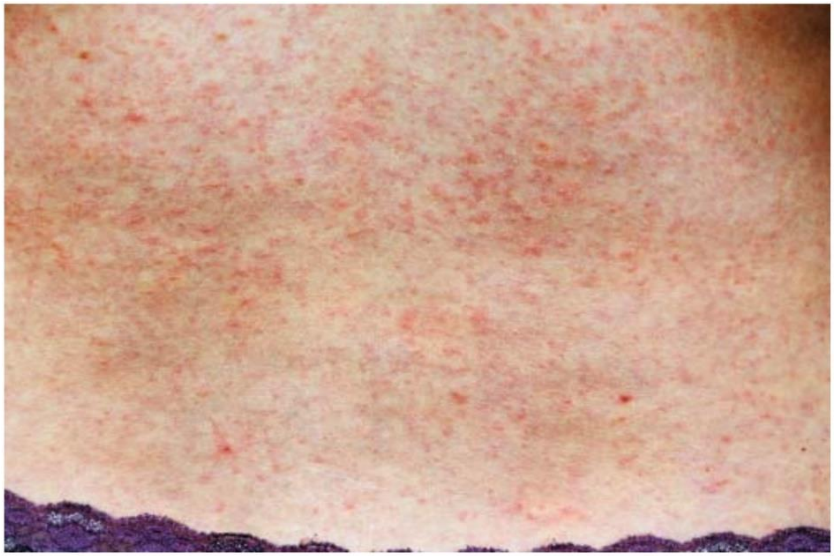
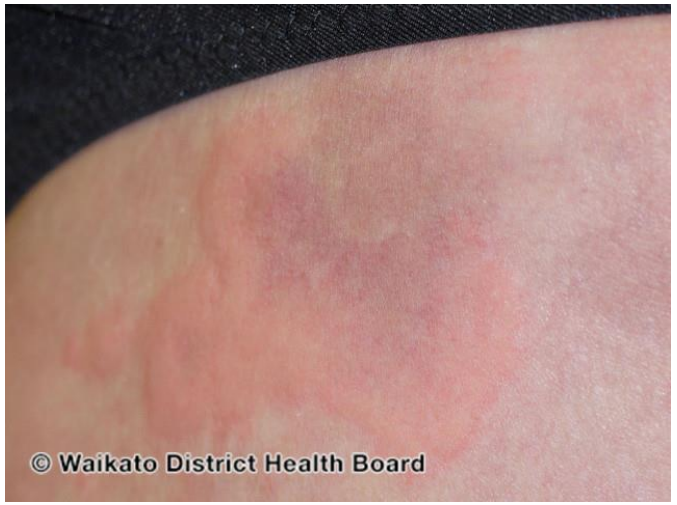
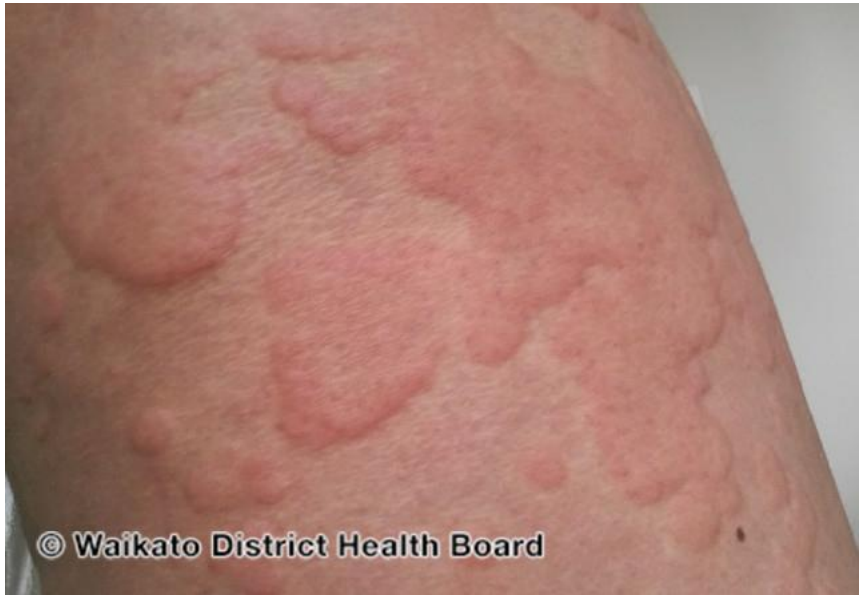


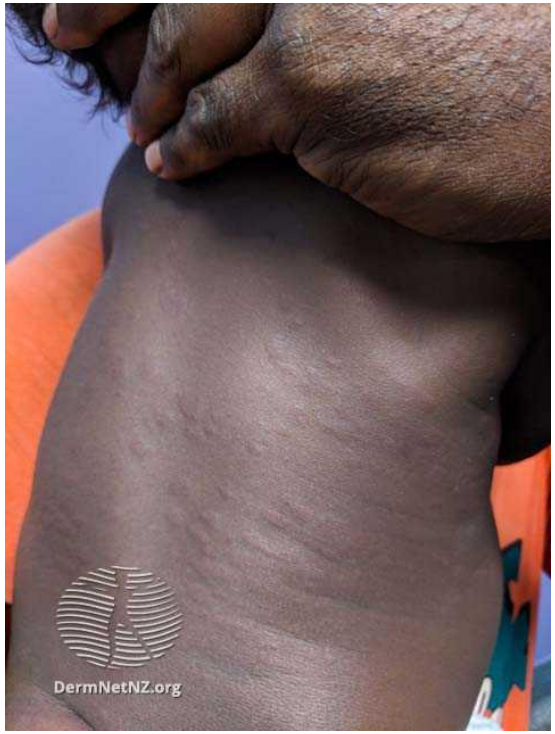
Figure 7.3 Maculopapular exanthem.

B-**Urticaria/angio-oedema**

- <u>Raised, red itchy wheals</u> in the skin.
- Occur alone or in combination with angio-oedema
  - The latter may be serious, and when it involves the soft tissue of the airway, may cause respiratory embarrassment.

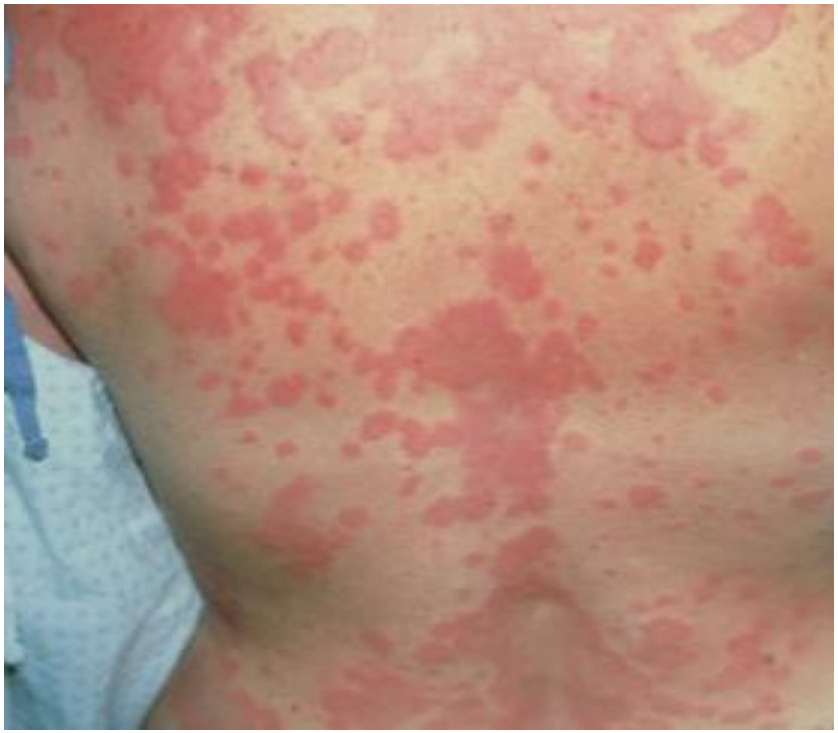






- Non-allergic or allergic; in the latter, a reaction occurs between a drug or its metabolite and a specific mast cell-bound IgE.

- A drug may cause **anaphylaxis**, occurring rapidly after drug ingestion (type I hypersensitivity) or may be delayed by a number of days following exposure to the drug (type IV hypersensitivity).



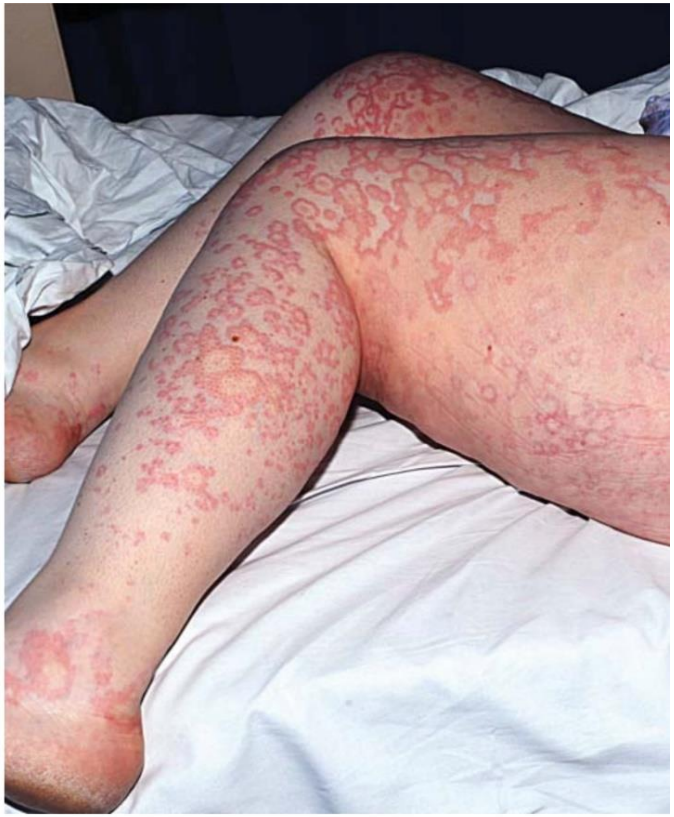
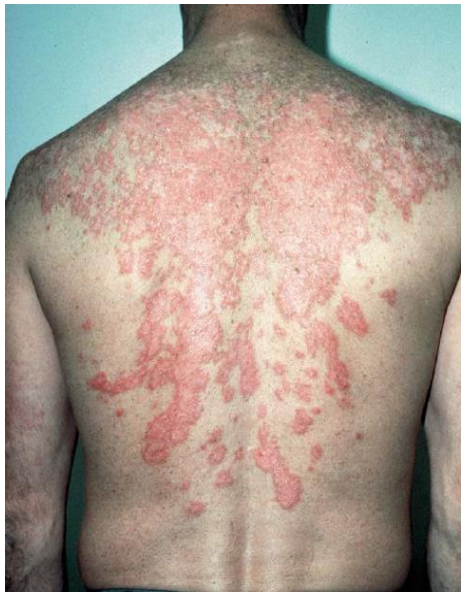
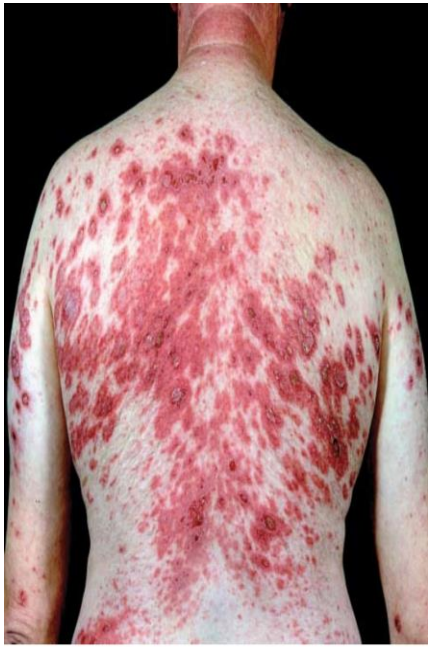


Figure 7.4 Urticaria secondary to penicillin.

C- **Drug-induced lupus**



- ✓ Eruption indistinguishable from cutaneous lupus – in particular, the rash of **sub-acute cutaneous lupus** (SCLE) .
- The **patient <u>does not have any pre-existing autoimmune disease</u>**, and the condition remits on withdrawal of the culprit drug.



- M/C >> **hydralazine, procainamide, quinidine, isoniazid, diltiazem, and minocycline .**

> "My Two HIPS": Methyldopa/Minocycline, TNF-α inhibitors, Hydralazine, Isoniazid, Procainamide/Phenytoin, and Sulfa drugs are triggers for DILE.

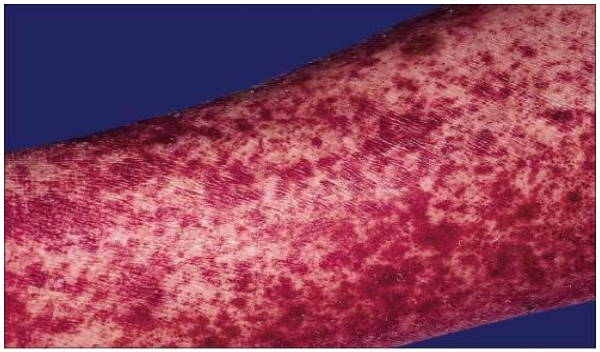
  - but a recent study named **terbinafine** as the most common culprit.(antifungal)

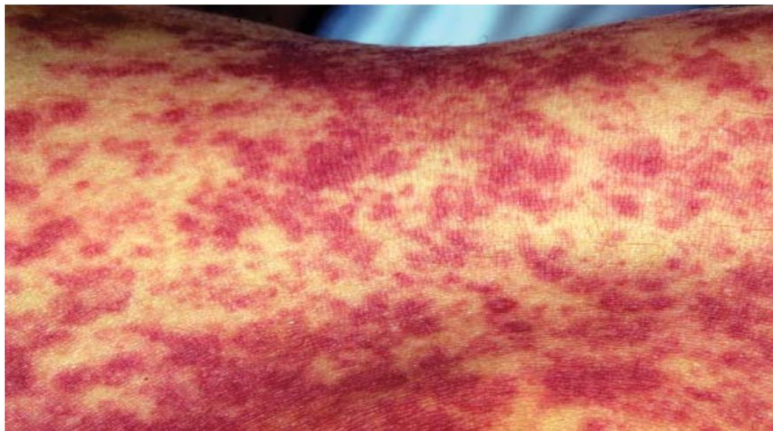
- **Antihistone antibodies** are present in *>95% of cases,* dsDNA is usually negative and complement levels are normal.

D- drug induced vasculitis

- Purpuric eruption, usually predominantly the lower limbs.
- As viral and bacterial infections may also cause vasculitis, it is often difficult to ascribe causality to a drug, as in cases where an antibiotic is suspected, the patient may also have had a recent infectious episode.
- In practice, in the absence of overt clinical signs of infection, causality is best determined by withdrawing the suspected culprit drug; if this brings about resolution of the vasculitis, then this adds weight to the diagnosis of a drug-induced phenomenon.

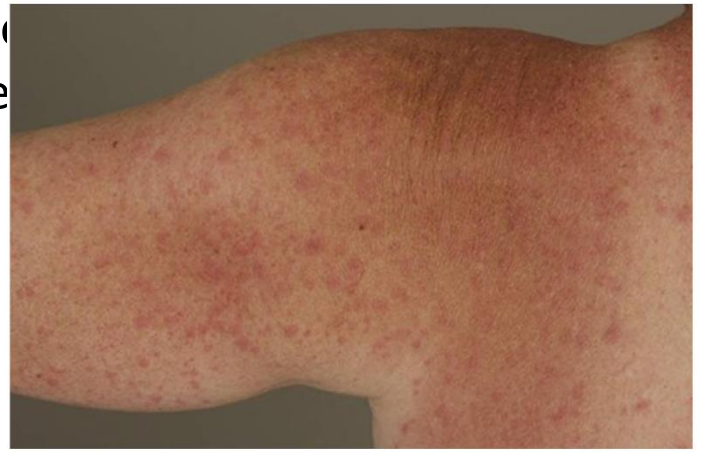
- Drugs associated with vasculitic eruptions include **antibiotics, anticonvulsants and NSAIDs.**





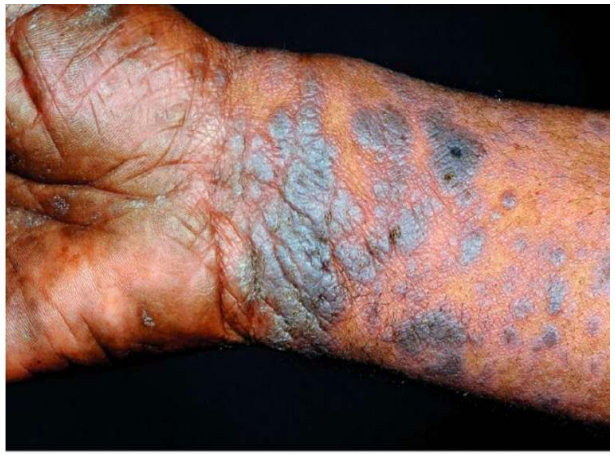
E- Lichenoid drug eruptions

- Resemble idiopathic lichen planus but may not be confined to the classic sites of predilection of the latter. The sites are forearms, the neck and inner thighs, and can appear anywhere.
- They consist of purplish papules which may have a lace-like white change on their surface
- Onset—months, so difficulties in dx.



Flat, erythematous/violaceous papules on the shoulder and upper arm of a patient with lichenoid drug eruption.

- M/C >> **Gold, mepacrine, tetracyclines, diuretics, amlodipine, carbamazepine, propranolol, NSAIDs, ACE inhibitors, proton-pump inhibitors, statins**



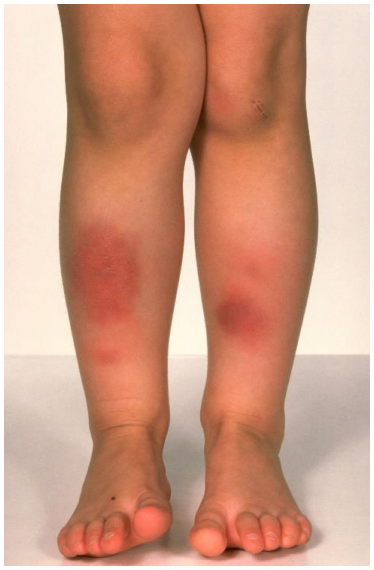
- Resolution can be slow and take up to 2months, and the **post-inflammatory hyperpigmentation left behind may be dramatic.**

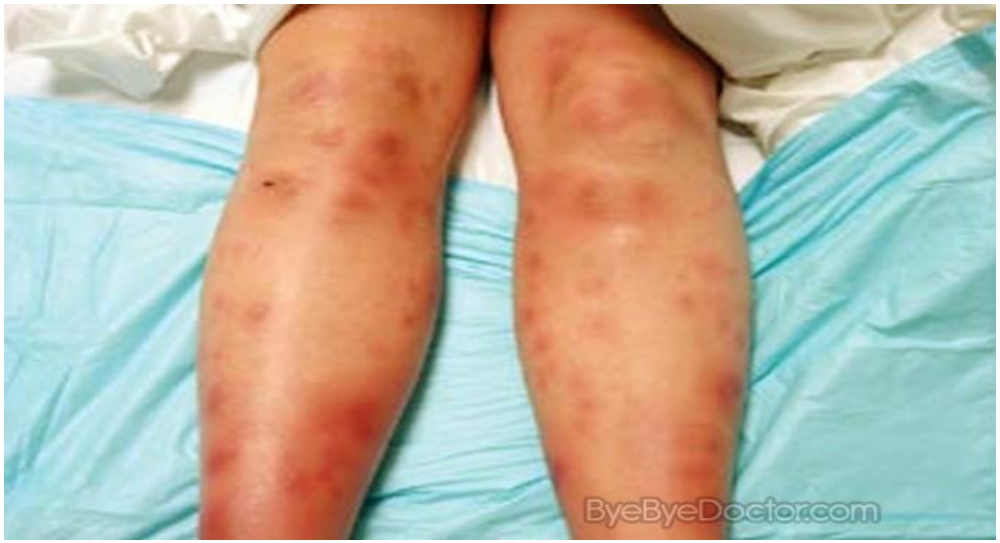
F- **Erythema nodosum**

- **Tender, nodular eruption**—appears on the anterior aspect of the legs.
- Histologically— **septal panniculitis** (inflammation in the subcutaneous fat).

✓ Can also be due to— infective and inflammatory triggers(such as TB, *Yersinia infections, RA, lupus* and IBD).

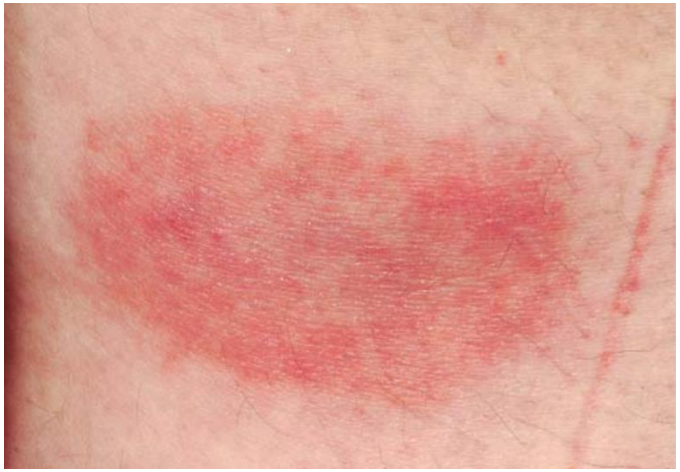
- M/C— **OCP, penicillin and sulphonamide antibiotics and salicylates.**

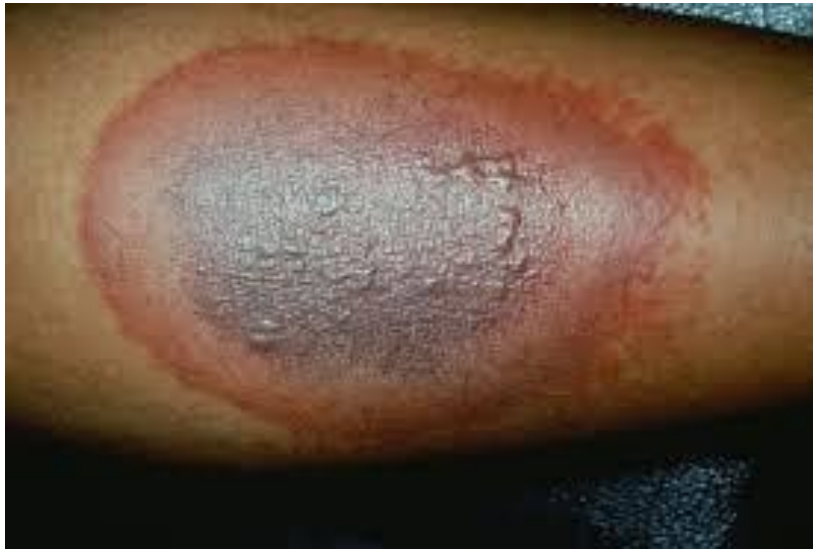




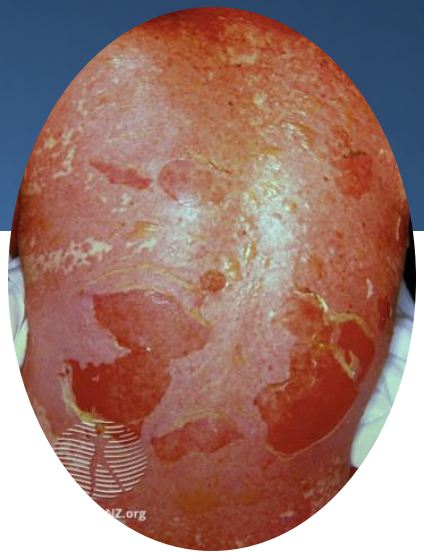
G- **Fixed drug eruption**

- One or more inflammatory patches appear **at the same cutaneous or mucosal site on each occasion** that the patient ingests a culprit drug.
- Time frame — vary from 2 to 24 h.
- Common sites —torso, hands, feet, face and genitalia.
- The patches resolve sometimes leaving post-inflammatory hyperpigmentation in the skin.
- Any drug, but M/C >> **Antibiotics, NSAIDs, oral contraceptive, barbiturates.**

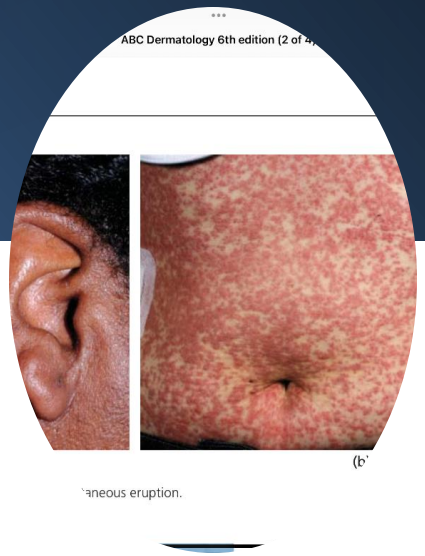




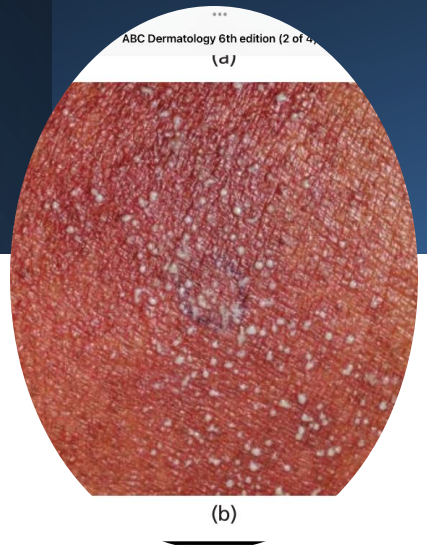
4-Severe drug reactions in the skin



Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)



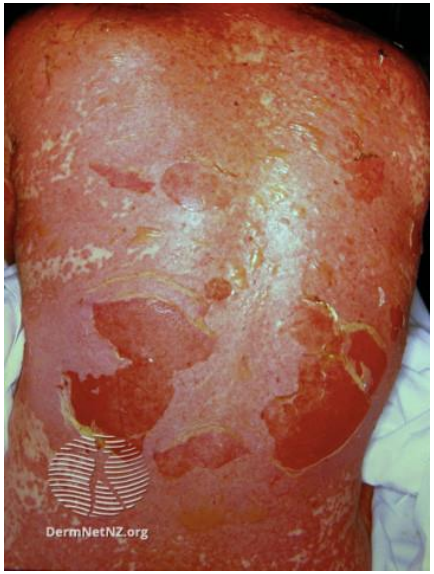
Drug reaction with eosinophilia and systemic symptoms (DRESS)

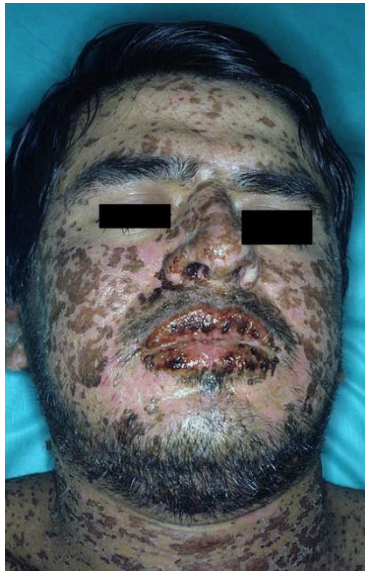


Acute generalized exanthematous pustulosis (AGEP)

A-**Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)**

- Rare, life-threatening drug-induced hypersensitivity reactions in the skin and mucous membranes.
- Characterized by widespread, painful areas of **epidermal detachment**, and **erosions of the mucous membranes**, including eyes, mouth, genitalia and respiratory tract.
- **M/C — anticonvulsants, allopurinol, HIV medications, and antibiotics particularly sulphonamide antibiotics.**





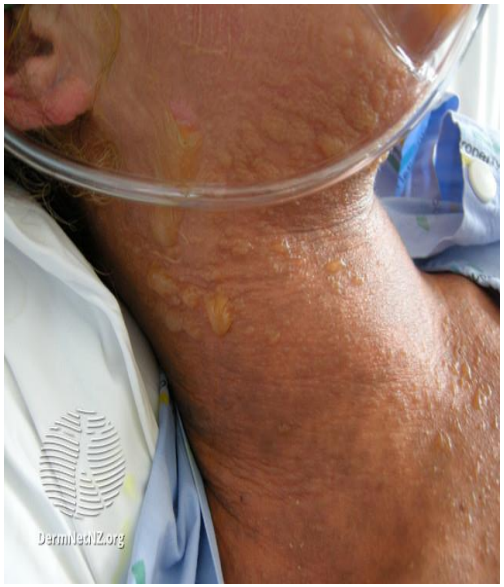
Disease course

Fever/malaise/ coryzal sx → Skin pain → Rash

- ✓ The appearance of the eruption may be preceded by a prodrome of fever, malaise and coryzal symptoms, and skin *pain is* often the first cutaneous manifestation, prior to the appearance of the rash.

SJS vs TEN

BSA involved
<10%…….SJS
>30%…….TEN



- ✓ The terms SJS and TEN represent points along a spectrum of severity, with SJS classically denoting *<10% BSA detachment,* TEN indicating *>30% BSA involvement, and the term 'SJS–TEN* overlap' being used to describe cases with between 10% and 30% loss.

Mortality from TEN may be as high as 90% and is estimated using the SCORTEN tool

Table 7.3 SCORTEN Parameters

SCORTEN parameters (1 point for each)	
Age (≥40 years)	
Heart rate (≥120 bpm)	
Cancer/haematological malignancy	
Body surface area (BSA) involvement (>10%)	
Serum urea (>10 mmol/L)	
Serum bicarbonate (<20 mmol/L)	
Serum glucose (>14 mmol/L)	
SCORTEN SCORE	Mortality
0–1	3%
2	12%
3	35%
4	58%
≥5	90%

➢ Management in the acute phase

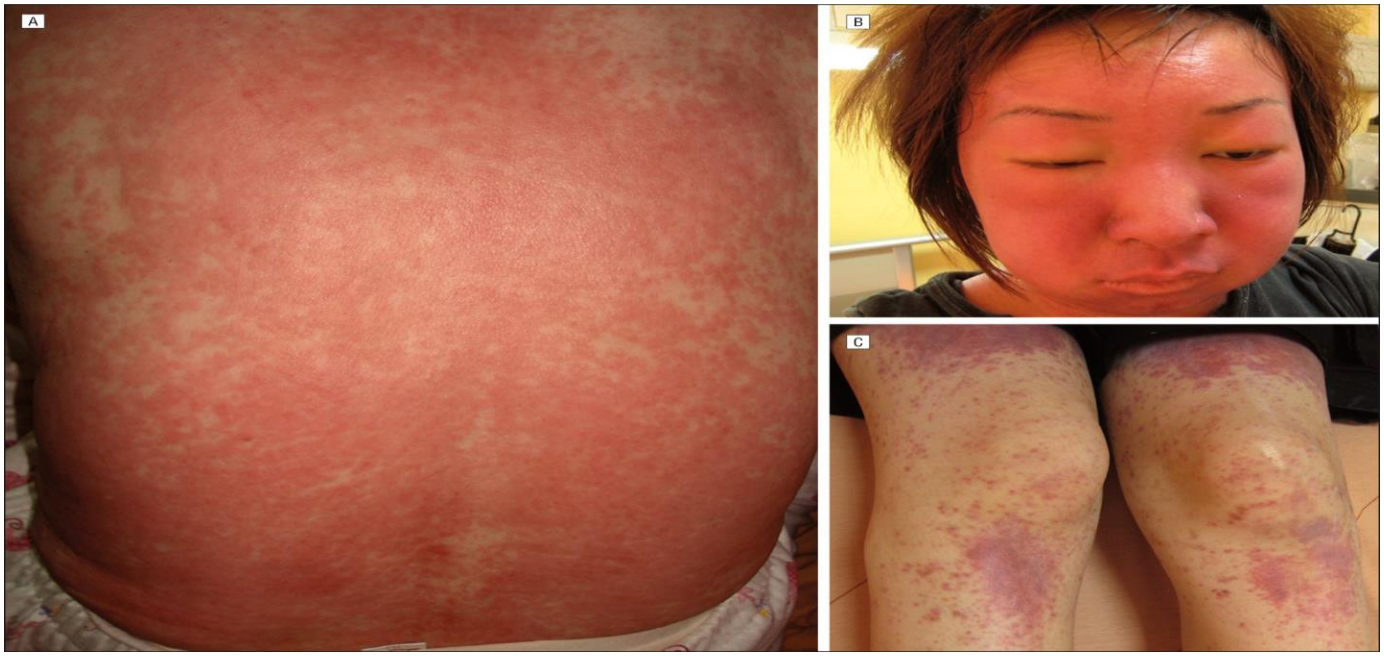
1. Stop the culprit drug
2. Supportive care; high dependency care in ICU, with organ support as dictated by clinical state.
3. The use of number of active agents in the treatment of SJS/TEN has been described, including intravenous immunoglobulin, ciclosporin, corticosteroids, thalidomide, and infliximab, but there is insufficient evidence to conclusively support the use of them.

- In addition to expertise from dermatologists and intensive care physicians, specialist input from ophthalmology, oral medicine, urology and gynaecology may be required for site-specific involvement.
- Skin loss and fragility demand specialist dermatology nursing care, with anti-shear handling, non-adherent dressings, and careful attention to antisepsis to prevent systemic infection.
- Expectant management of mucosal involvement will help prevent serious sequelae of the illness .

B-Drug reaction with eosinophilia and systemic symptoms (DRESS)

- Clinical features:

1. a characteristic rash (maculopapular exanthema)
2. associated with head & neck oedema, fever and lymphadenopathy
3. eosinophilia
4. involvement of one or more solid organs (usually the liver).

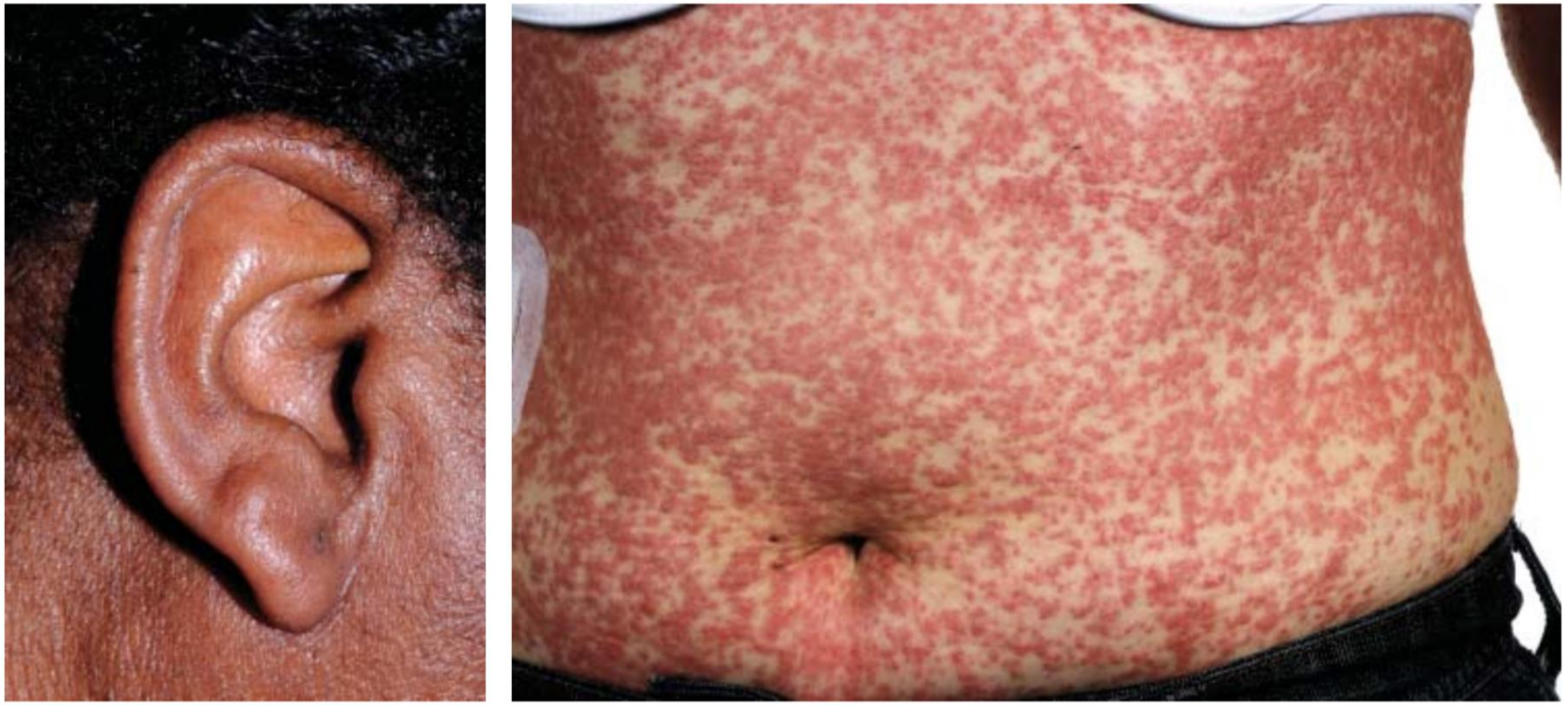


- M/C drugs >> antibiotics, anti-retrovirals, imatinib (Gleevec), NSAIDs, ACE inhibitors, calcium channel blockers, terbinafine.
  - ✓ with the **anticonvulsants and allopurinol** accounting for a large proportion of cases.

- Mortality is estimated at 5%, this being largely attributable to the small number of cases who develop **fulminant liver failure** in the context of DRESS.
- Other solid organs may also be involved, including the pancreas, the kidneys, the lungs, the heart and thyroid gland.
- The latency period following drug exposure is generally more protracted that in other drug-induced syndromes, being 15–60 days. For this reason, the diagnosis is often overlooked, and symptoms of rash, fever and lymphadenopathy attributed incorrectly to infection.

- Management

1. Withdrawal of the offending drug
2. Administration of corticosteroids; Topically —mildest cases, but generally **either oral** corticosteroids prednisolone, **or intravenously** methylprednisolone will be required.



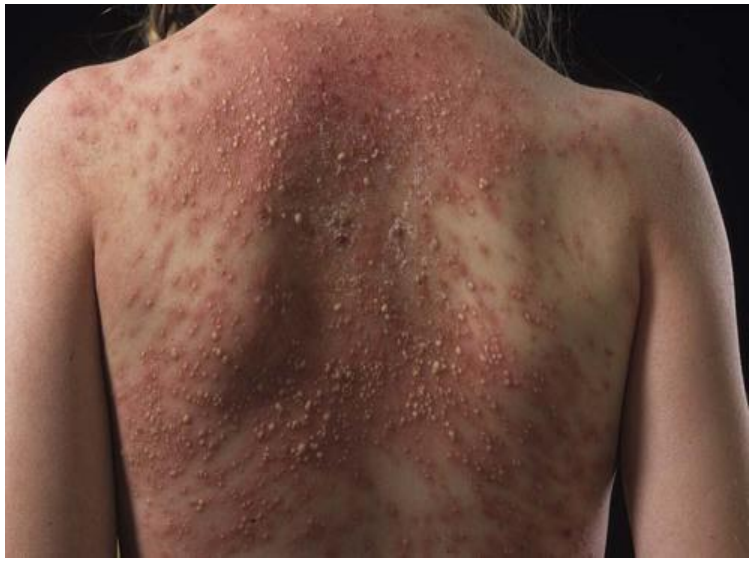
DRESS swollen ears. (b) DRESS cutaneous eruption.

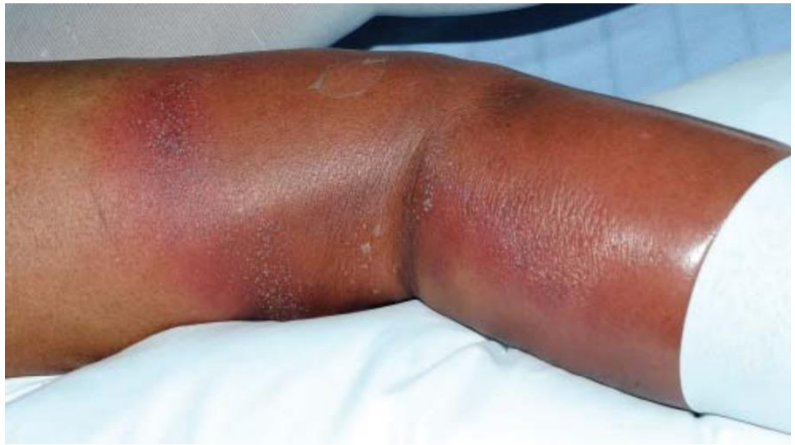
	DRESS	SJS/TEN
Latency	2-8 weeks	4-28 days
Rash	Morbilliform	Painful erythematous macules with purpuric centers → vesicles/bullae → sloughing
Mucosal involvement	50% have mild mucosal involvement, rarely with erosions	>90% have severe mucosal involvement with bleeding at 2 or more sites
CBC	Eosinophilia and atypical leukocytosis	Lympopenia
Hepatitis	50% or more	<10%
Kidney	Tubulointerstitial nephritis	Prerenal azotemia
Skin biopsy	Dermal edema with infiltration by lymphocytes and eos	Full-thickness epidermal necrosis

https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.grepmed.com%2Fimages%2F12669%2Ften-sjs-dermatology-dress-comparison&psig=AOvVaw0_TqnC3ce7faEybubvn48J&ust=1689851802377000&source=images&cd=vfe&opi=89978449&ved=0CBMQjhxqFwoTCIj_gtbSmoADFQAAAAAdAAAAABAD

C- Acute generalized exanthematous pustulosis (AGEP)

- This is a **rare pustular drug reaction** recognisable by the appearance of sheets of non-follicular pustules *(Aseptic pustules)* which have a predilection for the major flexures (axillae, groin and neck) appearing 3–7 days after ingestion of a culprit medication.
- The pustules resolve over 3–7 days, in a phase ***characterised by post-pustular desquamation.***
- **Antibiotics** are the most common culprit drugs.





- The rash may be accompanied by **fever and oedema**, and in a small number of cases by **systemic upset** with involvement of the lungs or the liver .

✓ Recovery may be accelerated by the use of topical or oral corticosteroids.

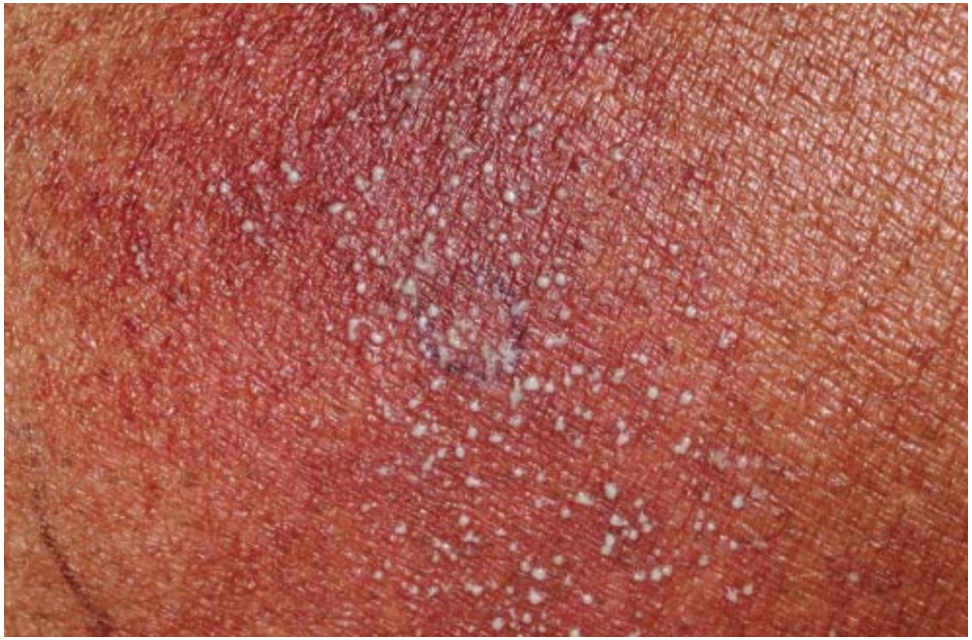


Table 7.2 Time from drug commencement to drug rash.

Time to onset of rash after starting the drug	Cutaneous drug reaction
Hours/days	Urticaria/angio-oedema, contact urticaria, fixed drug eruption, vasculitis/urticarial vasculitis
Weeks	Toxic erythema, Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis, contact dermatitis, erythroderma, photosensitive eruptions
Months	DRESS, Stevens–Johnson syndrome, pigmentation changes (Figure 7.2), contact dermatitis

Drug Eruptions

Alter normal skin function

A- Photosensitivity
- ✓ photo toxic
- ✓ photo allergic

B- Pigmentation
- hypo
- hyper
- discoloration

C- hair
1. Excess
   - hirsutism
   - hypertrichosis
2. loss
   - Rapid / delayed
   - Androgenic / non androgenic drugs

D- Nails
- ✓ onycholysis
- ✓ discoloration

Exacerbate Pre-existing condition

- Eczema
- Acne
- Psoriasis
- urticaria

Common ones

1- Exanthems
2- Urticaria
3- lupus
4- Vasculitis
5- lichenoid drug eruption
6- Erythema nodosum
7- Fixed drug eruption

Severe Drug-induced rashes

- SJS & TEN
- DRESS
- AGEP

Skin reaction	Drugs
Phototoxic Rxn	Amiodarone, NSAIDs, tetracyclines, chlorpromazine
Photosensitive Rxn	Amiodarone, tetracyclines, calcium channel blockers, diuretics, voriconazole, itraconazole, terbinafine, ritonavir, saquinavir
Photoallergic Rxn	NSAIDs, antibiotics, thiazides, anticonvulsants, allopurinol, quinolones, nelfinavir
Pigmentation changes	Chlorpromazine, phenytoin, hydroxychloroquine, cyclophosphamide, bleomycin, amiodarone, clofazimine, minocycline, mepacrine
Urticaria/angioedema	NSAIDs, opioid analgesics, ACE inhibitors, antibiotics, anti-retrovirals (nelfinavir/zidovudine), infliximab, PPI, IV contrast media
Drug-induced lupus Esp. sub-acute cutaneous lupus (SCLE)	**Terbinafine (MC)**, hydralazine, procainamide, quinidine, isoniazid, diltiazem, and minocycline
Drug-induced vasculitis	Antibiotics, NSAIDs,Anticonvulsants (ex phenytoin), ramipril, PPI , allopurinol, thiazides, adalimumab, indinavir
Lichenoid drug eruption	Gold, mepacrine, tetracyclines, diuretics, CCB(ex;**amlodipine)**, carbamazepine, propranolol, NSAIDs, ACE inhibitors, PPI , statins
Erythema nodosum	Oral contraceptives, antibiotics, gold, sulphonylurea
Fixed drug eruption	Antibiotics, NSAIDs, oral contraceptive, barbiturates
SJS/TEN	Antibiotics, anticonvulsants, NSAIDs, anti-retrovirals (indinavir/saquinavir) , allopurinol , barbiturates, ramipril, diltiazem
DRESS	**Allopurinol**, **anticonvulsants**, antibiotics, anti-retrovirals, imatinib (Gleevec), NSAIDs, ACE inhibitors, calcium channel blockers, terbinafine
AGEP "Acute generalized exanthematous pustulosis"	**Antibiotics** "MC", anticonvulsants, antitubercular medications

Antibiotics: most commonly sulfonamides, penicillins, ampicillin, tetracyclines and vancomycin.
Anticonvulsants: most commonly phenytoin, carbamazepine, sodium valproate and lamotrigine.
Calcium channel blockers: most commonly diltiazem, nifedipine and amlodipine.
NSAIDs: most commonly aspirin and ibuprofen

Thank you