Derma Team 436

# Drug Eruptions

## Objectives:

Not given

الشغل مبني على السلايدات لان الدكتور يقول محتوى السلايدات كافي

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**Before you start..** CHECK THE EDITING FILE

**Sources**: doctor's slides and notes
[ Color index: Important | 435 notes | gold | doctor notes | Extra ]

## Introduction:

- The skin is one of the most common targets for adverse drug reactions.
- 1-5% of patients receiving antibiotics and anticonvulsants may develop a drug eruption.
- ~2% of all drug-induced skin reactions are considered ''serious''
- Skin reactions to drugs are responsible for ~3% of all disabling injuries that occur during hospitalizations.
- Either due to:
- Immunologic response
- Non-immunologic (Overdose, side effect, drug-drug interaction, metabolism…etc.)

**In this lecture, I want you to know:**

1) •Types of eruptions
2) •How long does it take to appear after drug exposer
3) •How they look clinically
4) •Most important drug cause it

## Diagnostic approach for drug eruptions:

- **Clinical characteristics:**
  - Type of primary lesion
  - Distribution and number of lesions
  - Mucous membrane involvement, facial edema emergency
  - Associated signs and symptoms.
- **Chronological factors**
  - Document all drugs to which the patient has been exposed
  - Date of eruption, time interval...
- **Literature search to look for case reports**

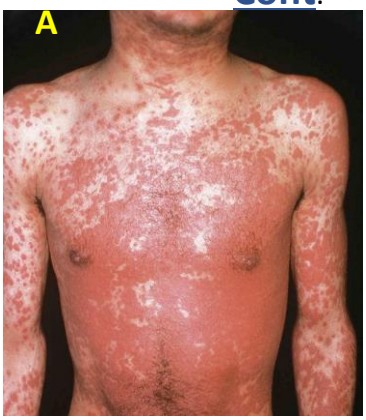
## Major drug-induced eruptions:

1. Exanthematous eruptions
2. Urticaria
3. Anaphylaxis
4. Fixed drug eruption
5. Acute generalized exanthematous pustulosis (AGEP)
6. Drug reaction with eosinophilia and systemic symptoms (DRESS)
7. Stevens-Johnson syndrome (SJS) emergency
8. Toxic epidermal necrolysis (TEN)

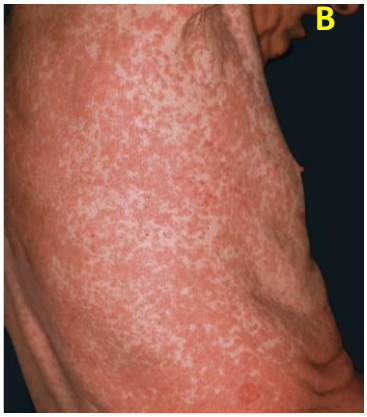
### Exanthematous Drug Eruptions:

The most common drug reaction affecting the skin.
Classically begins 7 to 14 days after the start of a new medication.
Begins as erythematous macules (symmetric) that sometimes becomes palpable.
Begins on the trunk and upper extremities and progressively becomes confluent.
Mucous membranes are usually spared. Conditions with mucous membrane involvement usually need urgent intervention.
Pruritis and low-grade fever and often present.
The eruption disappears spontaneously after 1-2 weeks without complications.
The following classes of drugs have a significantly higher incidence:
Aminopenicillins, Sulfonamides, Cephalosporins and anticonvulsants.

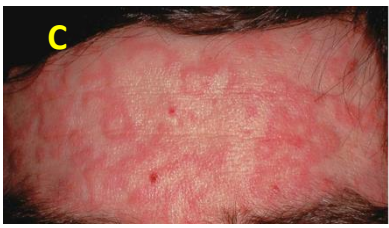
## Cont.




Numerous pink papules on the trunk due to a cephalosporin (A)




Confluence of lesions on the trunk (B)

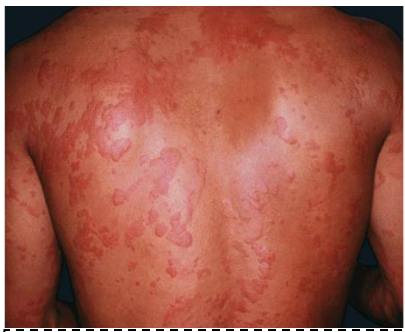



Annular plaques on forehead(C) secondery to phenobarbital. **Exanthematous Drug Eruptions can present as annular redness with white center**

•**Always look for the following:**
-Edema of the face + blood eosinophilia (DRESS)
-Mucous membrane lesions or painful dusky skin (SJS, TEN) Emergency
•**Histology: Biopsy**
-Nonspecific changes, eosinophils may be present.
•**The major DDx**
-Viral exanthem (often indistinguishable) thy look exactly the same
-Drug etiology favored in adults, viral favored in pediatric patients.
-The presence of peripheral blood eosinophilia favors a drug reaction.
•**Treatment:**
-Supportive
-Discontinue the offending drug. (risk vs benefit) some time you continue the treatment … if no substitute
-Topical antipruritic and corticosteroids may help to alleviate pruritis.

## Urticaria:

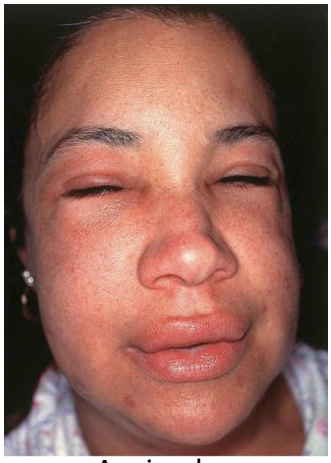
-Transient erythematous and edematous papules and plaques that are usually associated with pruritis.
-They can appear anywhere in the body including palms, soles and scalp.
-Duration is usually a few hours to 24 hours. The disease could last for few weeks-months, but each episode doesn't last more than 24 hours, then skin get back to normal.
-Skin is normal after they resolve.
-Acute: Less than 6 weeks. Chronic: Persist longer.
-Drugs associated with <10% of all cases of urticaria (acute > chronic)
-Mostly antibiotics (Penicillin's, cephalosporins).
-Tx: Discontinue drug, Antihistamines.



Urticaria secondary to penicillin. Several of the lesions have a figurate appearance.

## Angioedema:

-Transient edema of the dermal, subcutaneous and submucosal tissue.
-Associated with urticaria in 50% of cases.
-May be complicated by life-threatening anaphylaxis.
-ACE inhibitors (1 day to several years after starting)
-Usually on the face (eyelids, lips), less often on genitals and extremities.
-Unilateral or asymmetric.
-Can involve the larynx, epiglottis, oropharynx and intestinal wall.
-ACE inhibitors, Penicillin's and NSAIDs.



Angioedem

## Anaphylaxis:

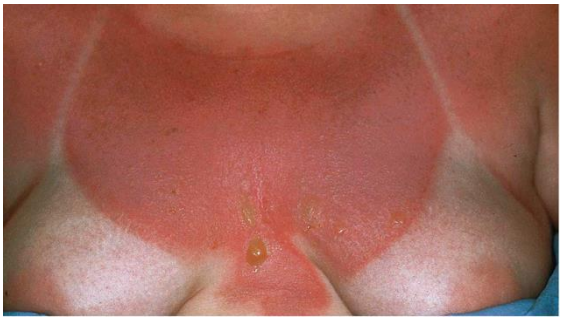
-An acute life-threatening reaction that can results from exposure to a number of drugs.
-Penicillin (1 per 5000)
-Combines skin with systemic manifestations (hypotension, tachycardia).
-Serious cases tend to appear within minutes and more common with parenteral administration as compared to oral ingestion.

- **Treatment:**

Discontinue drug and strict avoidance in the future.
Systemic steroids
SubQ epinephrine in cases of life-threatening angioedema or anaphylaxis.

## Photosensitivity:

Cutaneous photosensitivity may be:
Idiopathic
Due to endogenous photosensitizers (Porphyrins)
Due to Exogenous photosensitizers (Medications)
Three components:
1- Drug
2- Exposer to sun
3- Skin changes
The photosensitivity drug reactions are classically divided into 2 major types:
**1- Phototoxic (more common)**
**2- Photoallergic**



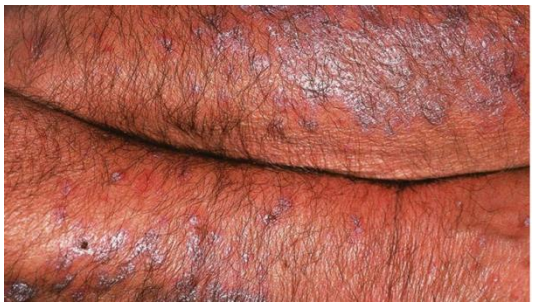
- Fairly common and predictable.

- Can occur in any person who receives a sufficient amount of a phototoxic drug together with sufficient exposure to UVR.
- Clinically: an exaggerated sunburn in a shorter than expected time.
- Limited to sun-exposed areas and followed by hyperpigmentation.

- Most common drugs: Tetracyclines* (doxycycline), NSAIDs, Fluoroquinolones.
*نعطيه كثير للي عندهم حب شباب ولازم ننبهم ان حساسيتهم للشمس تزيد
- Administering a short half-life drug in the evening decreases the risk.

## ❖ Photoallergy:

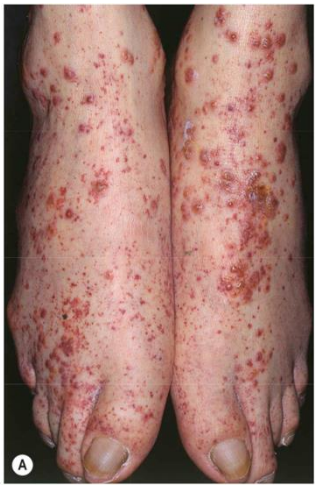
- Occur as a result of cell-mediated hypersensitivity (to an allergen activated or produced by the effect of light on a drug).
- UVR is required to convert the drug into an immunologically active compound (Photo-allergen) that induces the immune response.
- More chronic than phototoxic.
- Clinically: Pruritic and resemble dermatitis or lichen planus but primarily in sun-exposed sites.
- Most common drugs: Thiazide diuretics, Sulfonamides antibiotics, Sulfonylureas and phenothiazines (all contain sulfur)
- Tx: Drug withdrawal, Topical steroids, physical barriers, reduce sun exposure + broad-spectrum sunscreens.



Photolichenoid drug eruption due to hydrochlorothiazide
The lesions favored the extensor surfaces of the forearms.

## Vasculitis:

- ~10% of the cases are due to drugs.
- Clinically: Purpuric papules on the lower extremities.
- Systemic involvement is very unusual.
- Occurs 7-21 days after drug administration and less than 3 days following re-challenge.
- Most common drugs: Penicillin's, NSAIDs, Sulfonamides and cephalosporins.



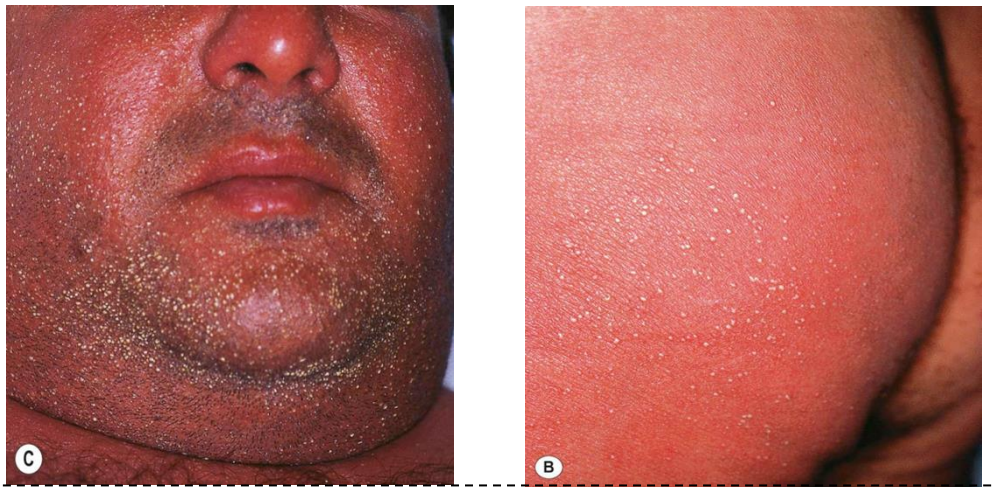

Phototoxic reaction in a patient receiving methotrexate.
The erythema and bullae are obviously limited to sun-exposed sites and resemble an exaggerated sunburn. Patients on methotrexate can also experience a "sunburn-recall" phenomenon

## ❖ Neutrophilic drug eruptions:

### Acute generalized exanthematous pustulosis (AGEP):

Acute febrile drug eruption.
Numerous small, non-follicular, sterile pustules, arising within large areas of edematous erythema.
More than 90% of cases are drug-induced.
The onset is usually within 2 days of starting the medication.
Lesions begin on the face or intertriginous zones (groin, axillae) and then disseminate within a few hours.
The lesions last for 1 to 2 weeks and are followed by a superficial desquamation.
DDx: Acute pustular psoriasis
Drugs: Antibiotics (Beta-lactam and macrolides), CCB and Antimalarials.
Easy to diagnose clinically, sterile if you do biopsy

Numerous small sterile pustules all over the body. DDx: Pustular psoriasis




Diffuse erythema of the buttock (due to cephalosporin, B) and face (due to metronidazole, C) studded with sterile pustules.

### Sweet's syndrome (Acute febrile neutrophilic dermatosis):

- This syndrome is characterized by fever, peripheral blood neutrophilia, and painful erythematous plaques that favor the face and upper extremities.

-Drugs represent <5% of all cases and starts about a week after the onset of drug administration.

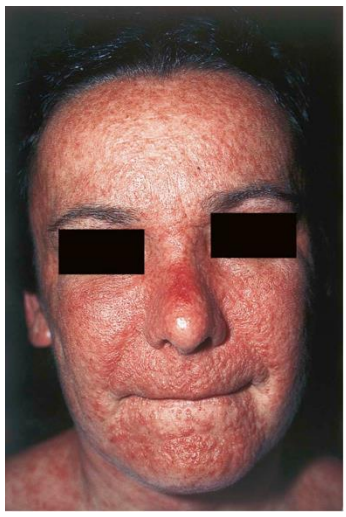
## Drug reaction with eosinophilia and systemic symptoms (DRESS):

AKA Drug-induced hypersensitivity syndrome (DIHS)
Due to alteration in the metabolism of drugs + immune mechanisms.
Possible role for viruses HHV-6 and HHV-7?
Drugs: Anticonvulsants (phenobarbital, Carbamazepine and phenytoin) and sulfonamides.

**Clinically:**

- Starts 2-6 weeks after drug initiation.
- Fever (85%) and a cutaneous eruption (75%) are the most common symptoms.
- Begins as a morbilliform eruption, which later becomes edematous, with follicular accentuation.
- The face, upper trunk and extremities are the initial sites of involvement.
- Edema of the face is a hallmark of DRESS.
- How to differentiate btw facial edema in DRESS & angioedema?
  DRESS (Face edema + skin rash), Angioedema (only edema, and it could be on the face and other parts of the body)
- Lymph nodes are often enlarged.
- The most common and most severe site of visceral involvement is the liver (majority of deaths associated with this syndrome.
- Other organs involved: Heart, lungs, kidneys and thyroid.
- Prominent eosinophilia is a very characteristic feature.

**Treatment:**
Early withdrawal the offending drug. (may not be sufficient for obtaining a full recovery)
Topical steroids for mild cases.
Systemic steroids for life-threatening heart and lung involvement. Unlike the other conditions the symptoms may last even after you stop the drug



Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). Multiple edematous papules are present.

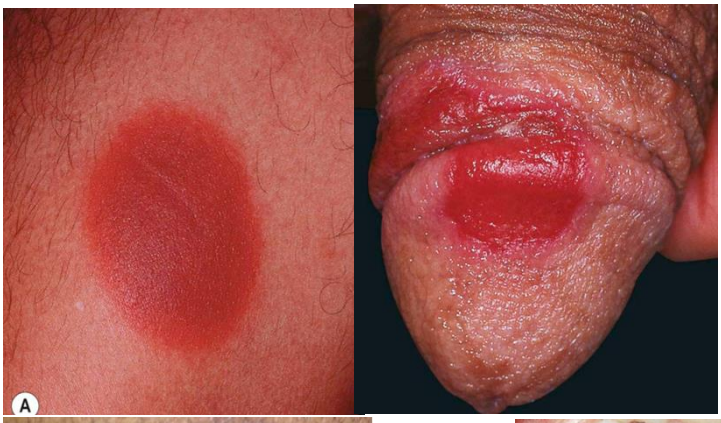
## ❖ Bullous Eruptions:

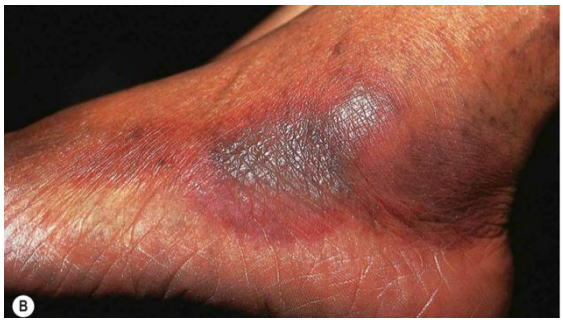
1. Fixed drug eruption
2. Linear IgA bullous dermatosis
3. Drug-induced bullous pemphigoid
4. Drug-induced pemphigus
5. Steven-Johnson syndrome and TEN

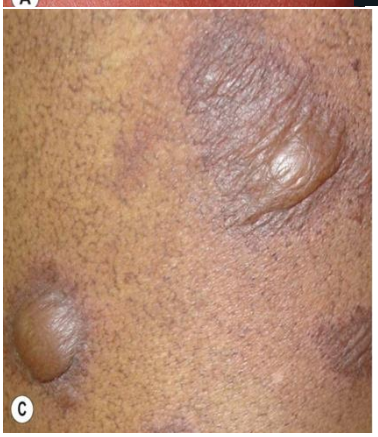
mostly one lesion in one area. If you stop the treatment and take it again for example after one year it will happen again in the same site.

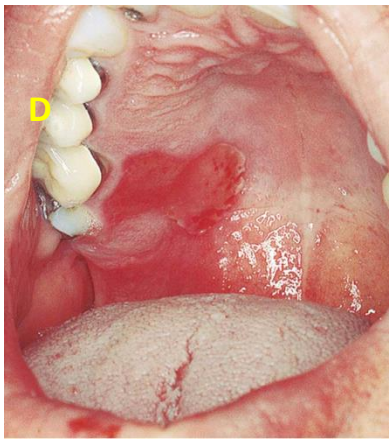
## Fixed drug eruption:

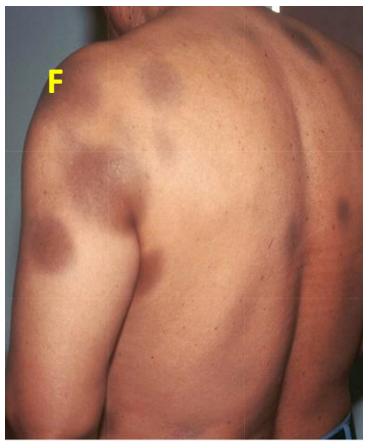
- Lesions develop **1-2 weeks after** a first exposure and within **24 hours within subsequent exposures.**
- One or a few round, sharply demarcated, erythematous and edematous plaques are seen.
- Sometimes a dusky, violaceous hue and a central blister may be seen
- Favors the **lips, face, hands, feet and genitalia.**
- The lesions progressively fade over several days (leaving PIH behind).
- Lesions recur at exactly the **same sites** upon re-administration of the drug.
- There is a generalized form of FDE (similar clinically to EM/SJS).
- A **non-pigmenting** variant of FDE occurs mainly with **pseudoephedrine.**
- Drugs: Sulfonamides, NSAIDs, Barbiturates, Tetracyclines and Carbamazepine.



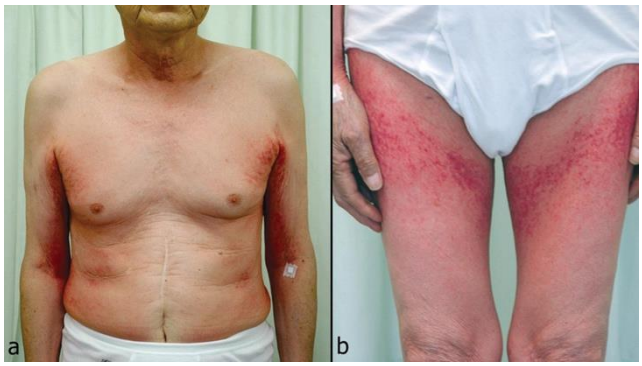



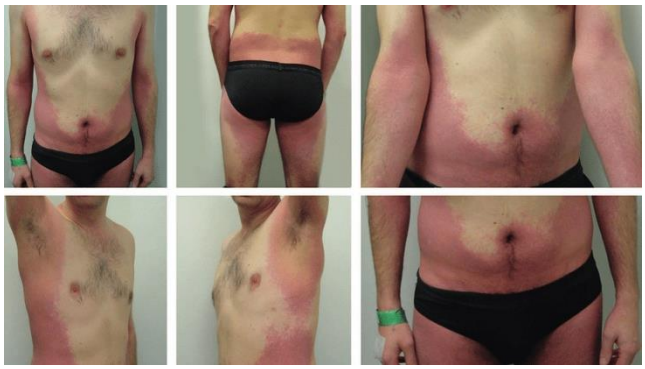

Fixed drug eruptions.
Well-demarcated erythematous (A) to violet–brown plaques that can develop a detached epidermis (B), bulla (C) or erosion (D) centrally. As lesions heal, circular or oval areas of hyperpigmentation are commonly seen (F)Responsible drugs were phenolphthalein (A), naproxen (B), ciprofloxacin (D), and trimethoprim–sulfamethoxazole (F).

## Symmetrical drug-induced intertriginous and flexural exanthema (SDRIFE): Not Important

-Sharply demarcated, symmetrical areas of erythema over the anogenital region after exposure to systemic drugs.
-Aminopenicillin & Cephalosporin are the most common drugs.
There is usually involvement of at least one flexural site.

| SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA (SDRIFE) – CLINICAL CRITERIA |
|---|
| • Exposure to a *systemically* administered drug*, occurring with either the initial or a repeated dose (excluding contact allergens)<br>• Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area<br>• Involvement of at least one other intertriginous site/flexural fold<br>• Symmetry of affected areas<br>• Absence of systemic symptoms and signs |



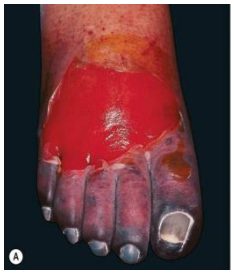



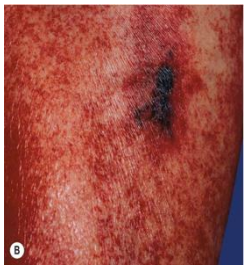
## ❖ Other drug-induced eruptions:

Anticoagulant-induced skin necrosis
Serum sickness-like eruption
Drug-induced lupus
Drug-induced psoriasis
Acneiform eruptions
Pigmentary changes
Pseudolymphoma
Chemotherapy reactions

## Anticoagulant-induced skin necrosis:

Rare, sometimes life-threatening.
Induced by Warfarin or Heparin.
Begins 2 to 5 days after therapy.
Erythematous, painful plaques evolve into hemorrhagic blisters and necrotic ulcers.
Mainly over the breasts, thighs and buttocks.
Patients with hereditary deficiency of protein C are at highest risk.
Tx: Discontinue warfarin & start Vitamin K + I.V infusion of protein C.

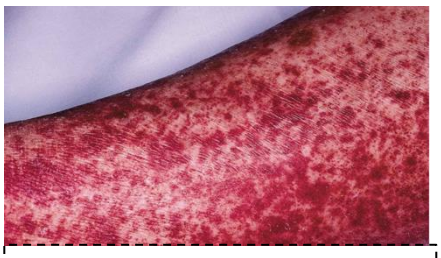



A Ischemia and necrosis of the foot.

## Serum sickness-like eruption:

- Mainly in children
- Fever, Arthralgias, arthritis, rash and lymphadenopathy.
- 1 to 3 weeks after drug exposure.
- Unlike true serum sickness, hypocomplementemia, vasculitis and renal disease are absent.
- Occurs in approximately 1 in 2000 children given cefaclor.



The purpuric lesions are due to small vessel vasculitis in this patient with aplastic

## Drug-induced Lupus:

**Drug-induced systemic lupus:**

- Fever, weight loss, pericarditis and pulmonary inflammation.
- Skin involvement is rare but includes: malar-erythema, photo eruption and discoid lesions.
- Vasculitis, renal and neurologic involvement is rare.
- Starts over a year after the medication is initiated.
- +ve anti-histone Abs in 95% of cases. (-ve DsDNA)
- Clinical symptoms resolve within 4 to 6 weeks.

Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, quinidine, D-penicillamine and Minocycline.

**Drug induced subcutaneous lupus:**

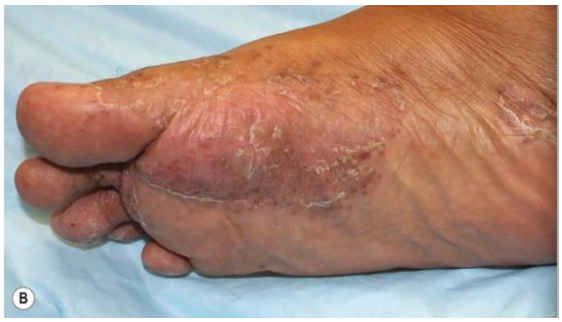
Psoriasiform and annular lesions on the upper trunk and extensor arms.
Hydrochlorothiazide, CCBs, Terbinafine, NSAIDs, Griseofulvin.
Resolution of the rash may or may not occur after discontinuation of the responsible drug.

## Drug-induced Psoriasis:

Drugs can affect a patient in 3 different ways:

1. Exacerbation of pre-existing psoriasis
2. Induction of lesions of psoriasis in clinically normal skin in a patient w psoriasis.
3. De novo psoriasis.

Terbinafine, NSAIDs, Antimalarials, ACE inhibitors, Lithium and B-blockers.
TNF-induced Psoriasis.
Lesions of drug-induced psoriasis usually regress within weeks to a few months of discontinuing the inciting drug.

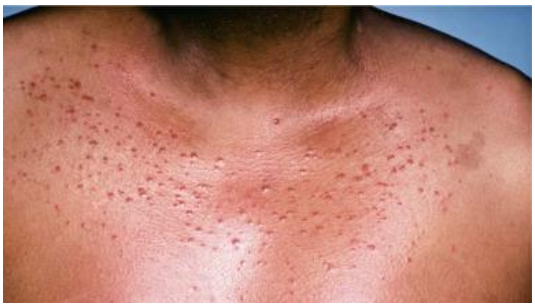



Psoriasiform eruptions due to TNF-α inhibitors.

A Widespread papulosquamous lesions in a patient being treated with infliximab for gastrointestinal GVHD. Histologically, there was no evidence of cutaneous GVHD. B Sterile pustulosis of the plantar surface developed in this patient with rheumatoid arthritis who had received infliximab for the previous 5 years. Neither patient had had a reduction in immunosuppression prior to the onset of the psoriasiform eruption.

## Acneiform eruptions:

- Represent ~1% of drug-induced skin eruptions.
- Clinically, just like acne but comedones are absent.
- Corticosteroids, Androgens, hydantoins, lithium, progestin-containing OCPs.



Acneiform eruptions: All acnes are monomorphic (same size & stage)
Typical distribution is to the face, chest and back

## Pigmentary changes:

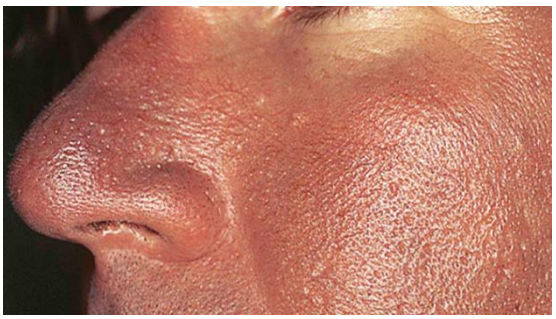
•Hyperpigmentation:

Usually more pronounced in sun-exposed areas.

-Minocycline site: teeth, bluish patches on the shins
-Antimalarials
-Amiodarone
-Silver, gold and arsenic
-Bleomycin

•Hypopigmentation:

- Chronic use of topical steroids



Gray–violet discoloration of the face due to amiodarone

# Summery:

| Type of eruptions | Onset | Clinically | Causes |
|---|---|---|---|
| Exanthematous Drug Eruptions | 7 to 14 days | erythematous macules (symmetric), sometimes palpable on the trunk and upper extremities, Pruritis | Aminopenicillins, Sulfonamides, Cephalosporins and anticonvulsants |
| Urticaria | | Transient erythematous and edematous papules and plaques associated with pruritis. palms,soles and scalp. | antibiotics (Penicillins, cephalosporins) |
| Angioedema | ACE inhibitors (1 day to several years after starting) | Transient edema of the dermal, subcutaneous and submucosal tissue. on the face (eyelids, lips) | ACE inhibitors, Penicillins and NSAIDs |
| Anaphylaxis | within minutes | Combines skin with systemic manifestations (hypotension, tachycardia). | Penicillins |
| Phototoxic | sunburn in a shorter than expected time. | The erythema and bullae are obviously limited to sun-exposed sites and resemble an exaggerated sunburn | Tetracyclines (doxycycline), NSAIDs, Fluoroquinolones. |
| Photoallergy | - | Pruritic and resemble dermatitis or lichen planus | Thiazide diuretics, Sulfonamides antibiotics, Sulfonylureas and phenothiazines |
| Vasculitis | 7-21 days | Purpuric papules on the lower extremities | Penicillins, NSAIDs, Sulfonamides and cephalosporins. |
| AGEP | 2 days | Numerous small, non-follicular, sterile pustules, arising within large areas of edematous erythema | Antibiotics (Beta-lactam and macrolides), CCB and Antimalarials. |
| Sweet's syndrome | 1 week | fever, peripheral blood neutrophilia, and painful erythematous plaques that favor the face and upper extremities | - |
| DRESS | 2-6 weeks | morbilliform eruption, which later becomes edematous, with follicular accentuation.<br>The face, upper trunk and extremities are the initial sites of involvement.<br>Edema of the face is a hallmark of DRESS. | Anticonvulsants (phenobarbital, Carbamazepine and phenytoin) and sulfonamides. |
| FDE | 1-2 weeks | One round, sharply demarcated, erythematous and edematous plaques. Sometimes a dusky, violaceous hue and a central blister. | Sulfonamides, NSAIDs, Barbiturates, Tetracyclines and Carbamazepine. |
| SDRIFE | - | Sharply demarcated, symmetrical areas of erythema over the anogenital region | Aminopenicillin & Cephalosporin |
| Anticoagulant-induced skin necrosis | 2 to 5 days | Erythematous, painful plaques evolve into hemorrhagic blisters and necrotic ulcers.<br>Mainly over the breasts, thighs and buttocks | Warfarin or Heparin |
| Serum sickness-like eruption | 1 to 3 weeks | Mainly in children. Fever, Arthralgias, arthritis, rash and lymphadenopathy. | Cefaclor |
| Drug-induced Lupus | 4 to 6 weeks | Fever, weight loss, pericarditis and pulmonary inflammation | Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, quinidine, D-penicillamine and Minocycline |
| Drug-induced Psoriasis | weeks to a few months | - | erbinafine, NSAIDs, Antimalarials, ACE inhibitors, Lithium and B-blockers.<br>TNF-induced Psoriasis. |
| Acneiform | - | Acne but comedones are absent. | Corticosteroids, Androgens, hydantoins, lithium, progestin-containing OCPs. |
| Hyperpigmentation | - | - | Minocycline, Antimalarials, Amiodarone, Silver, gold and arsenic, Bleomycin |
| Hypopigmentation | - | - | Chronic use of topical steroids |

credit: مهند الزهراني

## Test your knowledge:

The most common drug reaction affecting the skin:

a. Exanthematous Drug Eruptions
b. Urticaria
c. Anaphylaxis
d. Fixed drug eruption

a

Which of the following commonly cause Photoallergy?

a. NSAID
b. Thiazide diuretics
c. warfarin
d. Minocycline

b

Which of the following commonly cause angioedema?

a. Ace inhibitors
b. Sulfur
c. B-blockers
d. Thiazide