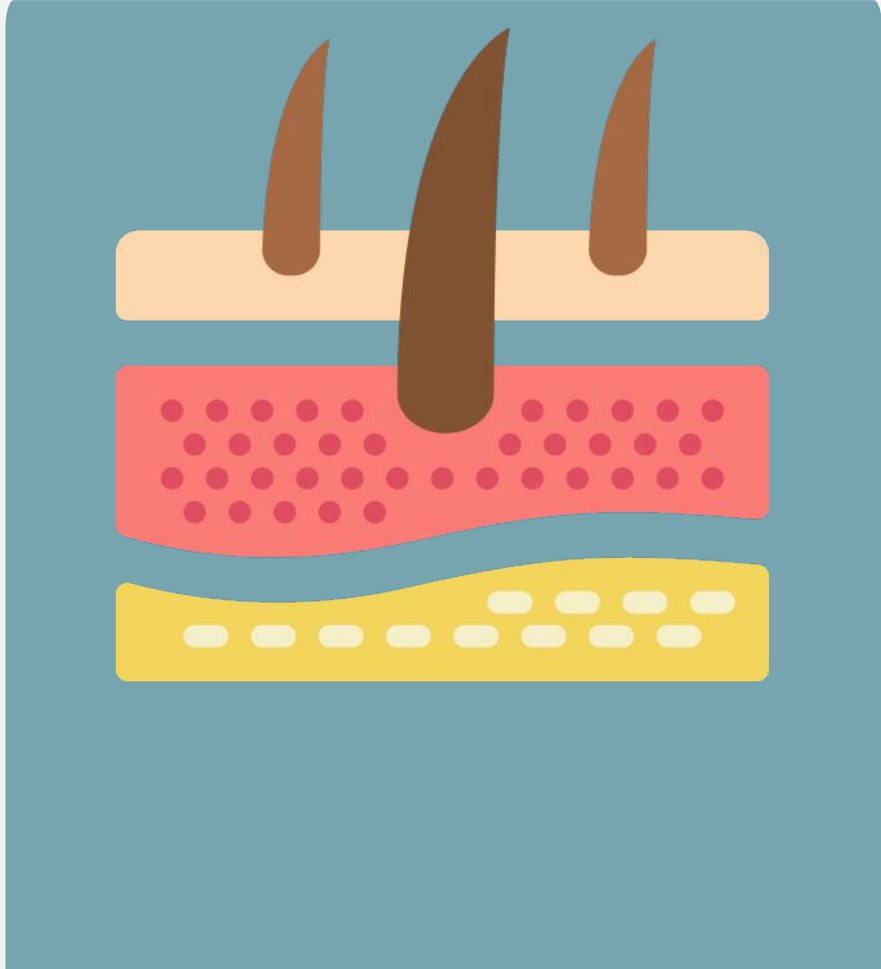


11-Dermatologic Emergencies

Objectives:
Not given.

Done by:
Abdulaziz Aldrgam, Rakan Almetary Fahad Al Hussein, Sultan Al Nasser AlHanouf AlJaloud, Hadeel Awartani
Revised by: Anas AlSaif, Rotana Khateeb

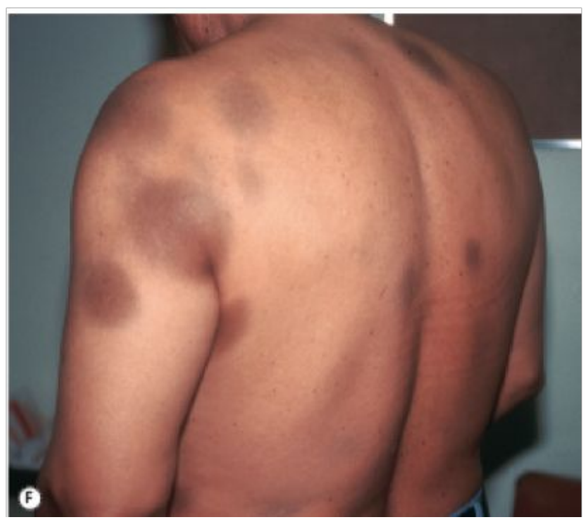
References: Doctor slides, Team 436

Color Index:

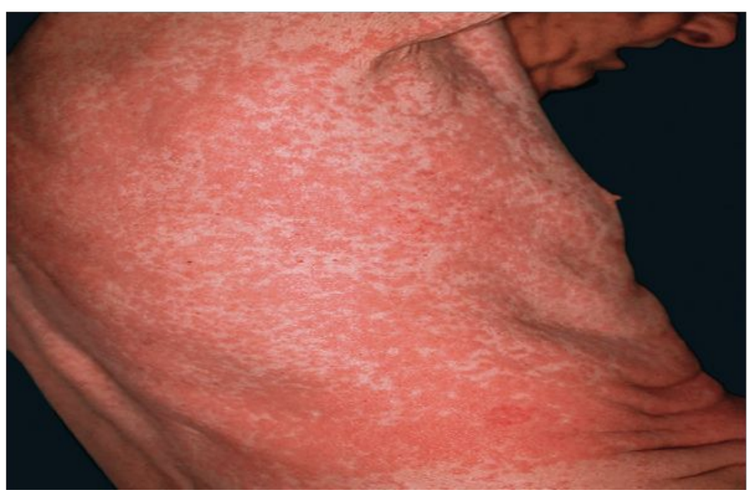
- Important
- Doctor's Notes
- Extra

Editing File

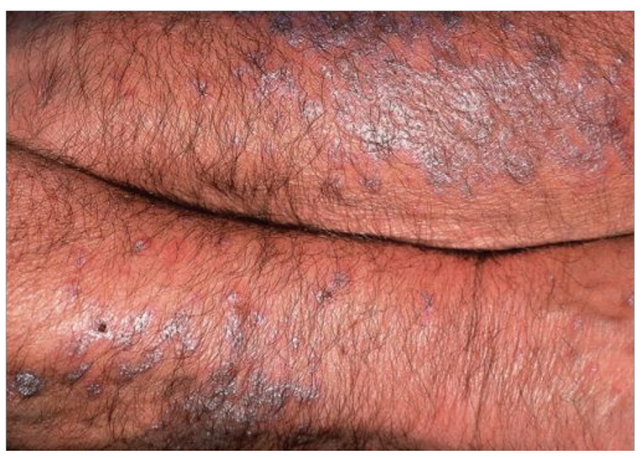
Fixed Drug reaction



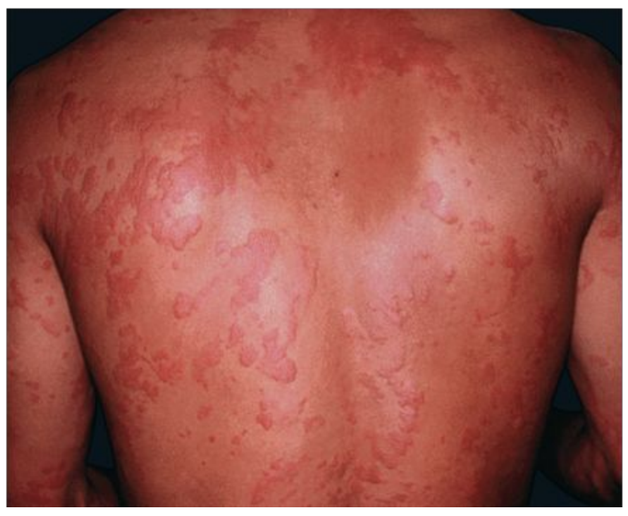
Exanthematous drug eruptions due to a cephalosporin



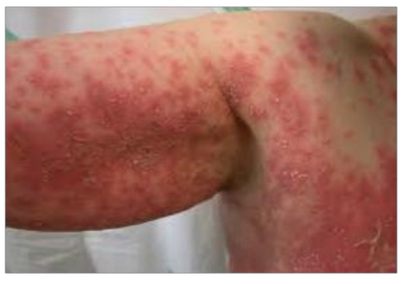
Photolichenoid drug eruption due to hydrochlorothiazide

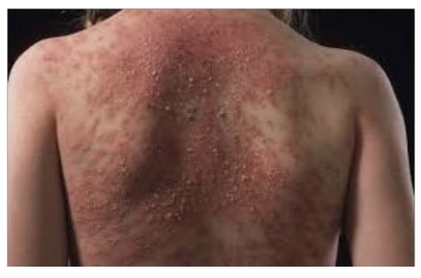


Urticaria secondary to penicillin

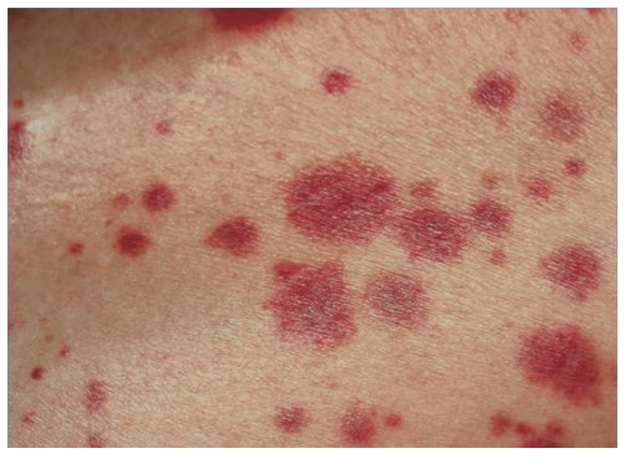


Acute generalized exanthematous pustulosis (AGEP)

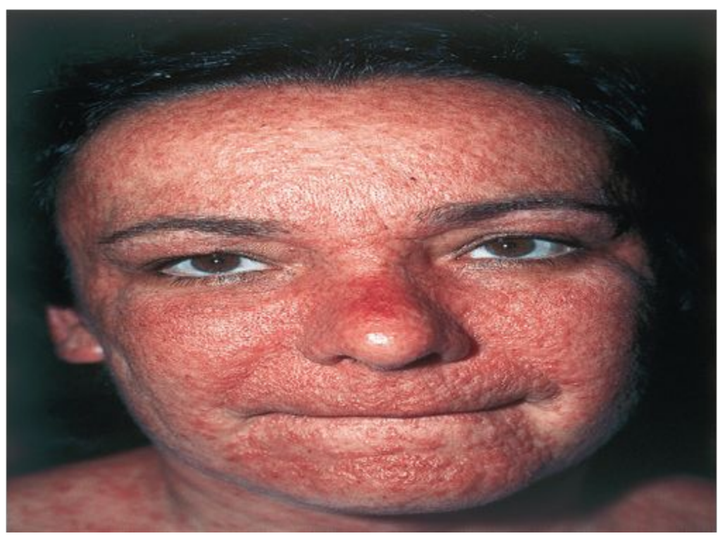




Cutaneous small vessel vasculitis due to Allopurinol



Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) due to phenytoin



DRUGS RECEIVED BY MORE THAN 1000 PATIENTS WITH NO SKIN REACTIONS (RATES ESTIMATED TO BE ≤3 PER 1000)
- Potassium chloride
- Milk of magnesia
- Digoxin
- Meperidine hydrochloride
- Dioctyl sodium sulfosuccinate
- Magnesium hydroxide
- Aluminum hydroxide
- Acetaminophen
- Multivitamins
- Bisacodyl
- Diphenhydramine hydrochloride
- Aspirin
- Aminophylline
- Prochlorperazine
- Ferrous sulfate
- Thiamine
- Prednisone
- Atropine
- Codeine
- Vitamin B complex and ascorbic acid
- Pentazocine
- Hydrochlorothiazide*
- Phosphate enema
- Castor oil
- Tetracycline*
- Morphine
- Regular insulin
- Warfarin
- Spironolactone
*Notably phototoxic reactions were not included.

SKIN REACTIONS TO "DRUGS" RECEIVED BY AT LEAST 1000 PATIENTS	
Drugs	Reaction rate (per 1000 recipients)
Ampicillin	52
Penicillin G	16
Cephalosporins	13
Packed red blood cells	8.1
Heparin	7.7
Nitrazepam	6.3
Barbiturates	4.7
Chlordiazepoxide	4.2
Diazepam	3.8
Propoxyphene	3.4
Guaifenesin	2.9
Furosemide	2.6
Phytonadione	0.9
Flurazepam	0.5
Chloral hydrate	0.2

MECHANISMS OF CUTANEOUS DRUG-INDUCED REACTIONS	
Immunologic mechanism (unpredictable)	• IgE-dependent drug reactions • Cytotoxic drug-induced reactions • Immune complex-dependent drug reactions • Cell-mediated reactions
Non-immunologic mechanisms (sometimes predictable)	• Overdose • Pharmacologic side effects • Cumulative toxicity • Delayed toxicity • Drug–drug interactions • Alterations in metabolism • Exacerbation of disease
Idiosyncratic with a possible immunologic mechanism (unpredictable)	• DRESS (DIHS) • TEN/SJS • Drug reactions in the setting of HIV infection • Drug-induced lupus erythematosus

Erythema multiforme(EM)

Only the pictures were included in drs lecture focus on what's red

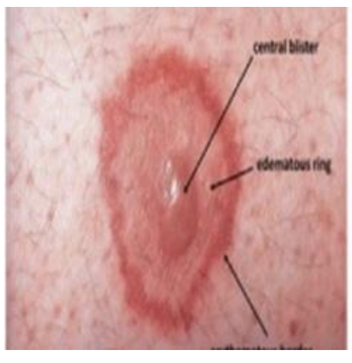
An acute, self-limited, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction **associated with certain infections (HSV),** medications, and other various triggers.

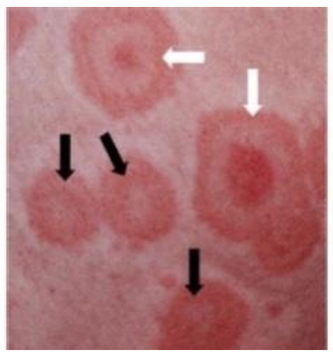
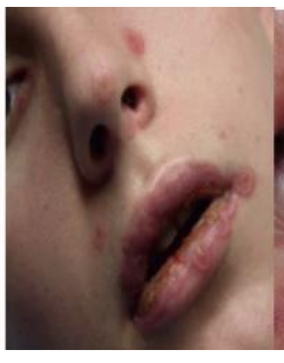
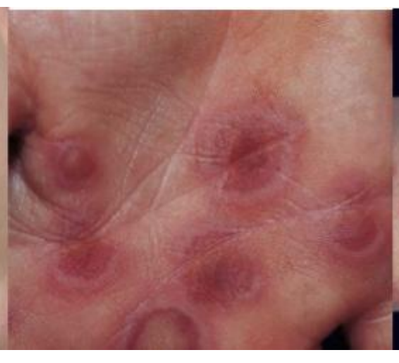
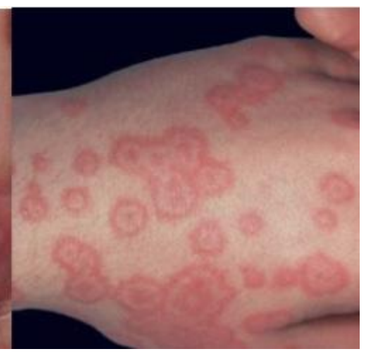
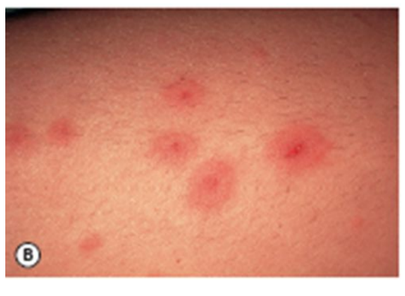
A mild, nonspecific URTI.

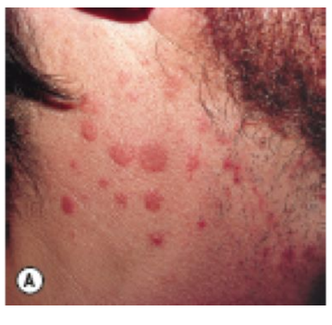
Abrupt onset of a skin rash usually occurs within 3 days, starting on the extremities symmetrically, with centripetal spreading.

Skin examination:

- The initial lesion is a dull-red, purpuric macule or urticarial plaque that expands slightly to a maximum of 2 cm over 24-48 H
- In the center, a small papule, vesicle, or bulla develops, flattens, and then may clear.
- An intermediate ring develops and becomes raised, pale, and edematous. The periphery gradually changes to become cyanotic or violaceous and forms typical concentric, target lesion.
- Some lesions consist of only 2 concentric rings. Target like
- Some lesions appear at areas of previous trauma (Koebner phenomenon). Explains why it appears more on extremities.
- Postinflammatory hyperpigmentation or hypopigmentation. But no scarring.
- Nikolsky sign is negative.
- The lesions are symmetrical (usual distribution in immune mediated diseases, usually small BSA but sometime might be generalized), predominantly on the acral extensor surfaces of the extremities, and they spread centripetally to involve the abdomen and back.
- Lesions may also coalesce and become generalized.
- The palms, neck, and face are frequently involved.
- Mucosal lesions usually heal without sequelae.
- The mucosal involvement SJS is more severe and more extensive than that of EM.
-Usually **preceded by herpes infection.** ask about herpes infection, do you have bullea on the sides of your lips?"





-Its basically an immune reaction to the virus.

- First picture: Bullous target/EM; Dark red borders - edematous ring - center can be red + vesicle or bullae.
- Second picture: White arrow: Target-lesions. Black arrow: Target-like/Targetoid lesions.
- Third picture: lips involvement but not severe.
- Palms are a very common site of involvement and should be one of the first areas you examine.

Investigations

-No specific laboratory tests are indicated to make the diagnosis of EM, which should be clinically.

- Specific HSV antigens have been detected within keratinocytes by IF study.
- The HSV DNA has been identified primarily within the keratinocytes by PCR amplification.
- Direct IF staining and examination may also identify an alternative diagnosis (eg, pemphigoid, immunoglobulin A [IgA] linear dermatosis.
- Histopathologic examination of Skin biopsy may be used to confirm the Dx of EM and to rule out the DDxA (e.g. blistering disorders)

-CXR to to r/o Pneumonia.

- Usually clinical but done for research purposes or if you cannot r/o blistering diseases.

Treatment

- The cause of EM should be identified.
- If a drug is suspected, it must be withdrawn as soon as possible.
- Infections should be appropriately treated. By ID -Local supportive care for eye involvement is important

Symptomatic Rx, including oral antihistamines, analgesics, local skin care, and soothing mouthwashes (e.g., oral rinsing with warm saline or a solution of diphenhydramine; antihistamine, xylocaine; analgesic).

Topical steroids. Because it is type 4 hypersensitivity inflammation, not an infection

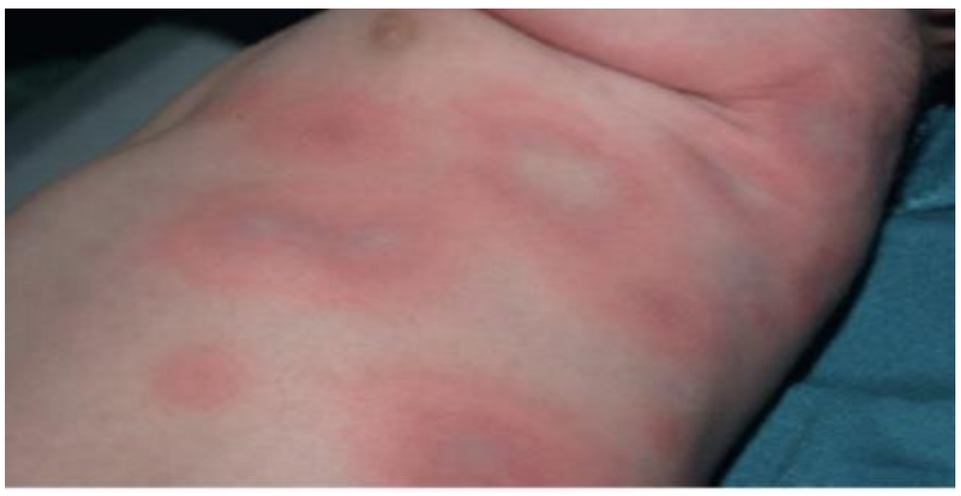
- Suppression of HSV can prevent HSV-associated EM, but antiviral Rx started after the eruption has no effect on the course of the erythema multiforme. It is not an infection, it is an immunoreaction to virus .

PRECIPITATING FACTORS IN ERYTHEMA MULTIFORME		
Infections (approx. 90% of cases)	Viral	- Herpes simplex virus (HSV-1, HSV-2) - Parapoxvirus (orf) - Vaccinia (smallpox vaccine) - Varicella zoster virus (chickenpox) - Adenovirus - Epstein-Barr virus - Cytomegalovirus - Hepatitis virus - Coxsackievirus - Parvovirus B19 - Human immunodeficiency virus
	Bacterial	- *Mycoplasma pneumoniae** - *Chlamydophila* (formerly *Chlamydia*) *psittaci* (ornithosis) - *Salmonella* - *Mycobacterium tuberculosis*
	Fungal	- *Histoplasma capsulatum* - Dermatophytes
Drugs (unusual)		Primarily: - Nonsteroidal anti-inflammatory drugs - Sulfonamides - Anticonvulsants - Other antibiotics, e.g. aminopenicillins - Allopurinol
Exposures (unusual)		- Poison ivy
Systemic disease (rare)		- Inflammatory bowel disease - Lupus erythematosus† (Rowell's syndrome) - Behçet's disease†

*Also precipitating factor for Stevens–Johnson syndrome and isolated oral mucositis.
†May be a pattern of cutaneous lesions in the disease rather than a precipitating factor

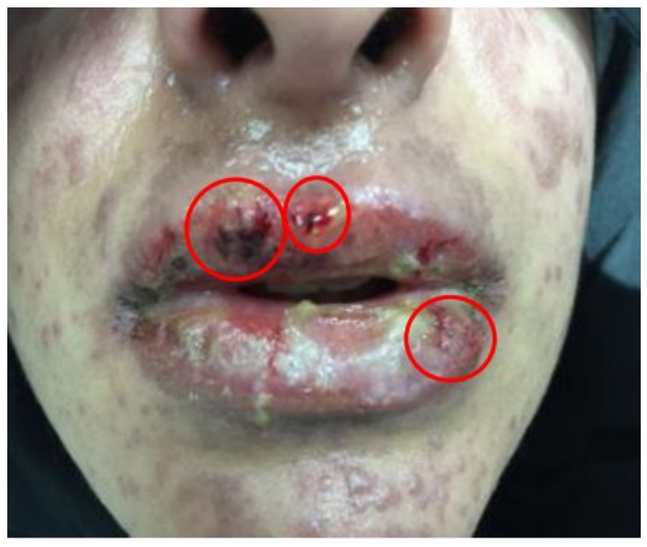
-Most common from viral HSV but not the only one
-Bacterial Mycoplasma Pneumoniae clues from history: Elderly immunocompromised just came back from hajj with a cough that is not responding to antibiotics. We ask for CXR and HSV antibodies.

DIFFERENCES BETWEEN URTICARIA AND ERYTHEMA MULTIFORME	
Urticaria	Erythema multiforme
Central zone is normal skin	Central zone is damaged skin (dusky, bullous or crusted)
Lesions are transient, lasting less than 24 hours	Lesions "fixed" for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
Associated with swelling of face, hands or feet (angioedema)	No edema

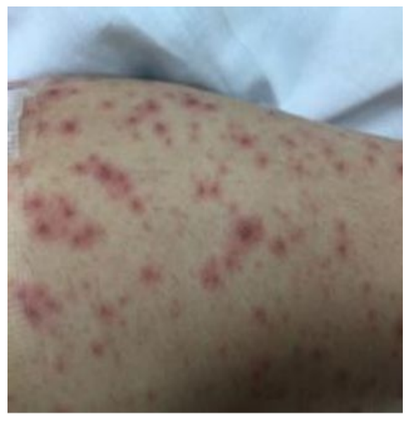


DX? Target-like lesions if blanchable most likely urticaria.

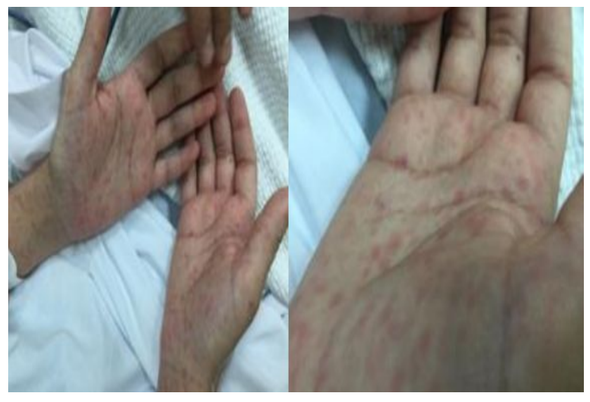
Real Clinical ER case:



Describe the lesions: On face: ill defined erythematous plaque with crustation. On lips: Hemorrhagic crustation with ulcers and erosions



Describe the lesion: Numerous irregular erythematous grouped papules.



Target like

Approach:

- Hx: 3 day onset ′ Painful ′ First time ′ No recent trauma ′ Recent URTI which she took abx for. (onset, progression, drug hx, pain, previous episodes, infections)
- O/E: We should examine her nails, mucous membranes(eye and genitalia) and scalp.
- LAB: Usually we diagnose clinically but we can order skin biopsy.
- DDx - Mx this pt had steven johnson syndrome
- Time interval is very important in differentiating different drug reactions.
- Exanthematous = maculopapular.
- Urticaria occurs very fast because its type 1 hypersensitivity. Caused by many reasons(drugs)
- Anaphylaxis is a systemic manifestation more than skin and is treated by medicine not derma.
- Focus on SJS and TEN as they carry high mortality rate (can reach up tp 50%) “allopurinol+NSAIDS”.

LOGICAL APPROACH TO DETERMINE THE CAUSE OF A DRUG ERUPTION	
DRUG RESPONSIBILITY ASSESSMENT	
Clinical characteristics	• Type of primary lesion (e.g. urticaria, erythematous papule, pustule, purpuric papule, vesicle or bulla) • Distribution and number of lesions • Mucous membrane involvement, facial edema • Associated signs and symptoms: fever, pruritus, lymph node enlargement, visceral involvement
Chronological factors	• Document all drugs to which the patient has been exposed (including OTC and complementary) and the dates of administration • Date of eruption • Time interval between drug introduction (or reintroduction) and skin eruption • Response to removal of the suspected agent • Consider excipients (e.g. soybean oil) • Response to rechallenge*
Literature search	• Bibliographic research (e.g. Medline) • Drug Alert Registry or Medwatch • Data collected by pharmaceutical companies • In the case of more recently released medications, extrapolation based on the class of drug and in particular the first drug released in the class
*Often inadvertent.	

CHARACTERISTICS OF MAJOR DRUG-INDUCED ERUPTIONS				
Clinical presentation	Percentage that are drug-induced (%)	Time interval	Mortality (%)	Selected responsible drugs
Exanthematous eruption	Child: 10–20 Adult: 50–70	4–14 days	0	Aminopenicillins Sulfonamides Cephalosporins Anticonvulsants Allopurinol
Urticaria	<10	Minutes to hours	0	Penicillins
Anaphylaxis	30	Minutes to hours	5	Cephalosporins NSAIDs Monoclonal antibodies Contrast media†
Fixed drug eruption	100	First exposure: 1–2 weeks Re-exposure: <48 hours, usually within 24 hours	0	TMP-SMX NSAIDs Tetracyclines Pseudoephedrine*
Acute generalized exanthematous pustulosis (AGEP)	70–90	< 4 days	1–2	β-Lactam antibiotics Macrolides Calcium channel blockers
Drug reaction with eosinophilia and systemic symptoms (DRESS)/ Drug-induced hypersensitivity syndrome (DIHS)	70–90	15–40 days	5–10	Anticonvulsants (aromatic) Sulfonamides Allopurinol Lamotrigine (especially in combination with valproate) Minocycline
Stevens-Johnson syndrome (SJS)	70–90	7–21 days	5	Sulfonamides
Toxic epidermal necrolysis			30	Anticonvulsants (aromatic) Allopurinol NSAIDs Lamotrigine
*Non-pigmenting. †Often anaphylactoid reaction.				

Overview

Alarming Morphological patterns :

- Urticaria/ Angioedema .
- Purpura/ Ecchymoses.
- Bullae/ Sloughing.
- Necrosis/Gangrene.
- Exfoliative Erythroderma syndrome.
- Generalized/ widespread rashes in the acutely ill febrile patient.

Dermatologic Emergencies:

- Urticaria/angioedema/anaphylaxis. Swelling of lips, eyes, airway and hypotension.
- Purpura.
- Bullous disease.
- Steven johnson syndrome ;(SJS)/ Toxic epidermal necrolysis(TEN).
- Erythroderma

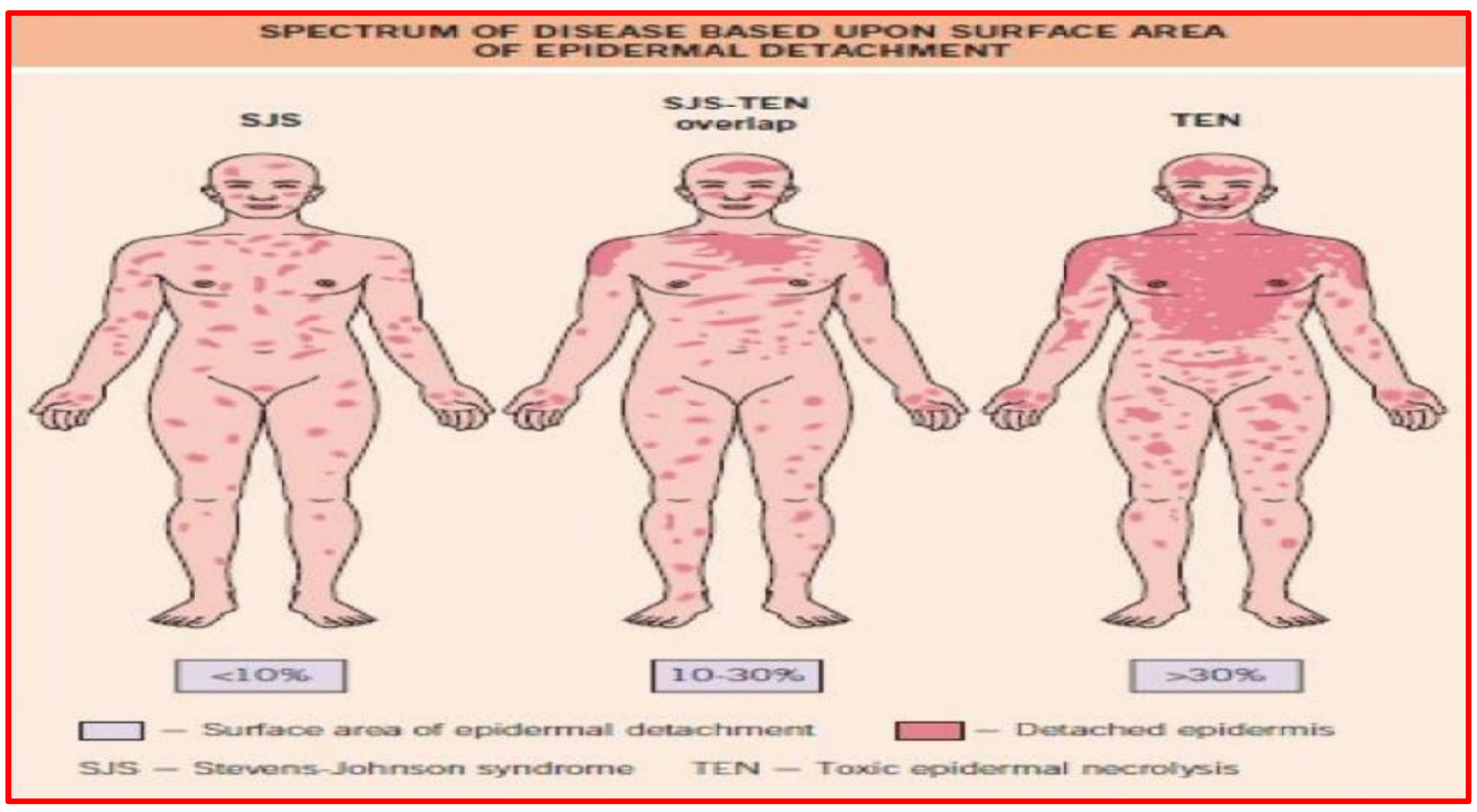
Steven's Johnson syndrome / Toxic epidermal necrolysis

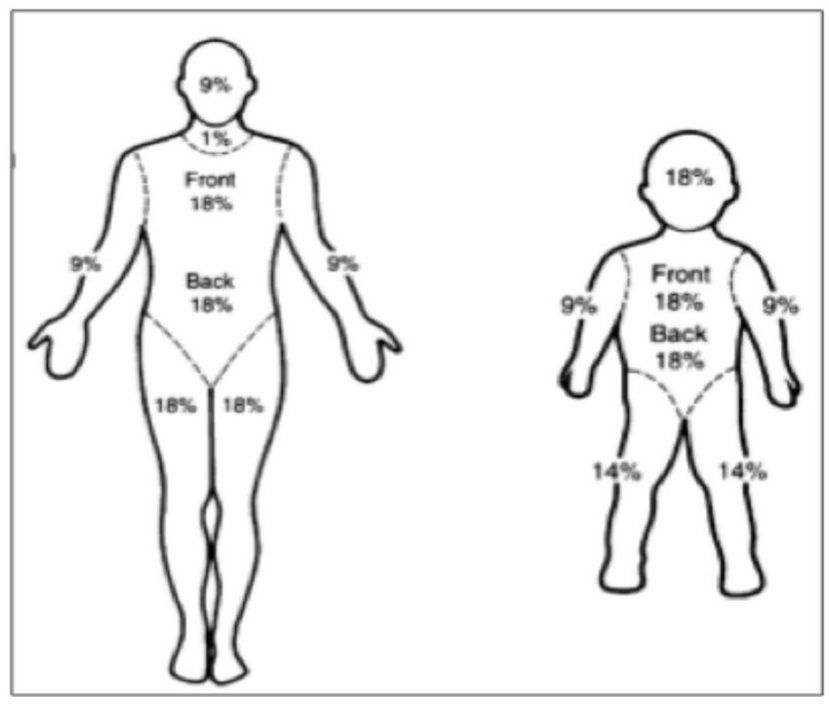
Review:

It has now become clear that Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are variants within a continuous spectrum (Same cause - Clinical presentation - Management. They only differ in severity) of adverse drug reactions, differing only by the extent of skin detachment..

- It was clear, that HSV was the major cause of EM, and that this virus was not related to TEN. Recently, Assier et al. clarified this issue by providing clinical evidence that EM and SJS are clinically distinct disorders with different causes and prognosis.
- EM was the first to be found, but later American physicians Steven and Johnson found a rash that is more severe and involves both skin and mucus membranes (conjunctivitis, stomatitis, necrosis). They named at as (EM like) at first then they changed it named it by their names (Steven-Johnson's) and the considered it severe mucocutaneous. What is the difference between SJS and EM? EM is viral (herpes simplex) and SJS is drug induced

- Rare, acute, life-threatening mucocutaneous (skin + mucous-membrane) disease.
- Nearly always drug-related. (patients have problems in drug metabolism)
- Keratinocyte death separation of skin at the dermal-epidermal junction.
- Characteristic symptoms: High fever, skin pain, anxiety and asthenia. Shivering
- It is crucial to diagnose it early so the causal drug can be discontinued. (with every day the risk of death increase)





*An extra picture to help you revise Body Surface Area

x SJS can progress to TEN if left untreated.
x Mainway to differentiate between the two is BSA. Less than 10% = SJS, >30% = TEN. 10-30% = SJS-TEN overlap. You must include the initial BSA to check progression.
x Calculating BSA is through areas of epidermal detachment NOT redness.
Do we measure the red areas or areas of detachment? Areas of detachment.

COMPARISON OF ERYTHEMA MULTIFORME (EM) MINOR, EM MAJOR AND STEVENS–JOHNSON SYNDROME (SJS)

	Type of skin lesions	Distribution	Mucosal involvement	Systemic symptoms	Progression to TEN	Precipitating factors
EM minor	• Typical targets • ± *Papular* atypical targets	Extremities (especially elbows, knees, wrists, hands), face	Absent or mild	Absent	No	• Herpes simplex virus • Other infectious agents
EM major	• Typical targets • ± *Papular* atypical targets • Occasionally bullous lesions	Extremities, face	Severe	Present	No	• Herpes simplex virus • *Mycoplasma pneumoniae* • Other infectious agents • Rarely, drugs
SJS	• Dusky macules with or without epidermal detachment • *Macular* atypical targets • Bullous lesions (<10% BSA detachment)	Trunk, face	Severe	Present	Possible	• Drugs • Occasionally, *Mycoplasma pneumoniae* • Rarely, immunizations

Epidemiology

Mortality rates range from 25 to 50% (average: 30-35%) for patients with TEN. 5% for patients with SJS.

- On average, death occurs in every third patient with TEN, and it is mainly due to infections (S. aureus and Pseudomonas aeruginosa)
- Drug use is reported in over 95% of patients with TEN.
- Other rare causes include infections and immunization.
- More than 100 drugs have been identified to date as being associated with SJS/TEN.
- Most common: (know names of drugs NOT only the class)

ම Allopurinol ḡout patient
ම Antibiotics (Sulfonamides)
ම NSAIDs; Diclofenac - Ibuprofen.
ම Anticonvulsants Lamotrigine.

STEVENS–JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN): EPIDEMIOLOGY AND RISK FACTORS	
Annual incidence	1.2–6 per million (SJS) 0.4–1.2 per million (TEN)
Ratio women:men	1.5:1
Risk factors	Slow acetylator genotypes
	Immunosuppression (e.g. HIV infection, lymphoma)
	Concomitant administration of radiotherapy and anticonvulsants (most commonly, those with brain tumors)
	HLA-B*1502: Asians and East Indians exposed to carbamazepine
	HLA-B*5801: Han Chinese exposed to allopurinol
	HLA-A*3101: Europeans exposed to carbamazepine

- It's more common here.
- Genetics play a role.

Drugs Associated with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis من باب العلم

Drugs Most Frequently Associated*	Drugs Also Associated
Sulfadoxine	Cephalosporins
Sulfadiazine	Fluoroquinolones
Sulfasalazine	Vancomycin
Co-trimoxazole	Rifampin
Hydantoins	Ethambutol
Carbamazepine	Fenbufen
Barbiturates	Tenoxicam
Benoxaprofen†	Tiaprofenic acid
Phenylbutazone	Diclofenac
Isoxicam†	Sulindac
Piroxicam	Ibuprofen
Chlormezanone	Ketoprofen
Allopurinol	Naproxen
Amithiozone	Thiabendazole
Aminopenicillins	

MEDICATIONS MOST FREQUENTLY ASSOCIATED WITH STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

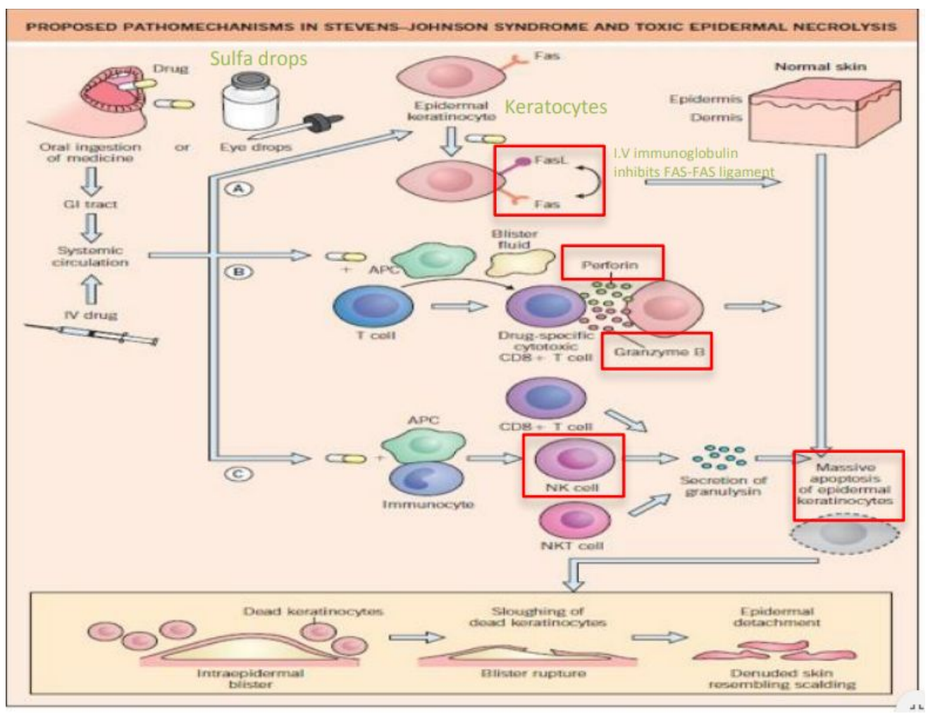
من باب العلم

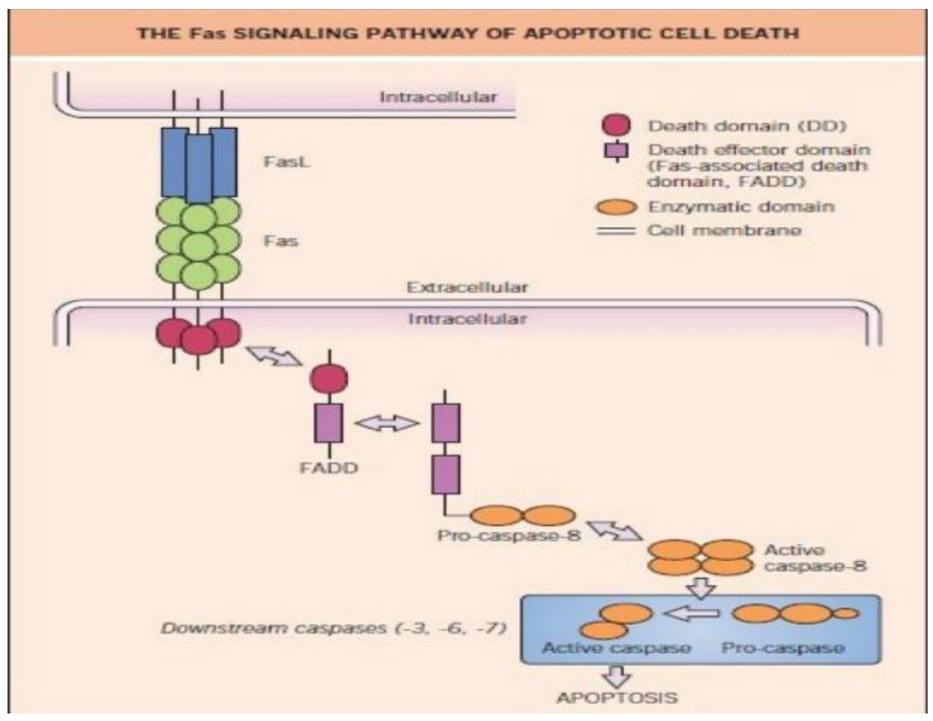
Allopurinol
Aminopenicillins
Amithiozone (thioacetazone)*,†
Antiretroviral drugs, especially NNRTIs
Barbiturates
Carbamazepine
Chlormezanone*,‡
Phenytoin anticonvulsants
Lamotrigine
Phenylbutazone*,§
Piroxicam
Sulfadiazine*,†
Sulfadoxine†
Sulfasalazine
Trimethoprim–sulfamethoxazole

*Not available in the US.
†Antibacterial.
‡Sedative/hypnotic.
§Nonsteroidal anti-inflammatory drug.

Pathogenesis of SJS/TEN:

- An idiosyncratic, delayed hypersensitivity reaction.
- TEN is associated with an impaired capacity to detoxify reactive intermediate drug metabolites.
- Slow acetylators.
- Immunocompromised pts.
- HIV, With AIDS, the risk of developing TEN is 1000-fold higher than in the general population.
- It is thought to be initiated by an immune response to an antigenic complex formed by the reaction of such metabolites with certain host tissues.
- There is evidence that systemic lupus is a risk factor
- **Genetic susceptibility** (increased incidence of **HLA-B12** in affected individuals)



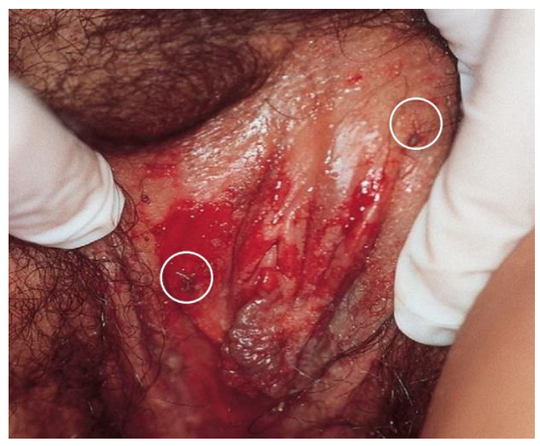


• Understanding pathogenesis is essential to understand the management. He took the medication whether IV – oral or drops the body will react to it as if its an antigen (theory B) and it will go to the keratocyte which can be an antigen presenting cell and recruits' T cells and the T cells will act as if it's a virus and starts making CD8 T cells and these cells will start producing cytotoxic compounds such as perforin and granzyme B and will cause necrolysis and apoptosis of skin cells and this is one of the theories and this is one of the treatment sites. Another theory (theory A) is that there are receptors on the skin cells called Fas and will become fas and fas ligand and sends signals to the cell to die (Site of action of immunoglobulins). The last theory (theory C) is through natural killer cells and they will secrete granulysin which is cytotoxic

Clinical Features of SJS

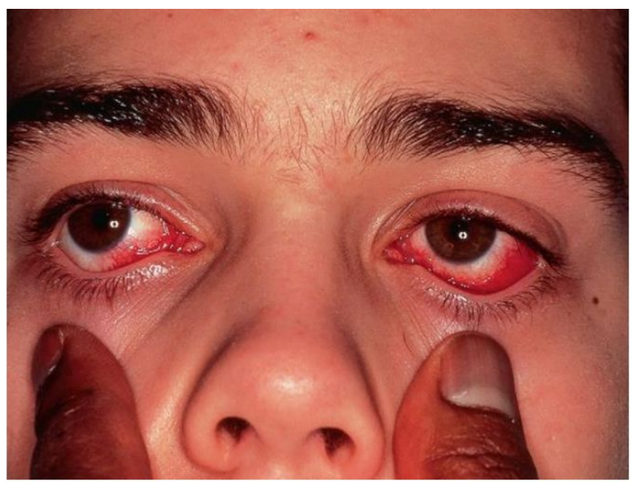
- There must be evidence of mucosal involvement.
- Fever, Stinging eyes, Headache, Malaise, Arthralgia.
- Cough productive of thick, purulent sputum. It's a dry cough in the beginning then becomes productive but its due to INJURY of the the respiratory mucosa not due to the URTI (may also involve GI mucosa)
- Burning rash begins symmetrically on the face & upper part of the trunk.
- Erythema and erosions of the buccal, ocular and genital mucosa are present in more than 90% of patients. Can even present without skin involvement!
- The epithelium of the respiratory tract is involved in 25% of patients with TEN, and gastrointestinal lesions (e.g. esophagitis, diarrhea) can also occur.
- **The cutaneous lesions** are characterized as follows:
  - The rash can begin as macules that develop into papules, vesicles, bullae, urticarial plaques, or confluent erythema
  - The typical lesion has the appearance of a target-like; this is considered pathognomonic
  - In contrast to the typical lesions of erythema multiforme (3 zones), these lesions have only 2 zones of color
  - The lesions have a tendency to coalesce.
  - Lesions may become bullous and later rupture, leaving denuded skin; the skin becomes susceptible to secondary infection (Impetigo, yellow golden crust).
  - Urticarial lesions typically are not pruritic. The lesions core may be vascular, purpuric or necrtotic; the zone is surrounded by macular erythema
  - Infection may be responsible for the scarring or if the ulcer is deep (Consult ophtha if injury reached the eye, can cause blindness) associated with morbidity.
  - Although lesions may occur anywhere, the palms, soles, dorsum of the hands, and extensor surfaces are most commonly affected.
- **Nikolsky sign** (positive in some area): Applying pressure to normal skin will induce detachment
- **Signs** of mucosal involvement can include the following:
  - Erythema, Edema, Sloughing , Blistering, Ulceration, Necrosis.
- Sometimes the systemic symptoms begin before the cutaneous symptoms, so patients are misdiagnosed
- The following **ocular signs** may be noted on slit-lamp examination:
  - **Eyelids**: Trichiasis, distichiasis, meibomian gland dysfunction, blepharitis
  - **Conjunctiva**: Papillae, follicles, keratinization, subepithelial fibrosis, conjunctival shrinkage, foreshortening of fornices, symblepharon, ankyloblepharon
  - **Cornea**: Superficial punctate keratitis, epithelial defect, stromal ulcer, neovascularization, keratinization, limbitis, conjunctivalization, stromal opacity, perforation

Call ophthalmology can cause scarring blindness



• Skin here is thin so you'll see erosions not ulcers (white circle).
• Know how to differentiate between ulcers (bleeding = mid of dermis) and erosions.(superficial)

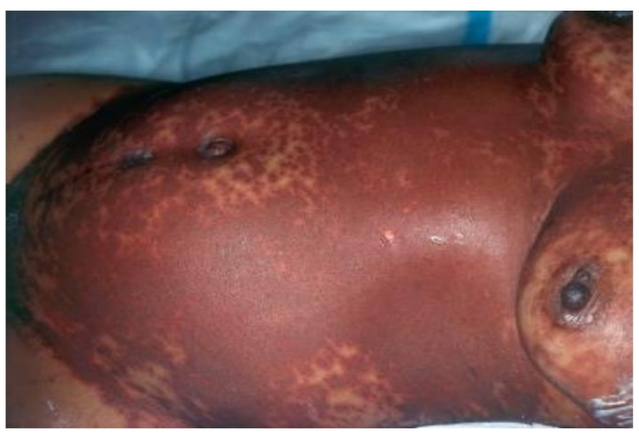
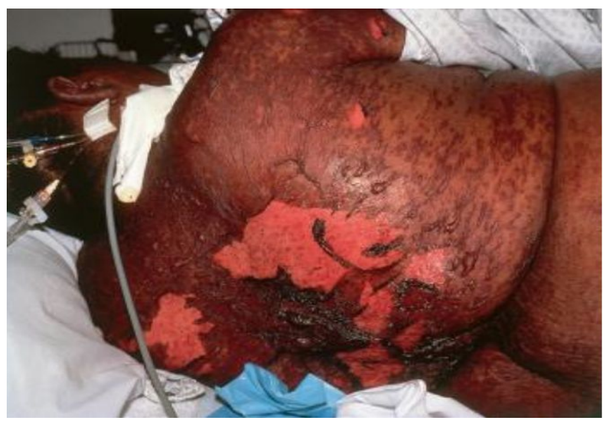
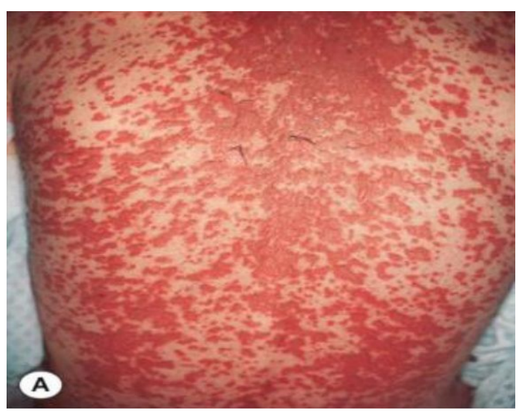
Could cause scarring, strictures of the urethra

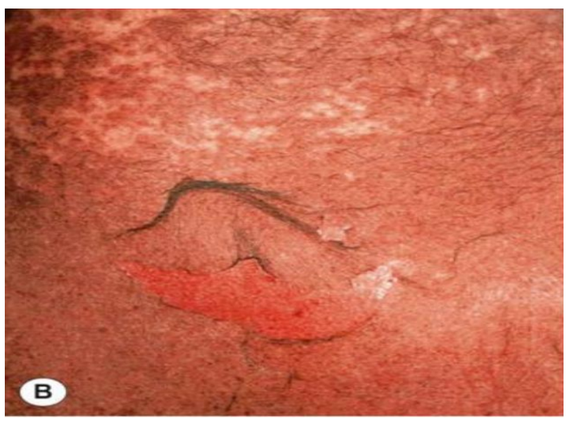


- You should examine genitalia.
- Slit lamp examination needed.
- Not to confuse with allergic conjunctivitis this is serious and you must stop the medication

Clinical Features of TEN

- Fever, stinging eyes, and pain upon swallowing, any of which can precede cutaneous manifestations by 1 to 3 days.
- Skin lesions tend to appear first on the trunk, spreading to the neck, face, and proximal upper extremities.
- The scalp, distal portions of the arms as well the legs are relatively spared, but the palms and soles can be an early site of involvement. Less mucous membrane involvement when compared to SJS.
- First, erythematous, dusky-red, or purpuric macules of irregular size and shape, and have a tendency to coalesce. - At this stage, and in the presence of mucosal involvement and tenderness, the risk of rapid progression to SJS or TEN should be strongly suspected.
- In the absence of spontaneous epidermal detachment, a Nikolsky sign should be sought by exerting tangential mechanical pressure with a finger on several erythematous zones. This sign is considered positive if dermo-epidermal cleavage is induced. Avoid dressing!!
- A target-like appearance.
- This process can be very rapid (hours), or several days.
- The necrotic epidermis then detaches from the underlying dermis, and fluid fills the space between the dermis and the epidermis, giving rise to blisters
- The blisters break easily (flaccid) and can be extended sideways by slight pressure of the thumb as more necrotic epidermis is displaced laterally (Asboe-Hansen sign: Pressing on a bulla will cause it to rupture).
- - Tense blisters are usually seen only on the palmar & plantar surfaces when the epidermis is thicker more resistant to mild trauma. How to differentiate from other blistering diseases? In TEN tense blisters involve the palms and soles only unlike other diseases involving the whole body

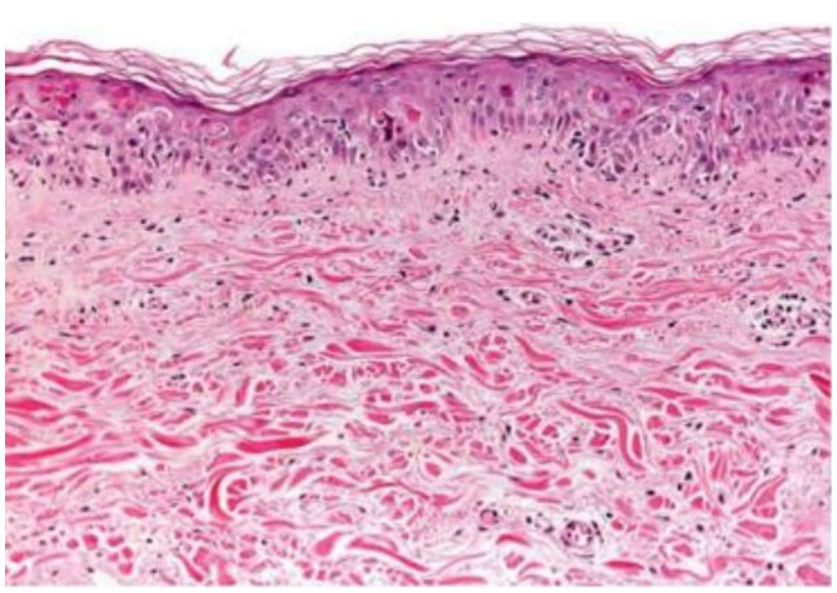
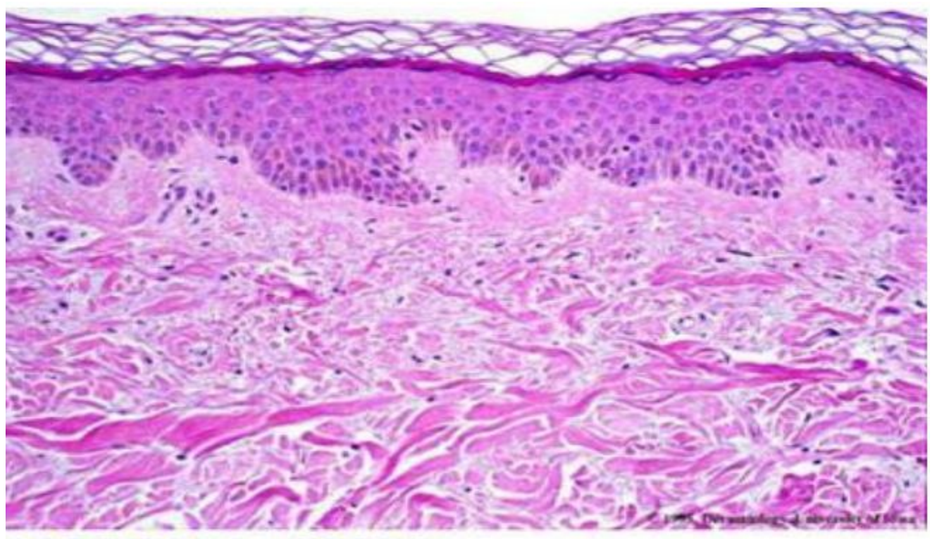






x TEN: Patient is ill probably in ICU if more than 10% of BSA involved its either TEN overlap or TEN.
x Skin looking like Cigarette paper (Positive Nikolosky)
x Dusky-Red ´ Non blanchable.
x Picture (A) Steven overlap based on BSA. Picture (B) TEN. (important to revise how to calculate BSA).
x The back alone is almost 15% so if you see back involvement defiantly it's more than 10%

Histology:

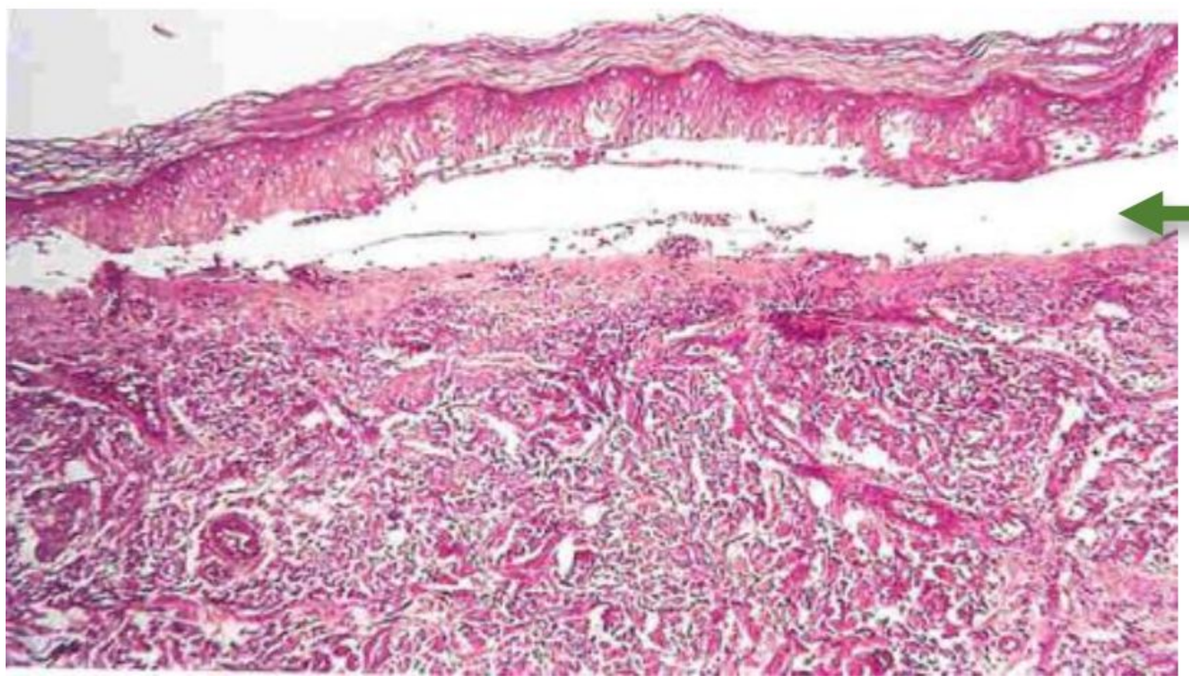
- Biopsy is helpful specially to convince other medical teams.
- Biopsy showing inflammation, death and shrinkage of keratocytes.

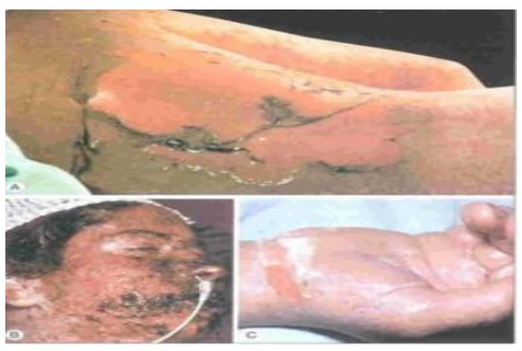



Pathology of TEN

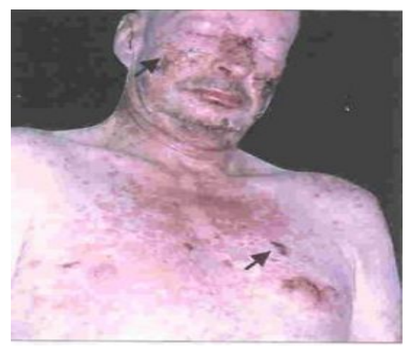
A subepidermal blister with overlying confluent necrosis of the entire epidermis and a sparse perivascular infiltrate composed primarily of (CD8) lymphocytes.

Why do we biopsy if it obvious? Sometimes it is not obvious, we want to see clinically insignificant detachment





TEN



SJS

DDx of TEN:

(Biopsy can be helpful in differentiating)

- Stevens-Johnson Syndrome
- Staphylococcal Scalded Skin Syndrome (Peds)
- Toxic Shock Syndrome (Adult women)

CLINICAL FEATURES THAT DISTINGUISH STEVENS–JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), AND SJS–TEN OVERLAP

Clinical entity	SJS	SJS–TEN	TEN
Primary lesions	Dusky and/or dusky red lesions Flat atypical targets	Dusky and/or dusky red lesions Flat atypical targets	Poorly delineated erythematous plaques
			Epidermal detachment – spontaneous or by friction
			Dusky red lesions
			Flat atypical targets
Distribution	Isolated lesions	Isolated lesions	Isolated lesions (rare)
	Confluence (+) on face and trunk	Confluence (++) on face and trunk	Confluence (+++) on face, trunk and elsewhere
Mucosal involvement	Yes	Yes	Yes
Systemic symptoms	Usually	Always	Always
Detachment (% BSA)	<10	10–30	>30

Prognosis of TEN

SCORTEN A prognostic scoring system for patients with TEN:

- Age >40 years
- HR >120 bpm
- Cancer or hematologic malignancy
- BSA involved on day 1 above 10%
- Serum urea level > 10 mmol/l
- Serum bicarbonate level <20 mmol/l
- Serum glucose level >14 mmol/l

Mortality rate:

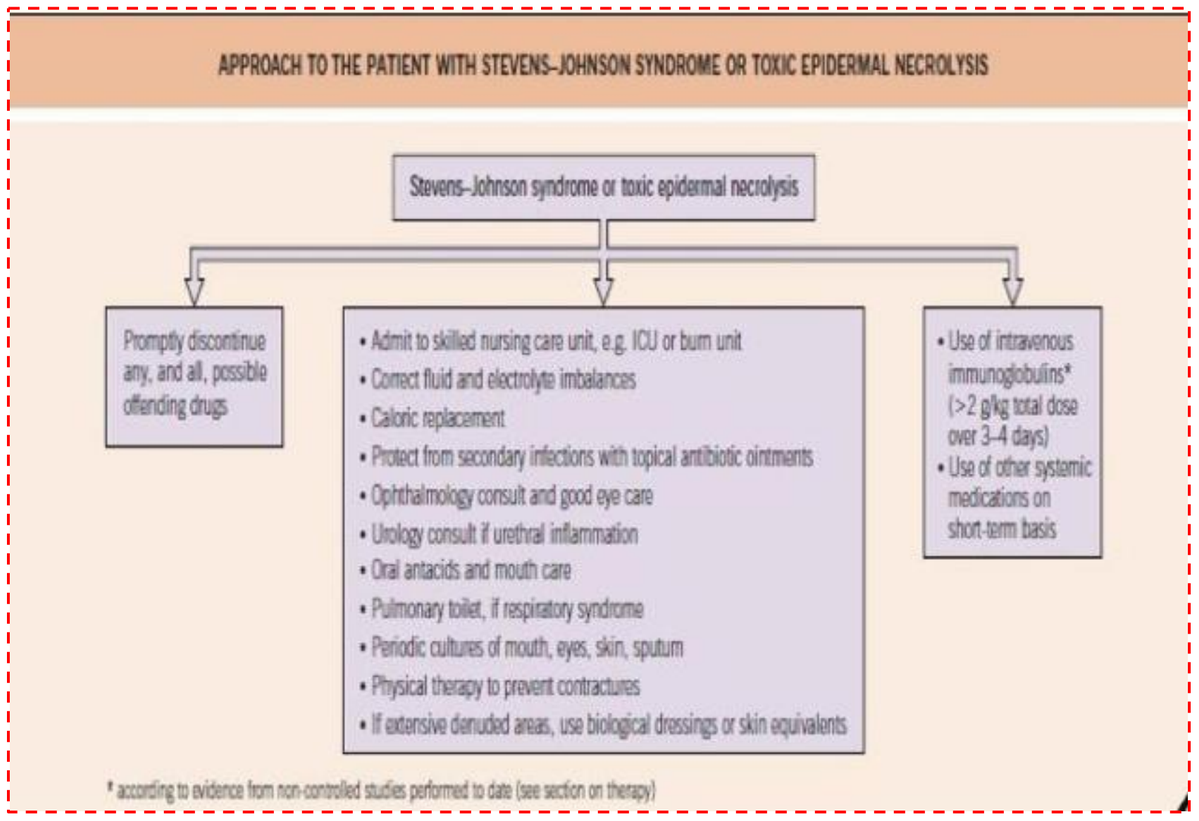
0-1 ----- 3.2%

2 ----- 12.1%

3 ----- 35.8%

4 ----- 58.3%

5 or more ---- 90%



Management TEN/ SJS

Death occurs in 1/3 of pts with TEN (mainly due to infections). (We don't usually give antibiotics as prophylaxis , we only give until we have infection ASAP)

General measures: (First two most important steps)

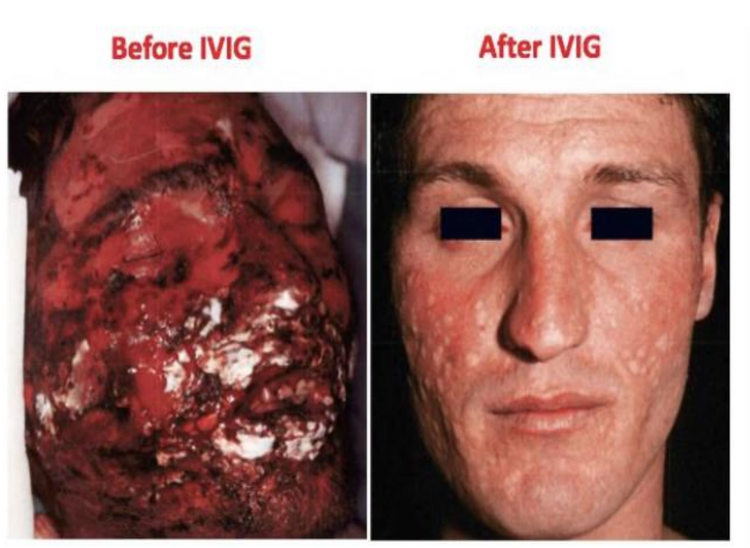
- Early diagnosis.
- Immediate discontinuation of the causative drug(s)
- Management on a specialist ICU or burn unit.
- Multidisciplinary teamwork. (call Derma , □ ID ,□ Ophtha □ Pedia □ ,OBGYN □ ,GI □ , Pulmo)
- Supportive care. Temp of the room, no dressing (if you want to put dressing just vaseline it acts like a barrier and will allow re-epitheliazation) (very important)
- Specific therapy.

Supportive care

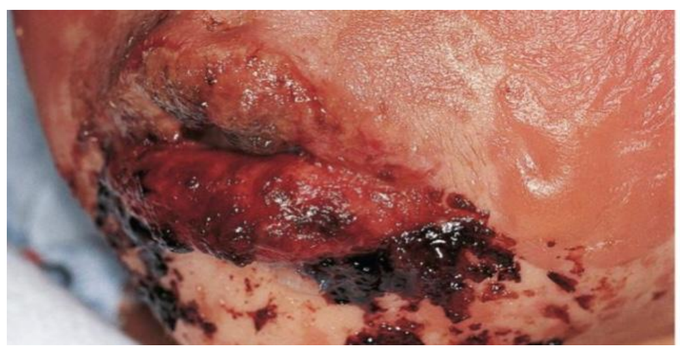
- Pt should be manipulated as little as possible as every movement is a potential cause of epidermal detachment Avoid dressing.
- all patient manipulations should be performed sterilely.
- venous catheters should be placed, if possible, in a region of non-involved skin
- Non-detached areas are kept dry and not manipulated.
- Detached areas, should be covered with Vaseline® gauze until re-epithelialization has occurred. Normally skin will heal within 30 days. Keep it dry as possible to promote healing. Infection or diabetes delay wound healing.
- Careful monitoring of fluid & electrolyte status with therapy for any imbalance. Treat as if you would a burn patient. Risk of renal failure, no urine output, heart failure, same complications as burn patients.
- Nutritional support.
- Warming of environment to reduce the increase in metabolic rate.
- Appropriate analgesia. (codeine not NAIDS)
- Prevention, early detection & treatment of infection.
- There is NO evidence that prophylactic antibiotic provide benefit & most authors reserve antibiotics therapy for treatment of proven infection (care must be taken in screening for sepsis & surveillance of lines/catheters to allow prompt intervention).
- For the eyes regular examination by an ophthalmologist is recommended.
- Eyelids should gently cleansed daily with isotonic sterile sodium chloride solution, and an ophthalmic antibiotic ointment applied to the eyelids.

Specific therapy

- To date, no specific therapy has shown efficacy in prospective, controlled clinical trials.
- Cyclosporine
- Cyclophosphamide
- Systemic steroids (their use has been much debated & remains controversial) more mortality.
- Intravenous Immunoglobulins (IVIG): (most promising, ↑survived) Contain antibodies against Fas that are able to block the binding of FasL to Fas.
- When used in high doses (0.75 g/ kg/day for 4 consecutive days) to treat patients with TEN, IVIG consistently and rapidly blocked the progression of epidermal detachment and disease in 10 of the 10 patients treated in a preliminary pilot study



TEN, there is scarring but at least the patient lived.



SJS hemorrhagic crust.

PUBLISHED STUDIES (WITH ≥10 PATIENTS) ON THE USE OF IVIG FOR THE TREATMENT OF TOXIC EPIDERMAL NECROLYSIS

	Viard 1998	Trent 2003	Prins 2003	Campione 2003	Al-Mutairi 2004	Shortt 2004	Tan 2005	Stella 2007	Bachot 2003	Brown 2004	Schneck 2008
Study	Prospect NC	Retro NC	Retro NC	Prospect NC	Prospect NC	Retro NC	Retro NC	Retro C	Prospect NC	Retro NC	Retro C
No. of patients	10	24	48	10	12	16	12	23	34	24	75
Detachment of epidermis (% BSA)	39	44	45	49	58	"65"	–	–	19	49	–
Dose of IVIg (g/kg)*	3	4	3	2	2-5	2.8	2	–	2	1.6	1.9 (0.7–2.3)
Predicted mortality (scoring system)	–	33% (SCORTEN)	–	35% (SCORTEN)	–	38% (APACHE)	–	36% (SCORTEN)	24% (SCORTEN)	29% (SCORTEN)	25% (SCORTEN)
Actual mortality	6%	4%	12%	10%	0%	25%	8%	26%	32%	42%	34%

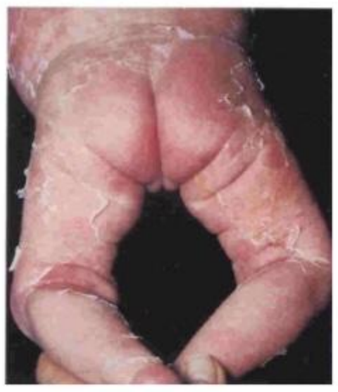
*Usually administered over 3-4 days

Corticosteroids:

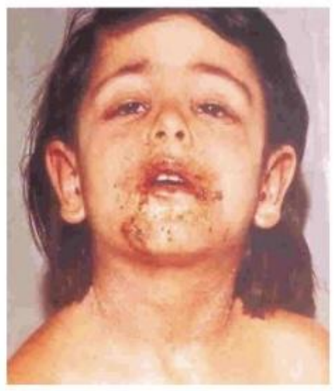
- It have been used in management of TEN for the last 30 years.
- Their use has been much debated & remains controversial.
- Action:-
  - Anti-inflammatory.
  - Immunosuppressant.
  - Anti-apoptotic
- One series (n=44) reported excessive mortality associated with prolonged use of systemic steroid therapy.
- The balance of available evidence suggests that, corticosteroid have no significant beneficial effect on TEN.
- Corticosteroid can not be recommended as a therapy for TEN.
- (British journal of dermatology 2005. 153, pp 241-253).

Staphylococcal scalded skin syndrome

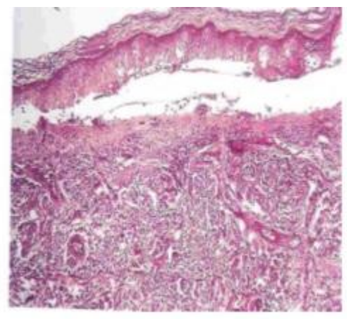
- Usually occur in newborns and young children.
- It is induced by a staphylococcal exotoxin (epidermolysis) that targets desmoglein 1.
- The areas of erythema are tender and widespread, but spare the mucous membranes (very important!!), palms, and soles.
- The Nikolsky sign may be positive as in TEN (Doctor said it will be (-) in ssss), but it results in a superficial subcorneal cleavage, not a dermo-epidermal separation. Fragile bullous lesions then develop, and they are rapidly followed by exfoliation of sheets of epidermis.
- **Histologically**: Subcorneal split with normal underlying epidermis. On biopsy in TEN there is total necrosis of epidermis, in SSSS it is only superficial.



Superficial peeling.

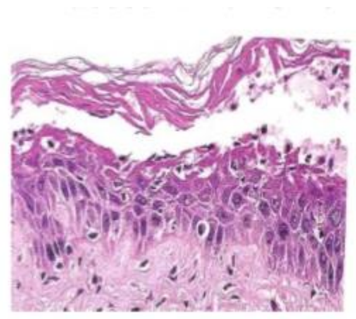


Secondary infection NOT mucosal involvement.



TEN

- At the junction.
- Treatment: STOP THE MEDICATION.



SSSS

- Superficial dermis only.
- Treatment: ADD MEDICATION.

COMPARISON BETWEEN TOXIC EPIDERMAL NECROLYSIS (TEN) AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME		
	TEN	SSSS
Cause	Usually drug-induced	Toxin-producing *S. aureus* infection
Age	Adults	Infants and young children
Histology	Dermo–epidermal separation; dermis has a dense inflammatory infiltrate	Granular layer split in epidermis; dermis lacks inflammatory infiltrate
Distribution of rash	Areas of sparing present	Generalized
Mucous membranes	Involved	Uninvolved
Nikolsky's sign	In some areas, difficult to elicit	Present in seemingly uninvolved skin
Face	Lip and mucous membrane redness, edema	Perioral crusting and fissuring with mild facial swelling and erosions
Treatment	Standard burn treatment, IVIG, corticosteroids (controversial)	Antibiotics (β-lactamase resistant) and supportive care

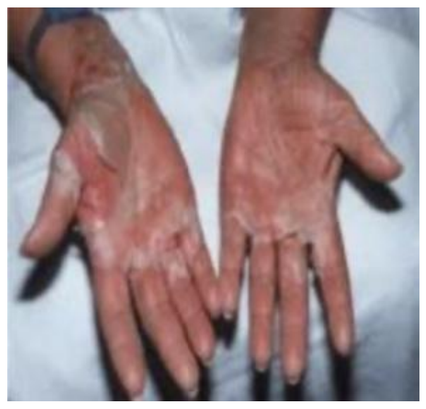
In SSSS: The peeling will occur in areas that are NOT erythematous
In TEN: The peeling will occur in the dusky erythematous area.
Very importan tod iffrientiate between SSSS and TEN cause if u have mistaken TEN for SSSS and gave ABX this could aggravate TEN and make it worse.

Toxic shock syndrome (TSS)

- Is an inflammatory response syndrome characterized by fever, rash, hypotension and multiorgan involvement.
- TSS has been typically associated with tampon use in healthy menstruating women.
- The disease is now known to also exist in men, neonates, and non-menstruating women.
- It has been linked to many bacterial infections, including pneumonia, osteomyelitis, sinusitis, and skin and gynecologic infections.

Staphylococcal TSS	(15 - 35 years)	Higher in women	mortality rate is less than 3%
Streptococcal TSS	(20 -50 years)	both sex	mortality rate is 30 - 70%.

- Prodromal period of 2-3 days:
- Fever, nausea and/or vomiting
- Profuse watery diarrhea with abdominal pain.
- Pharyngitis and/or headache, confusion.
- Hypotension.



Why does the skin start peeling and becomes erythematous? Because the body can't detoxify the toxins anymore.

-Negative Nikolsky – No mucous membrane involvement.

-Skin findings:

- Diffuse rash, occasionally patchy and erythematous, with desquamation (this is what makes it a differential diagnosis) occurring approximately 1-2 weeks later
- Rash initially appearing on trunk, spreading to arms and legs, and involving palms and soles
- Signs of multiorgan involvement

Take home messages

- Prodrome of URT symptoms, fever and painful skin
- SJS and TEN are two rare, potentially fatal, adverse cutaneous drug reactions of differing severity, characterized by mucocutaneous tenderness and erythema as well as extensive exfoliation.
- SJS is characterized by <10% body surface area of epidermal detachment, SJS–TEN overlap by 10–30%, and TEN by >30%
- The average mortality rate is 1–5% for SJS and 25–35% for TEN; it can be even higher in elderly patients and in those TEN pts with a very large surface area of epidermal detachment
- Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), and rapid initiation of supportive care and specific therapy
- Specific therapies that have the potential to selectively block keratinocyte apoptosise.g high-dose IVIg, may provide added benefit over supportive care alone

Questions:

1) A 4 years old child presented with macular scarlatiniform rash and sandpaper rash. Nikolsky sign is positive. What is the diagnosis?

A. Kawasaki syndrome
B. Staphylococcal Scalded Skin Syndrome
C. Scarlet fever
D. Drug eruption

2) A 20 year old lady who is epileptic present with 2 days history of fever, sore throat, malaise & painful cutaneous eruptions with dusky red color, 40% of epidermal detachment & hemorrhagic crusts of the lips- One month back, the epileptic medication was changed from valproate to carbamazepine- What is your diagnosis?

A. TEN secondary to carbamazepine
B. SJS secondary to carbamazepine
C. SJS secondary to valproate
D. TEN secondary to valproate

3) A patient known to have grand mal seizures, just started on carbamazepine. He came to A/E with 1 week history of fever, malaise, target lesions and erythema and areas of skin necrosis, with painful crusted lesions on lips. Body surface involvement is 20%. What is the most likely diagnosis?
A. Steven johnson syndrome.
B. Toxic Epidermal Necrolysis.
C. Erythema Multiforme.
D. Erythrodermic psoriasis

4) 38 years old man referred to the on call dermatologist with a 2-day history of sore throat, malaise and rash. Three weeks previously his antiepileptic medication had been changed to carbamazepine, on examination less than 10% of the skin surface is involved with erythematous, a typical target lesion on trunk, limbs and face, cheilitis, oral ulcers, conjunctivitis and erosions of the urethra. What is the most likely diagnosis?

A. Pemphigus vulgaris.
B. Toxic epidermal necrolysis
C. Stevens-Johnson syndrome
D. Erythema multiforme minor

5) Ten year old known to have epilepsy want to start carbamazepine, which HLA typing recommend be done before starting the treatment:

A. HLA-B1502
B. HLA-B1301
C. HLA-DCW4
D. HLA-B27

Answers:
1-B. 2-A>30%. 3-B (Depends on surface area, this is most likely SJS TEN overlap) 4- C. 5-A