Derma Team 436

Dermatological Emergencies

Objectives:

- **Not given**

Main Objective of this lecture is to differentiate betweet SJS – TEN – EM.

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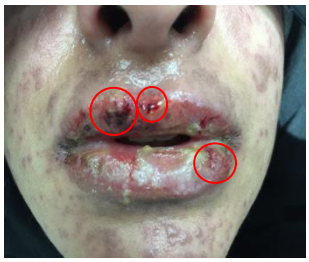
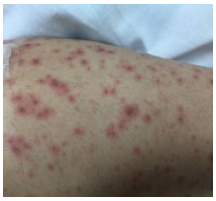
Template by group B
Before you start.. CHECK THE EDITING FILE
Sources: doctor's slides and notes + 436 group B team
[Color index: Slides| Slides| Important|doctor notes|Extra]

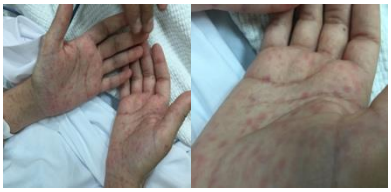
Clinical Real ER case



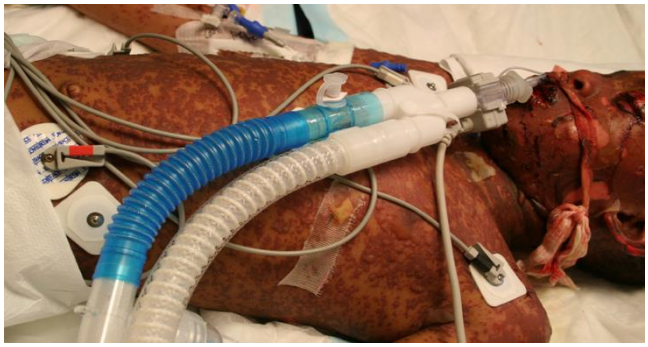
Describe the lesions:
On face: ill defined erythematous plaque with crustation.
On lips: Hemorrhagic crustation with ulcers and erosions



Describe the lesion:
Numerous irregular erythematous grouped papules.



Target like



Describe the lesion:
Numerous erythematous papules, bullae and, blistering.
It's basically a drug induced burn.

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 table is important

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 Cephalosporins NSAIDs Monoclonal antibodies Contrast media[1]
Anaphylaxis	30	Minutes to hours	5	
Fixed drug eruption	100	First exposure: 1–2 weeks Re-exposure: <48 hours, usually within 24 hours	0	TMP-SMX NSAIDs Tetracyclines Pseudoephedrine[a]
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 Anticonvulsants (aromatic) Allopurinol NSAIDs Lamotrigine
Toxic epidermal necrolysis			30	

[a]Non-pigmenting.
[1]Often anaphylactoid reaction.

- Time interval is very important in differentiating different drug reactions.
- Exthanthematous = 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 to 50%) "Allopurinol+NSAIDs".

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's Johnson syndrome(SJS)/Toxic epidermal necrolysis(TEN).
- Erythroderma.

Steven's Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN)

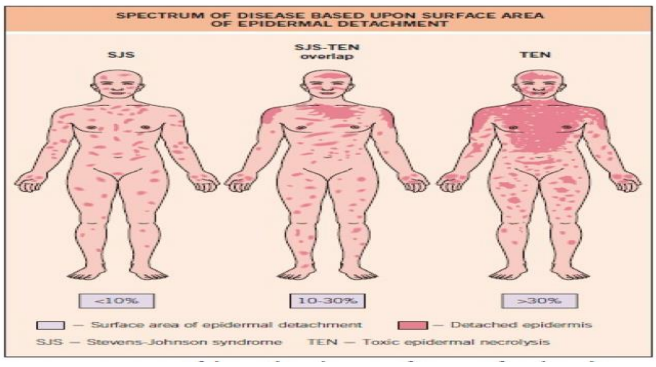
- Rare, acute, life-threatening mucocutaneous (skin + mucous-membrane) disease.
- Nearly always drug-related. (patients have problems in drug metabolism)
- Keratinocyte death separation of skin at the dermal-epidermal junction.
- Characteristic symptoms: High fever, skin pain, anxiety and asthenia. Shivering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

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.

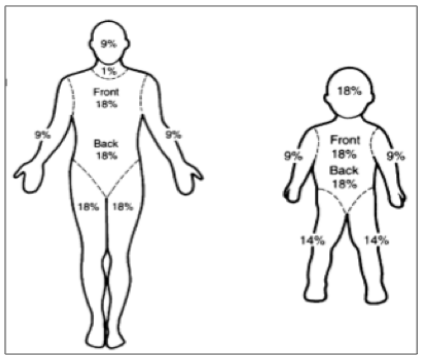
History:
- EM (erythema multiform) was first described by the Austrian dermatologist Ferdinand von Hebra in 1860.
- In 1922, two US physicians, Stevens and Johnson, described an acute mucocutaneous syndrome in two young boys.
- Characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and "EM-like" cutaneous lesions. It became known as Stevens–Johnson syndrome (SJS) and was recognized as a severe mucocutaneous disease with a prolonged course and occasional fatalities.
- SJS was later designated as EM major by Bernard Thomas in 1950. However, recent clinical investigations have made it clear that the term "EM major" should not be used to describe SJS as they are distinct disorders.
- In 1956, Alan Lyell described four pts with an eruption 'resembling scalding of the skin objectively and subjectively', which he called toxic epidermal necrolysis or TEN. 'Toxic' referred to toxemia – circulation of a toxin – which was thought to be responsible for the constitutional symptoms and epidermal necrosis.
- Lyell coined the term 'necrolysis' by combining the key CF 'epidermolysis' with the characteristic histopathological feature 'necrosis'.
- He also described an attack on the mucous membranes as part of the syndrome, with very little inflammation in the dermis, a feature that was later referred to as 'dermal silence.
- Erythema multiforme, SJS, and TEN were, at the time, considered to be part of a continuous spectrum of cutaneous reactions.
- 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.
- Increasingly, **SJS**, and **TEN** are considered to be **two ends of a spectrum** of severe epidermolytic adverse cutaneous drug reactions, differing only by the extent of skin detachment.

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



- SJS can progress to TEN if left untreated.
- 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.
- Calculating BSA is through areas of epidermal detachment NOT redness.



*An extra picture to help you revise Body Surface Area

Epidemiology

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

- Its more common here.
- Genetics play a role.

- 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**)**
  - Allopurinol "Gout patient"
  - Antibiotics (Sulfonamides)
  - NSAIDs; Diclofenac – Ibuprofen.
  - Anticonvulsants.

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

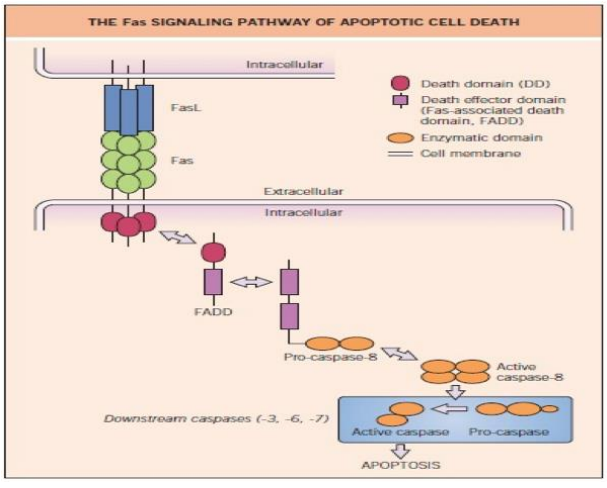
*Not available in the US.
†Antibacterial.
‡Sedative/hypnotic.
§Nonsteroidal anti-inflammatory drug.

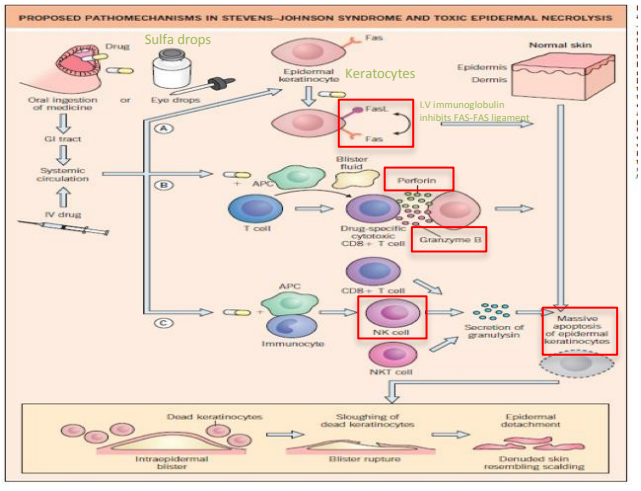
Drugs Associated with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis من باب العلم

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	

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)





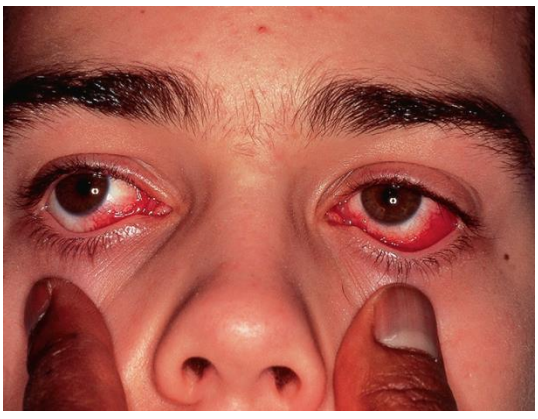
• Understanding pathogenesis is essential to understand the management. He took the medication whether IV – oral or drops the body will react to it as if its an antigen (theory B) and it will go to the keratocyte which can be an antigen presenting cell and recruits' T cells and the T cells will act as 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

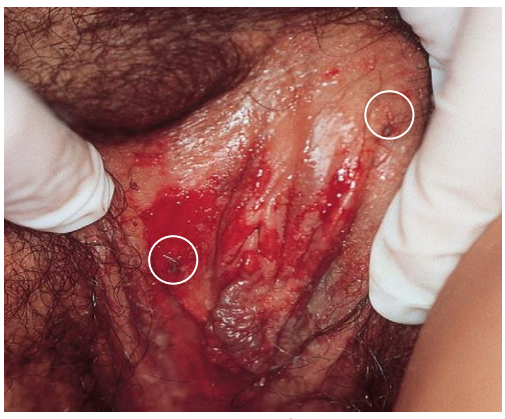
- There must be evidence of **mucosal involvement**.
-Fever, stinging eyes.
- Cough productive of thick, purulent sputum. The cough here is not due to the URTI its due to involvement of the respiratory mucosa.
- Headache. Malaise, Arthralgia.
- Burning rash begins symmetrically on the face & upper part 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
- 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



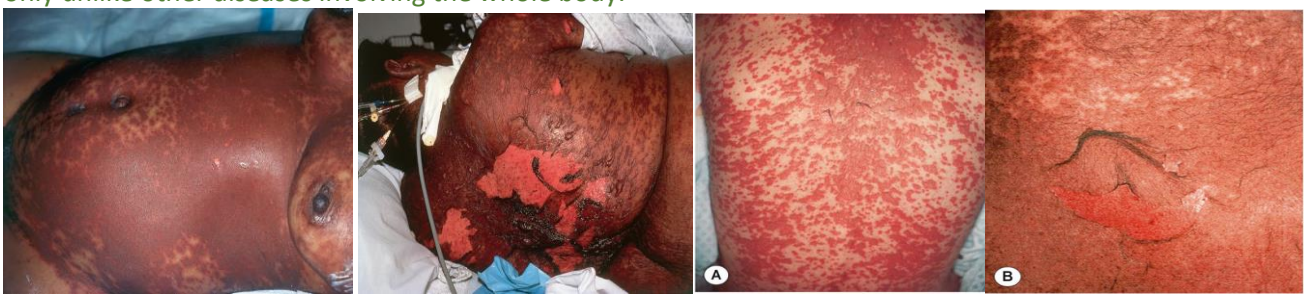
- You should examine genitalia.
- Slit lap examination needed.
- Not to confuse with allergic conjunctivitis this is serious and you must stop the medication



- 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)

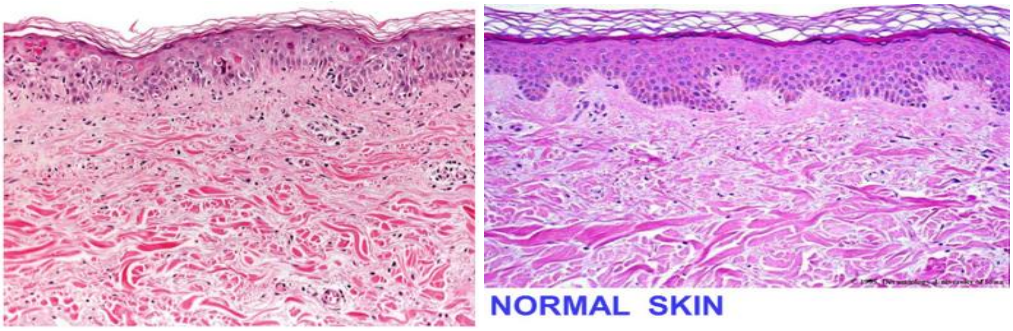
Clinical Features of TEN

- 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.



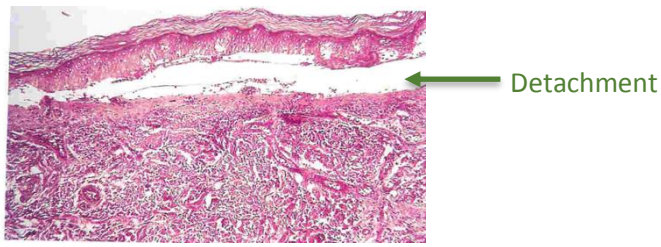
- TEN: Patient is ill probably in ICU if more than 10% of BSA involved its either TEN overlap or TEN.
- Skin looking like Cigarette paper (Positive Nikolosky)
- Dusky-Red – Non blanchable.
- Picture (A) Steven overlap based on BSA. Picture (B) TEN. (**important to revise how to calculate BSA**).
- The 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.

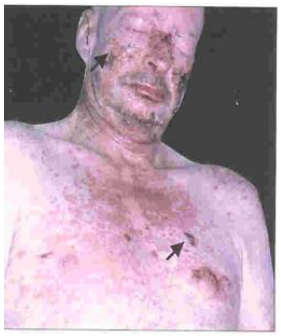
Pathology of TEN:
A subepidermal blister with overlying confluent necrosis of the entire epidermis ad a sparse perivascular infiltrate composed primarily of (CD8) lymphocytes.
Why do we biopsy if it obvious? Sometimes it is not obvious, we want to see clinically insignificant detachment



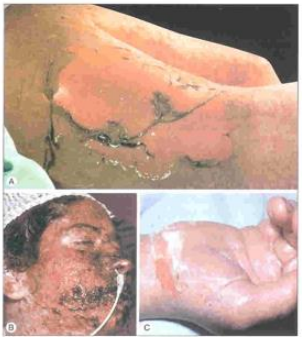
DDx of TEN: (Biopsy can be helpful in differentiating)
- Stevens-Johnson Syndrome
- Staphylococcal Scalded Skin Syndrome (Peds)
- Toxic Shock Syndrome (Adult women)

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



SJS



TEN

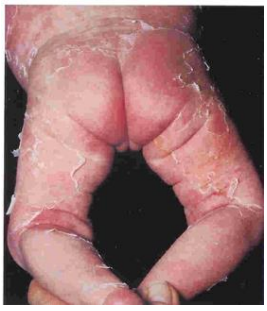
Staphylococcal scalded skin syndrome

- 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 shows a subcorneal split with normal underlying epidermis.

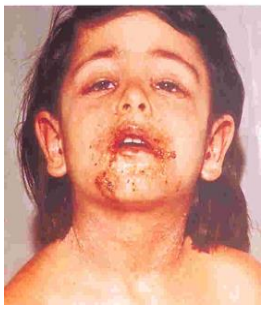
COMPARISON BETWEEN TOXIC EPIDERMAL NECROLYSIS (TEN) AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME

	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

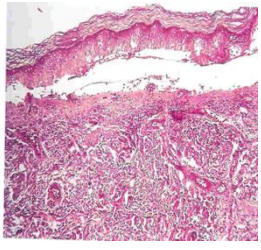
In SSSS: The peeling will occur in areas that are NOT erythematous
In TEN: The peeling will occur in the dusky erythematous area.



- Superficial peeling.

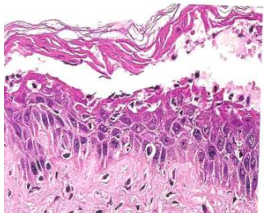


- Secondary infection NOT mucosal involvement.



TEN

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



SSSS

- Superficial dermis only.
- Treatment: ADD MEDICATION.

Toxic shock syndrome (TSS) (not common in our society)

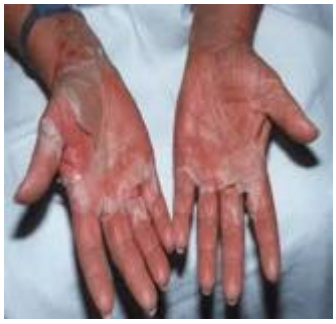
- Is an inflammatory response syndrome characterized by fever, rash, hypotension and multiorgan involvement.
- TSS has been typically associated with tampon use in healthy menstruating women. (it's a risk not a cause)
- The disease is now known to also exist in men, neonates, and non-menstruating women.
- 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

-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



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

Prognosis of TEN:

SCORTEN

Prognostic factors	Points
Age >40 years	1
Heart rate >120 bpm	1
Cancer or hematologic malignancy	1
BSA involved on day 1 above 10%	1
Serum urea level (>10 mmol/l)	1 Renal function
Serum bicarbonate level (<20 mmol/l)	1 Metabolic acidosis
Serum glucose level (>14 mmol/l)	1
SCORTEN	**Mortality rate (%)**
0–1	3.2
2	12.1
3	35.8
4	58.3
≥5	90

- A calculation of mortality.

Management:

Death occurs in 1/3 of pts with TEN (mainly due to infections). (but we don't give prophylactic!! We only give if there're signs of infection اول ظهور لبوادر انفكشن and we give it 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. (very important)
- Specific therapy.

Supportive care.

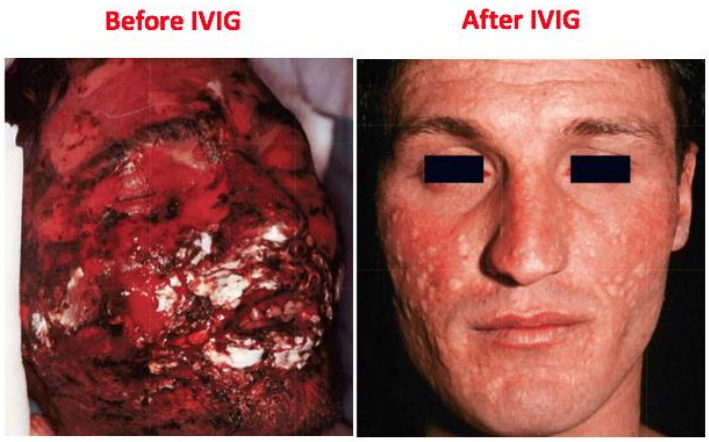
- Pt should be manipulated as little as possible as every movement is a potential cause of epidermal detachment Avoid dressing.
- all patient manipulations should be performed sterilely.
- venous catheters should be placed, if possible, in a

Specific therapy

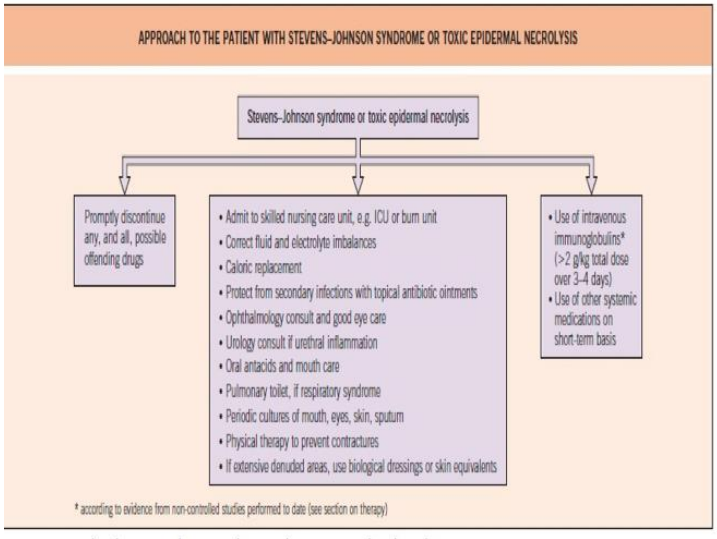
- To date, no specific therapy has shown efficacy in prospective, controlled clinical trials.
- Cyclosporine
- Cyclophosphamide
- Systemic steroids (their use has been much debated & remains controversial) more mortality.

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.

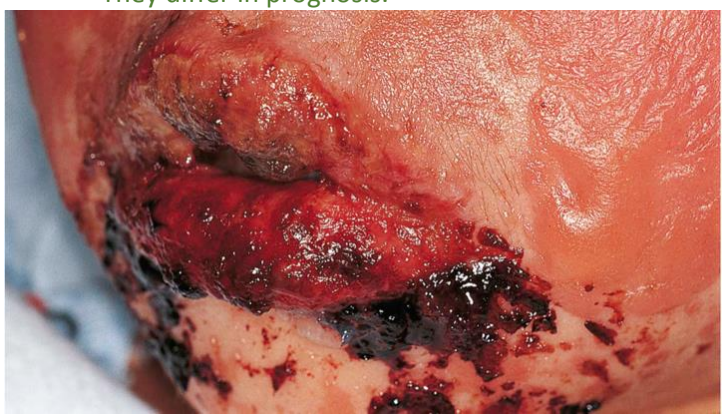
- Intravenous Immunoglobulins (IVIG): (most survived)
Contain antibodies against Fas that are able to block the binding of FasL to Fas.
- Used in high doses (0.75 g/ kg/day for 4 consecutive days) to treat patients with TEN.



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



- They differ in prognosis.

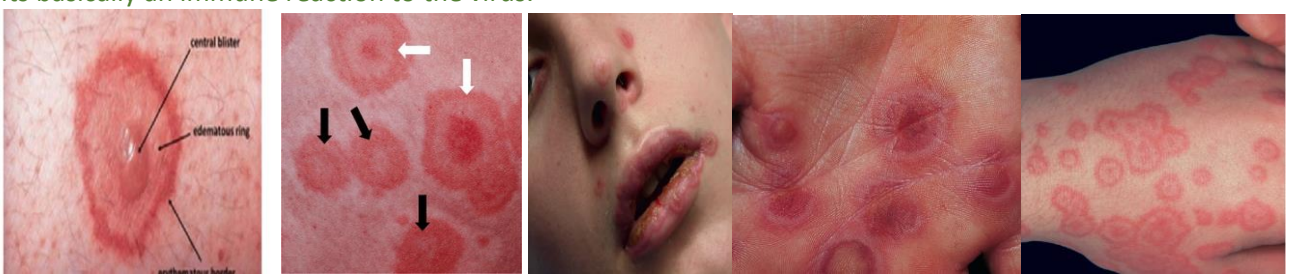


- SJS hemorrhagic crust.

Erythema multiforme (EM)

- 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 " do you have bullae 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: Usually clinical but done for research purposes or if you cannot r/o blistering diseases.
- 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.

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 EM has no effect on the course of the erythema multiforme. It isn't an infection, is it an immunoreaction to the virus

Course & complications:
- Most patients with (EM) have an uncomplicated course, healing of the mucosal areas is usually complete.
- Scars and strictures of the esophageal, urethral, vaginal, and anal mucosa rarely occur. In mucosa, not skin.
- Severe eye complications (20%), such as purulent conjunctivitis, anterior uveitis, scarring of the conjunctiva, symblepharon, may result in permanent blindness.

DIFFERENCES BETWEEN URTICARIA AND ERYTHEMA MULTIFORME

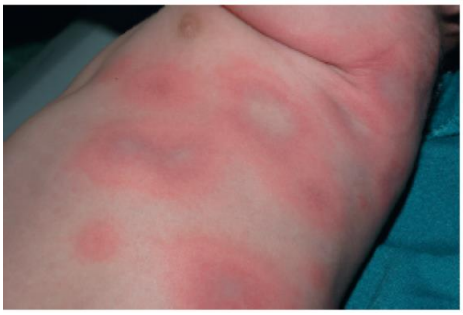
Urticaria	Erythema multiforme
Central zone is normal skin	Central zone is damaged skin (dusky, bullous or crusted)
Lesions are transient, lasting less than 24 hours	Lesions "fixed" for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
Associated with swelling of face,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

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.



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

Erythroderma

- Erythro=red. Derma=skin.
- its not a diagnosis but rather a clinical presentation.
- Generalized redness and scaling of >90% of the skin surface.
- Considered a serious, at times life-threatening condition.
- It does not represent a disease but rather a clinical presentation of a variety of diseases.
- M > F (avg age is ~50 yrs)

Causes of Erythroderma:
- Pre-existing dermatosis (psoriasis, eczema) 50%
- Drugs 15%
- Lymphoma, leukemia 10%
- Undetermined 25% Idiopathic

Clinical features of erythroderma:
- Erythema precedes exfoliation by 2-6 days.
- Pruritis in 90% of patients. Remember that in TEN and SJS one of the main symptoms was pain NOT pruritis.
- Palmoplantar keratoderma. Thick palms and soles.
- Nail changes in 40%.
- Diffuse non-scarring alopecia.

Systemic manifestations:
- Generalized peripheral lymphadenopathy (50%).
- Pedal or pretibial edema in ~50% of patients.
- Tachycardia, risk of high output cardiac failure (esp. in the elderly)
- Thermoregulatory disturbances (hyper-hypothermia).

Manifestations based on causative disease:

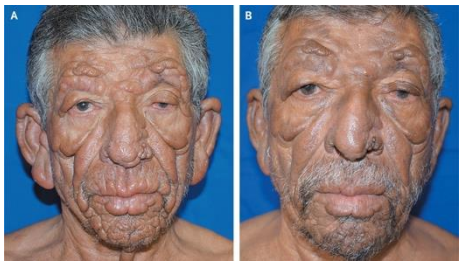
1) Psoriasis:
-Nail changes (Oil-drop, onycholysis, nail pits)

2) Atopic dermatitis:
- Pruritus is intense
- Lichenification

3) Drug reactions:
-Morbilliform or scarlatiniform exanthem

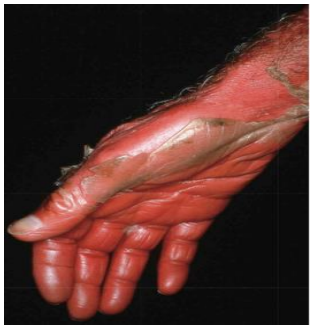
4) Idiopathic erythroderma:
-Elderly men
-Lymphadenopathy and extensive palmoplantar keratoderma.
-Peripheral edema

5) CTCL: Cutaneous T-cell Lymphoma
-Sezary syndrome: Erythroderma, Malignant (atypical) T lymphocytes and generalized lymphadenopathy.
-Painful fissured keratoderma, diffuse alopecia, leonine facies. Lion face.



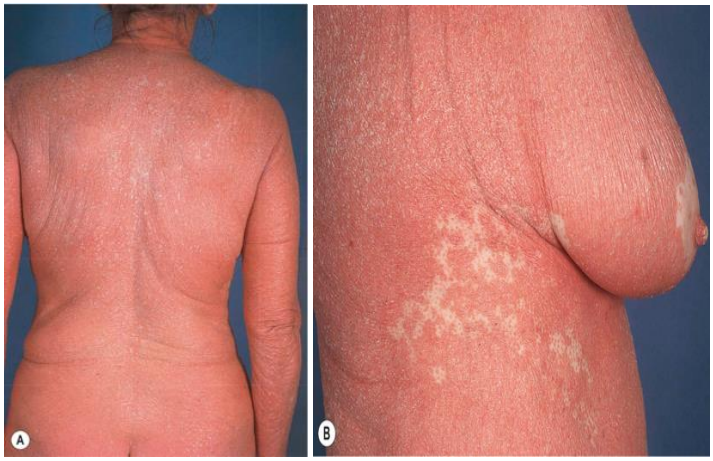
Extra picture

6) PRP: pityriasis rubra pilaris (papulosquamous)
- Salmon to orange color, scaly black areas, keratoderma on palms and soles.
- Follicular keratotic papules on the knees, elbows and dorsal fingers.
- Islands of sparing.

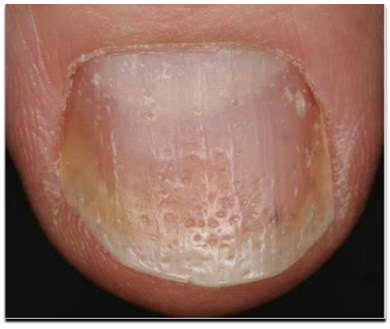


- Sometimes during examination, you might find clues to the cause; an old eczematous lesion or a psoriatic plaque on the elbow

Treatment:
- First thing you need to ask is it psoriasis or lymphoma?
- Psoriasis? Treat accordingly.
- Lymphoma? Chemo.
- Otherwise give steroids.
- Hospitalization may be required.
- **Regardless of cause:** Nutritional assessment, correction of fluid and electrolyte imbalance, prevention of hypothermia and tx of secondary infections.
- Idiopathic: Topical and systemic corticosteroids. Anti-histamines.
- Treat the cause of erythroderma.
- If caused by psoriasis don't give steroids as it might cause a flare up.



- Describe the lesion: Scaling over diffuse erythema with sparing on some areas.
- Diagnosis: PRP
- Examine lymph nodes for lymphadenopathy.
- Examine lower limbs for edema.
- Examine heart for tachycardia and signs of heart failure.
- Check temperature for hyper/hypothermia (remember that skin is important for thermoregulation).



Psoriatic nail changes:
-Pitting.
-Onycholysis.
-Oil spots.

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

Answer: B

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

Answer: A >30%

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

Answer: B (Depends on surface area, this is most likely SJS TEN overlap)

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

Answer: C

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

Answer:A