
بسم الله الرحمن الرحيم

Drug Reactions

MECHANISMS AND CUTANEOUS MANIFESTATIONS

HESAM NABAVIZADEH

Epidemiology and Burden of Drug Hypersensitivity

- 10-20% of hospitalized patients and up to 25% of outpatients
- Most are Type A
- Type B around 10-15% of all ADRs*

Classification of Adverse Drug Reactions

Drug Reaction	Example
TYPE A: REACTIONS OCCURRING IN MOST NORMAL PATIENTS GIVEN SUFFICIENT DOSE AND DURATION OF THERAPY	
Overdose	
Side effects	
Secondary or indirect effects	
Drug interactions	
TYPE B: DRUG HYPERSENSITIVITY REACTIONS RESTRICTED TO A SMALL SUBSET OF THE GENERAL POPULATION	
Intolerance	
Idiosyncrasy	
Immunologic drug reactions (allergy)	

Drug Reaction	Example
TYPE A: REACTIONS OCCURRING IN MOST NORMAL PATIENTS GIVEN SUFFICIENT DOSE AND DURATION OF THERAPY	
Overdose (acetaminophen)	Hepatic failure
Side effects methylxanthin)	Nausea, headache (with
Secondary or indirect effects **antibiotics**	**GI bacterial alteration with**
Drug interactions theophylline levels	Erythromycin increasing
TYPE B: DRUG HYPERSENSITIVITY REACTIONS RESTRICTED TO A SMALL SUBSET OF THE GENERAL POPULATION	
Intolerance	Tinnitus after a single aspirin
Idiosyncrasy after (pharmacogenetics)	G6PD deficiency: anemia antioxidant drugs
Immunologic drug reactions (allergy) **lactam antibiotics**	**Anaphylaxis from beta**

TYPE B: DRUG HYPERSENSITIVITY REACTIONS RESTRICTED TO A SMALL SUBSET OF THE GENERAL POPULATION

- Intolerance
- Idiosyncratic
- Immunologic (allergic)

Intolerance:
Side effects at subtherapeutic doses

- Reflects altered drug metabolism or end-organ hyperacuity

Idiosyncratic: Qualitatively distinct from the known pharmacologic toxicity profile

- May result from defined genetic defect eg., Primaquine-sensitive hemolytic anemia secondary to deficiency of the enzyme glucose-6-phosphate dehydrogenase
- Reflects a complex interaction of metabolic and constitutional factors eg., reactions to radiocontrast media

Immunologic Drug Reactions (Allergy):

drug-specific immune response

- Some drug allergies are defined by human leukocyte antigen (HLA) alleles and therefore can be predicted and tested for (personalized medicine).
- Immediate = onset of symptoms within one hour = IgE mediated
- Delayed = onset of symptoms later than one hour = T lymphocyte
- Distinction between idiosyncratic and allergic drug reactions can be difficult to discern.

Immunologic Drug Reactions (Allergy)

- Mechanisms
- Which Drugs
- Factors influencing immunogenicity of the drug
- Patient risk factors for developing drug allergy

Mechanisms

- Hapten-Prohapten
- Pharmacoimmune (P-i)

Hapten- Prohapten: the drug or its metabolite binds to an endogenous peptide and the resultant hapten is recognized by a highly restricted MHC

- Most pharmaceutical agents do not qualify as drug allergens because they are simple structures and small.
- If less than 1kD can be recognized by the immune system by
  1. Directly binding with macromolecules on cell surfaces
  2. Direct haptenation in plasma
  3. Conversion into reactive intermediates during drug metabolism followed by haptenation

P-i Concept: drug-HLA complexes that can directly activate T-cell immune responses

- Results in strong T cell immune response:
  - Allergy
  - Cytokine production, proliferation, and cytotoxicity
- Selective T cell population is stimulated, expands, and infiltrates the skin and other organs

Immunopathologic Penicillin Reactions

Gell-Coombs Classification	***Mechanism***	***Examples of Adverse Penicillin Reactions***
I	Anaphylactic (IgE mediated)	Acute anaphylaxis Urticaria
II	Complement-dependent cytolysis (IgG/IgM)	Hemolytic anemias Thrombocytopenia
III	Immune complex damage	Serum sickness Drug fever Some cutaneous eruptions and vasculitis
IV	Delayed or cellular Hypersensitivity	Contact dermatitis Morbilliform eruptions SJS/TEN Hepatitis

Immunologic Drug Reactions

- Most common drug groups:
  - Beta lactam antibiotics
  - Non steroidal anti inflammatory drugs
  - Radiocontrast media
  - Neuromuscular blocking agents
  - Antiepileptic drugs
- Increasing reports
  - Anticancer drugs such as platins and taxanes
  - Biologic cytokines and anticytokines

Drug Reaction Quiz:

- What are the most common drug groups causing immunologic drug reactions?
  - A. Beta lactam antibiotics, Non steroidal anti inflammatory drug, Radiocontrast media, Neuromuscular blocking agents, Antiepileptic drugs
  - B. Beta lactam antibiotics, Acetaminophen, Radiocontrast media, Neuromuscular blocking agents, Antiepileptic drugs

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Drug Reaction Quiz:

- What are the two mechanisms of drug recognition by the immune system?
  - A. Hapten Pro Hapten and Fast Acetylator phenotype
  - B. Hapten Pro Hapten and P-i mechanism
  - C. Fast Acetylator phenotype and P-i mechanism
  - D. Fast Acetylator phenotype and Cross reactivity to native or cross reactive epitopes

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Epidemiology

- Cutaneous reactions such as maculopapular eruptions and urticaria are the most common clinical manifestations of ADRs.
- Rarely drugs induce more severe and potentially life-threatening reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Immune hepatitis, and drug-induced hypersensitivity syndromes (DiHS) of which drug reaction with eosinophilia and systemic symptoms (DRESS) is an example.

Factors that influence Drug immunogenicity

- Genetic Factors
- Metabolic Factors
- Drug structure
- Adjuvants
- Concomitant infections
- Occult exposure to native or cross-reactive epitopes

Drug Reaction Quiz:

- Which is not a patient risk factor for drug hypersensitivity?
  - A. High dose/long term exposure
  - B. Chronic disease states
  - C. HLA phenotype
  - D. HIV status
  - E. Age

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Risk Factors for Drug Hypersensitivity

- High dose, long term, and frequent drug treatment
- Existence of naturally occurring cross-reacting epitopes (in children drug exposure in utero or breast milk)
- Contaminants in drug preparation
- Chronic disease states eg. Cystic fibrosis (repeated courses of therapy)
- Allopurinol administered with amino-penicillins
- Patients with atypical/abnormal lymphocytes with amino-penicillins
- HIV patients and sulfonamides

Risk Factors for Drug Hypersensitivity

- History of allergic drug reaction
- Atopic background for severe and fatal penicillin anaphylaxis
- Familial propensity
- HLA subtypes

Genetic Susceptibility to Drug Hypersensitivity is Specific for the Drug, Clinical Phenotype, and Ethnicity

Culprit Drug	Disease	HLA Allele	Ethnicity
Carbamazepine	SJS/TEN	HLA-B 1502	Han Chinese
Carbamazepine	SJS/TEN	HLA-B 1511	Japanese
Carbamazepine	DiHS/SJS/TEN	HLA-A 3101	Caucasians
Allopurinol	SJS/TEN	HLA-B 5801	Han Chinese
Allopurinol	DiHS/SJS/TEN	HLA-B 5801	Caucasians
Abacavir	DiHS	HLA-B 5701	Caucasians
Flucloxacillin	Hepatitis	HLA-B 5701	Caucasians

Drug Reaction Quiz:

- The physical characteristics that would make drug reaction a consideration would include:
  - A. Fever, Rash, Adenopathy, Facial swelling
  - B. Fever, Rash, Adenopathy, Fingernail dystrophy
  - C. Fever, Rash, Adenopathy, Alopecia
  - D. Fever, Rash, Adenopathy, Eosinophilia

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When to suspect a drug eruption

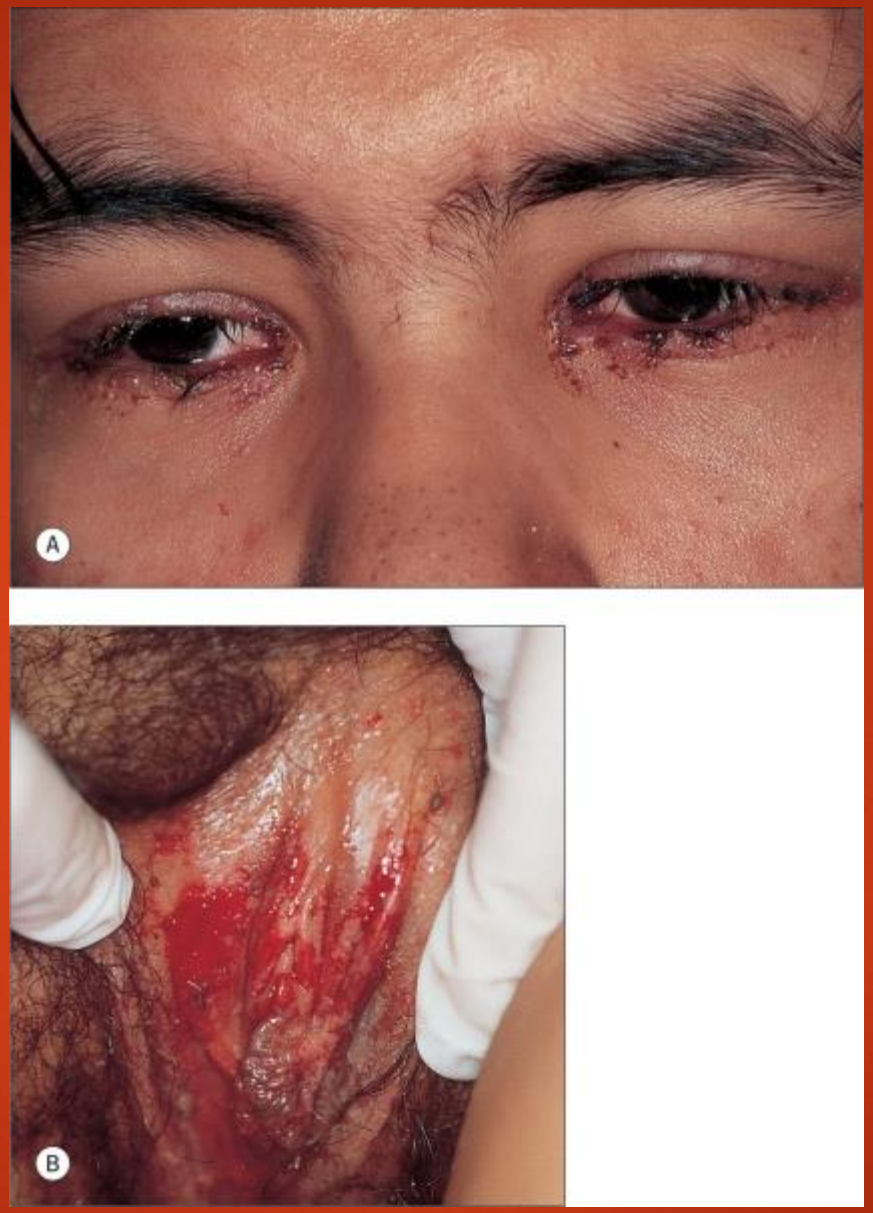
- Cutaneous Findings
  - Confluent erythema
  - Facial edema or central facial involvement
  - Skin pain
  - Palpable purpura
  - Skin necrosis
  - Blisters or positive Nikolsky's sign
  - Mucous membrane erosions
  - Urticaria
  - Swelling of tongue

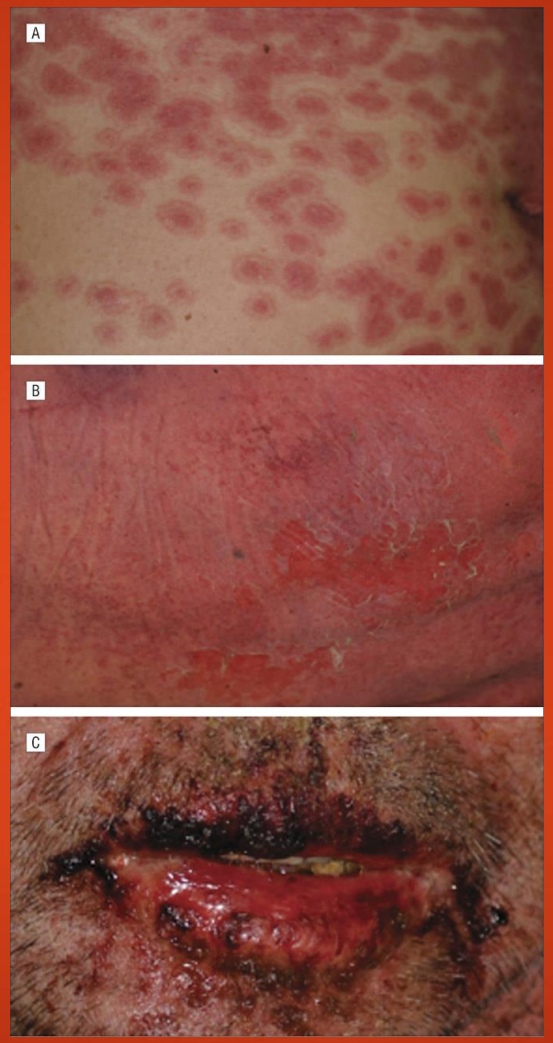
When to suspect a drug eruption

- General clinical findings
  - High fever (>40C^0)
  - Adenopathy
  - Arthralgias/arthritis
  - Shortness of breath/wheezing/hypotension
- Laboratory Results
  - Eosinophilia (>1000mm^3)
  - Lymphocytosis with atypical lymphocytes
  - Abnormal results on liver function tests

Case # 1

- CC: painful rash
- History : 34 year old woman with a 1 week history painful rash which is located on trunk, extremities, eyes, mouth and genitalia but not palms and soles. Prior to rash had fever and felt unwell. No other family members ill and recently started taking Piroxicam for a sprained ankle.
- PH/FH/SH: unremarkable
- PE: skin tenderness; diffuse erythematous, purpuric patches, bullae, erosions, targetoid lesions; ocular, oral, genital erosions, + fever, no adenopathy, BSA >30%
- Lab: leukocytosis with normal smear, slightly elevated BUN/Cr and LFT


A
B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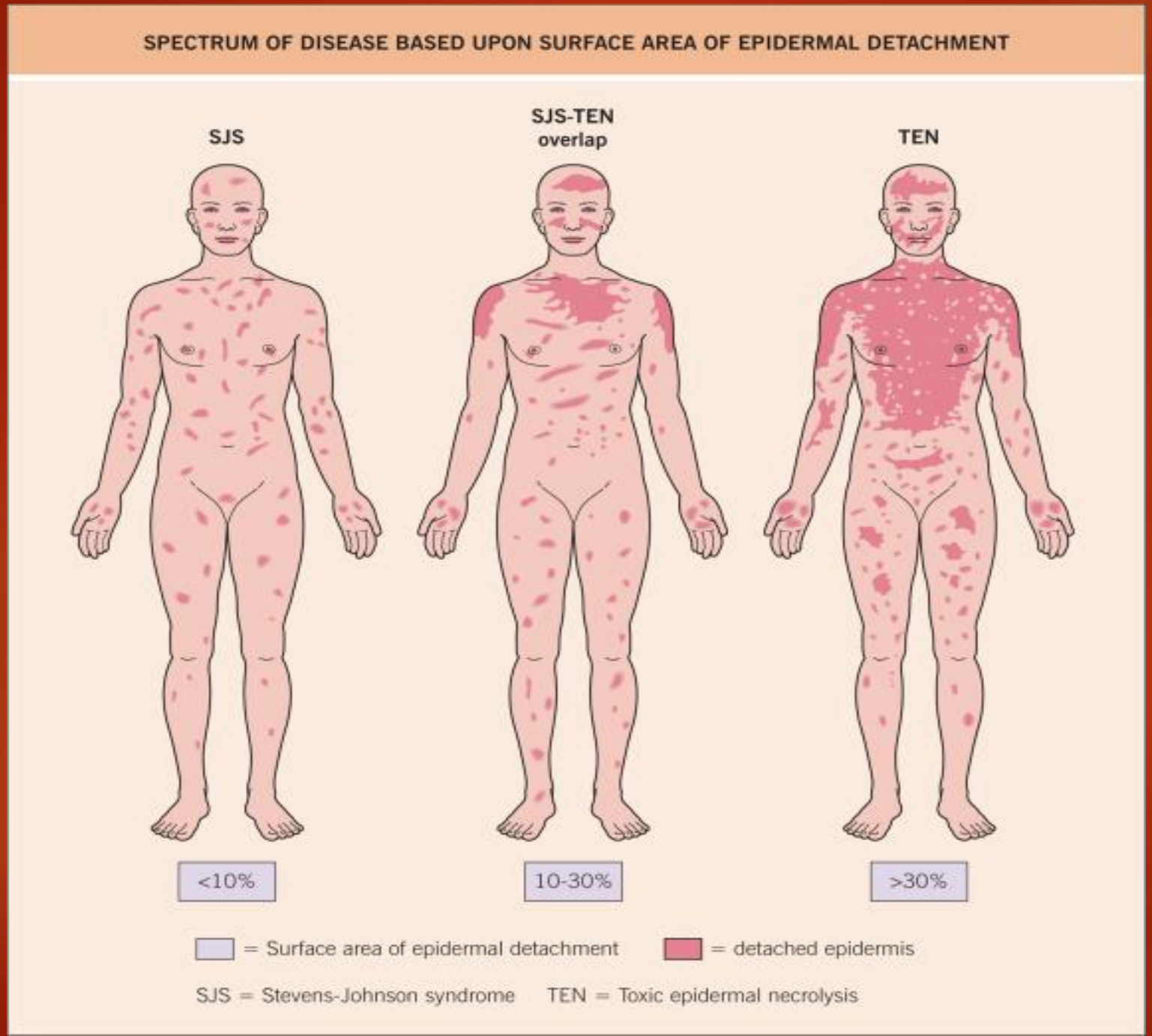
C

SJS/TEN

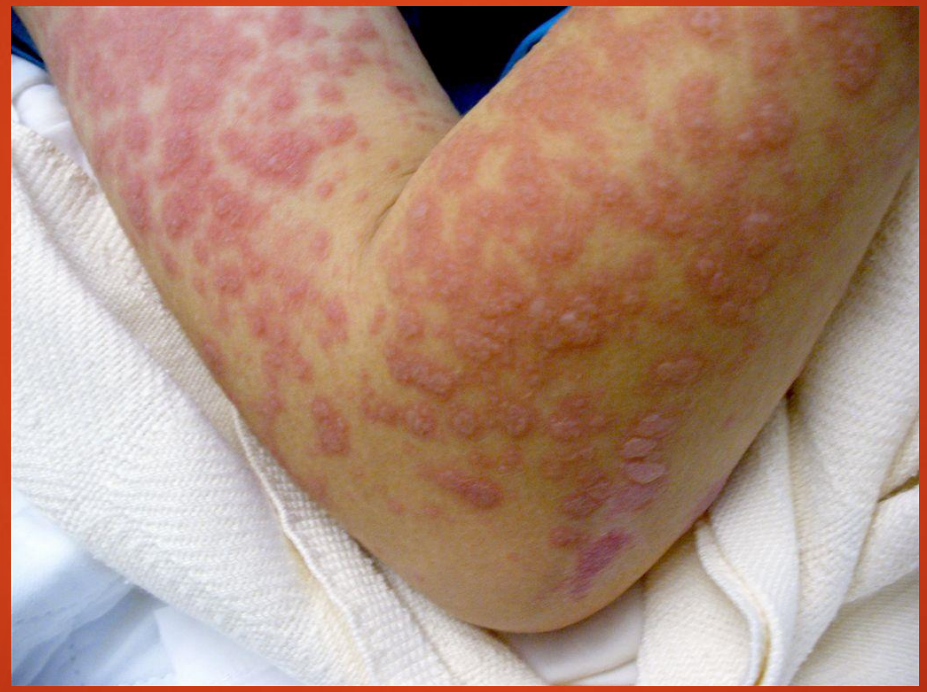
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous reactions, most commonly triggered by medications, characterized by extensive necrosis and detachment of the epidermis.
- Spectrum of involvement from SJS (<10%) to TEN (>30%) body surface area.
- Systemic disease involving the ophthalmic, pulmonary, genitourinary, and gastrointestinal systems, in addition to the skin
- Skin Biopsy: Necrotic keratinocytes; minimal inflammation; full-thickness epidermal/epithelial necrosis

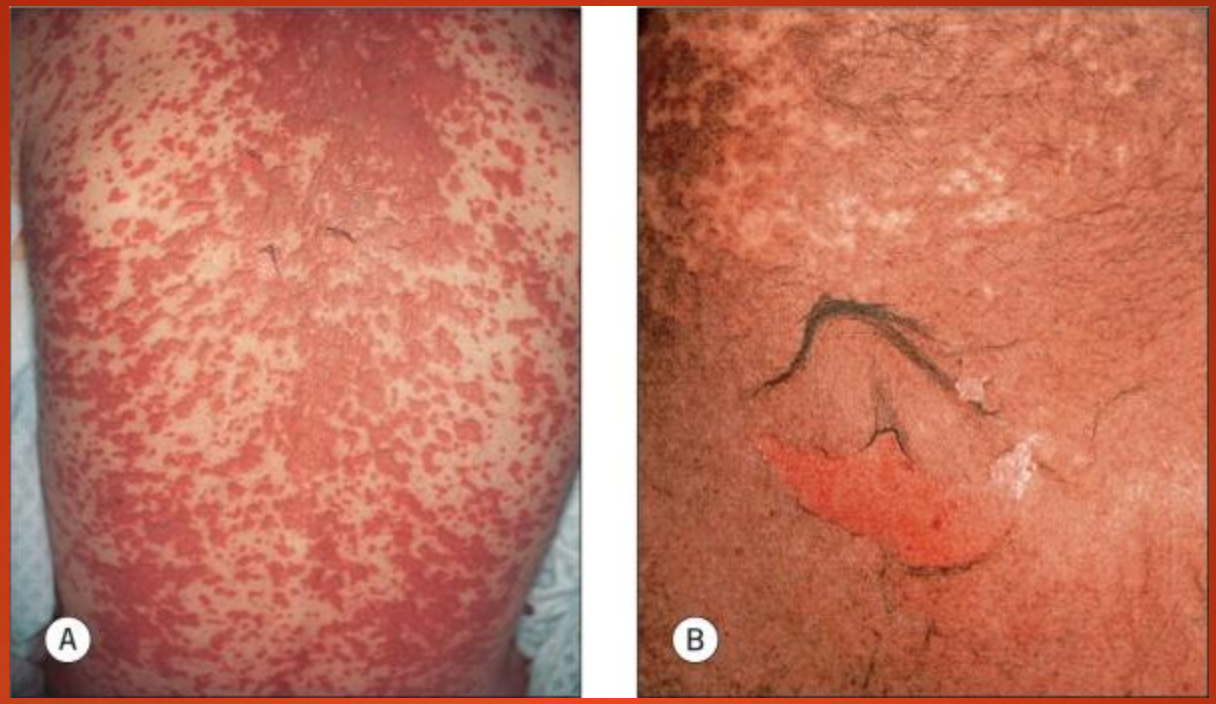

SPECTRUM OF DISEASE BASED UPON SURFACE AREA OF EPIDERMAL DETACHMENT
SJS
SJS-TEN overlap
TEN
<10%
10-30%
>30%
= Surface area of epidermal detachment
= detached epidermis
SJS = Stevens-Johnson syndrome
TEN = Toxic epidermal necrolysis

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 or dusky/red lesions Flat, atypical targets
Distribution	Isolated lesions Confluence (+) on face and trunk	Isolated lesions Confluence (++) on face and trunk	**Isolated lesions (rare)** **Confluence (+++)** on face and trunk
Mucosal Involvement	Yes	Yes	Yes
Systemic Symptoms	Usually	Always	Always

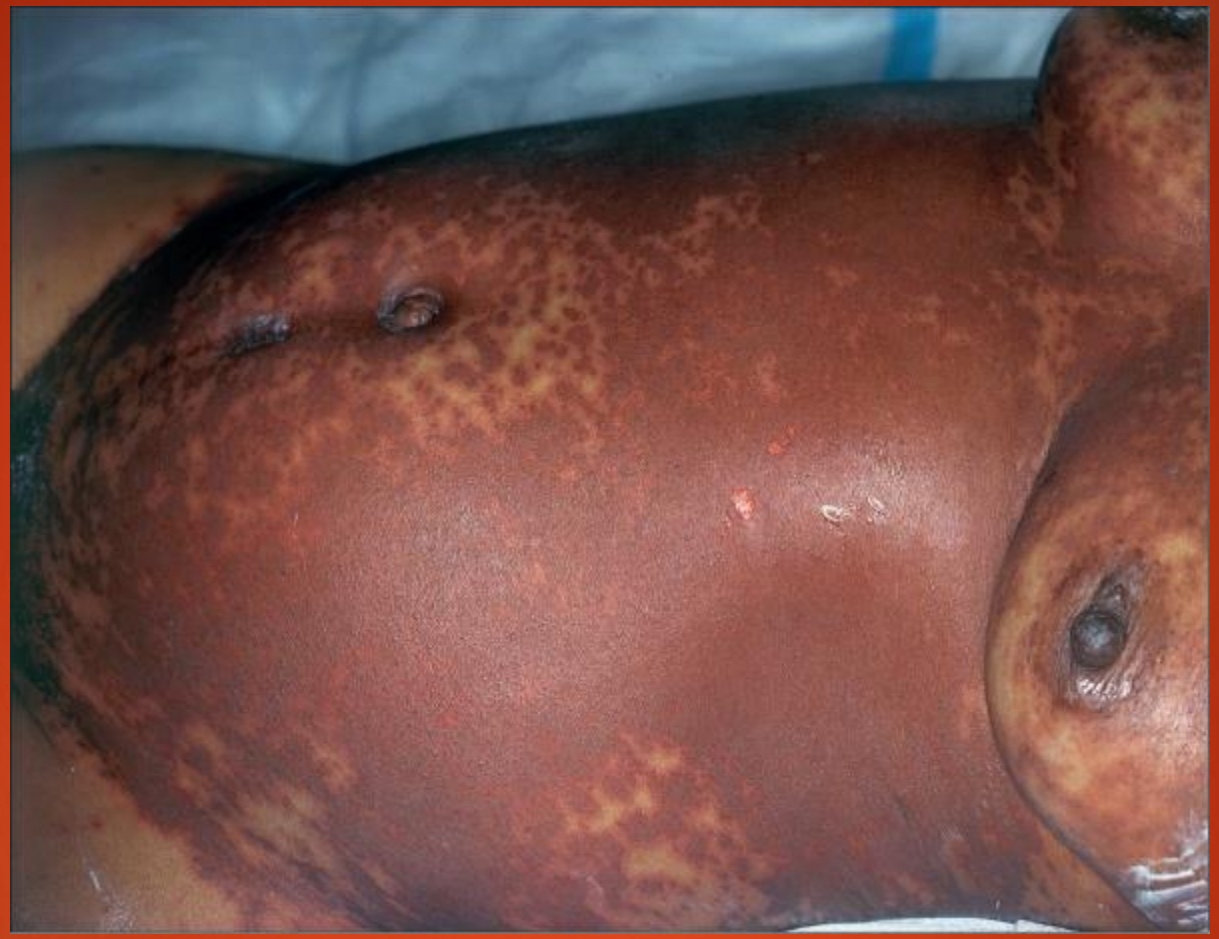
Dermatology Bologna et al, 2nd edition

Stevens-Johnson Syndrome



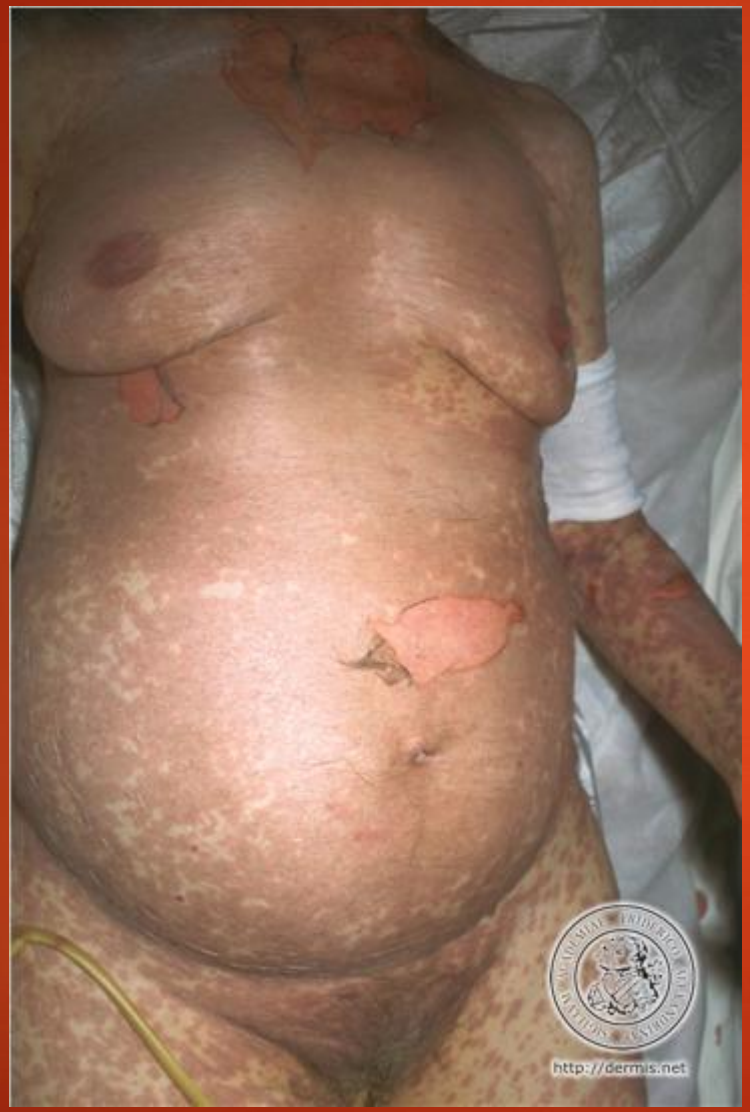


In addition to mucosal involvement and numerous dusky lesions with flaccid bullae, there are areas of coalescence and multiple sites of epidermal detachment. Because the latter involved >10% body surface area, the patient was classified as having SJS–TEN overlap. **B** Close-up of epidermal detachment, whose appearance has been likened to wet cigarette paper.

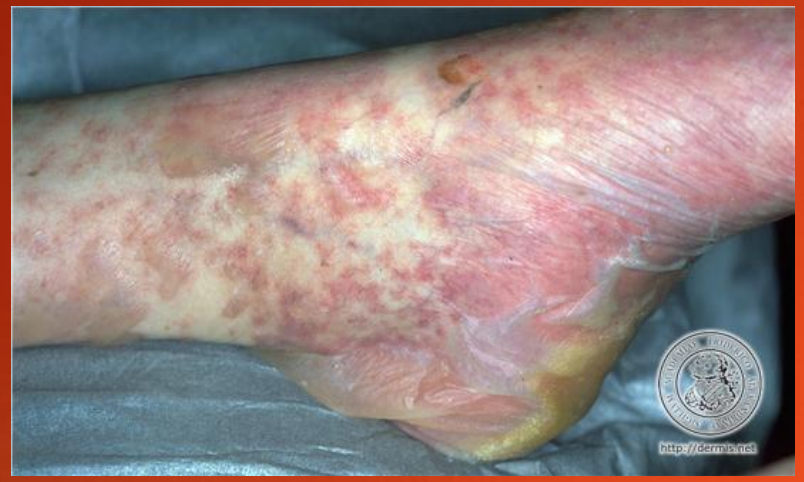


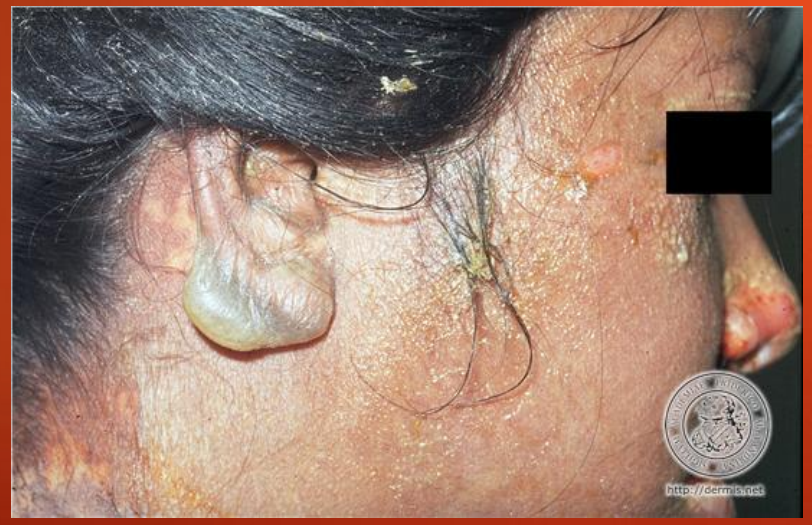
Cutaneous features of toxic epidermal necrolysis (TEN). Characteristic dusky red color of the early macular eruption in TEN. Lesions with this color often progress to full-blown necrolytic lesions with dermal–epidermal detachment.

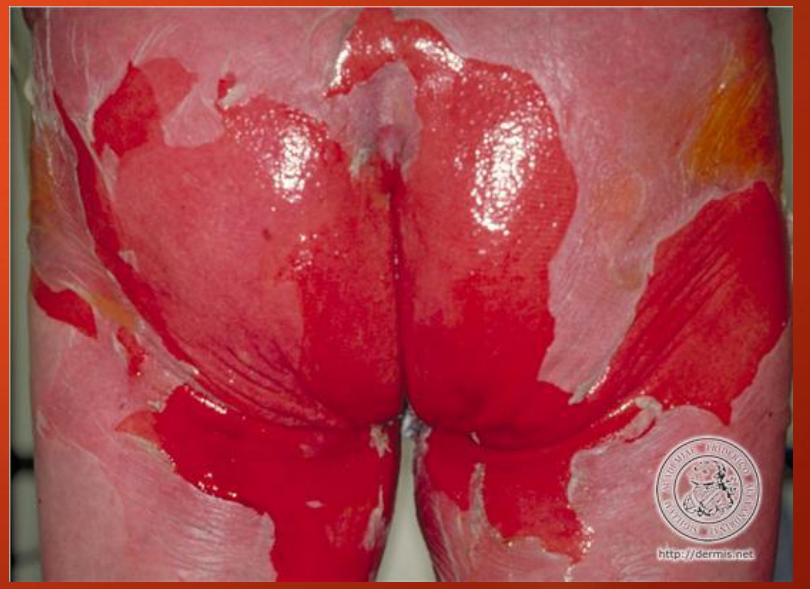
Toxic Epidermal Necrolysis



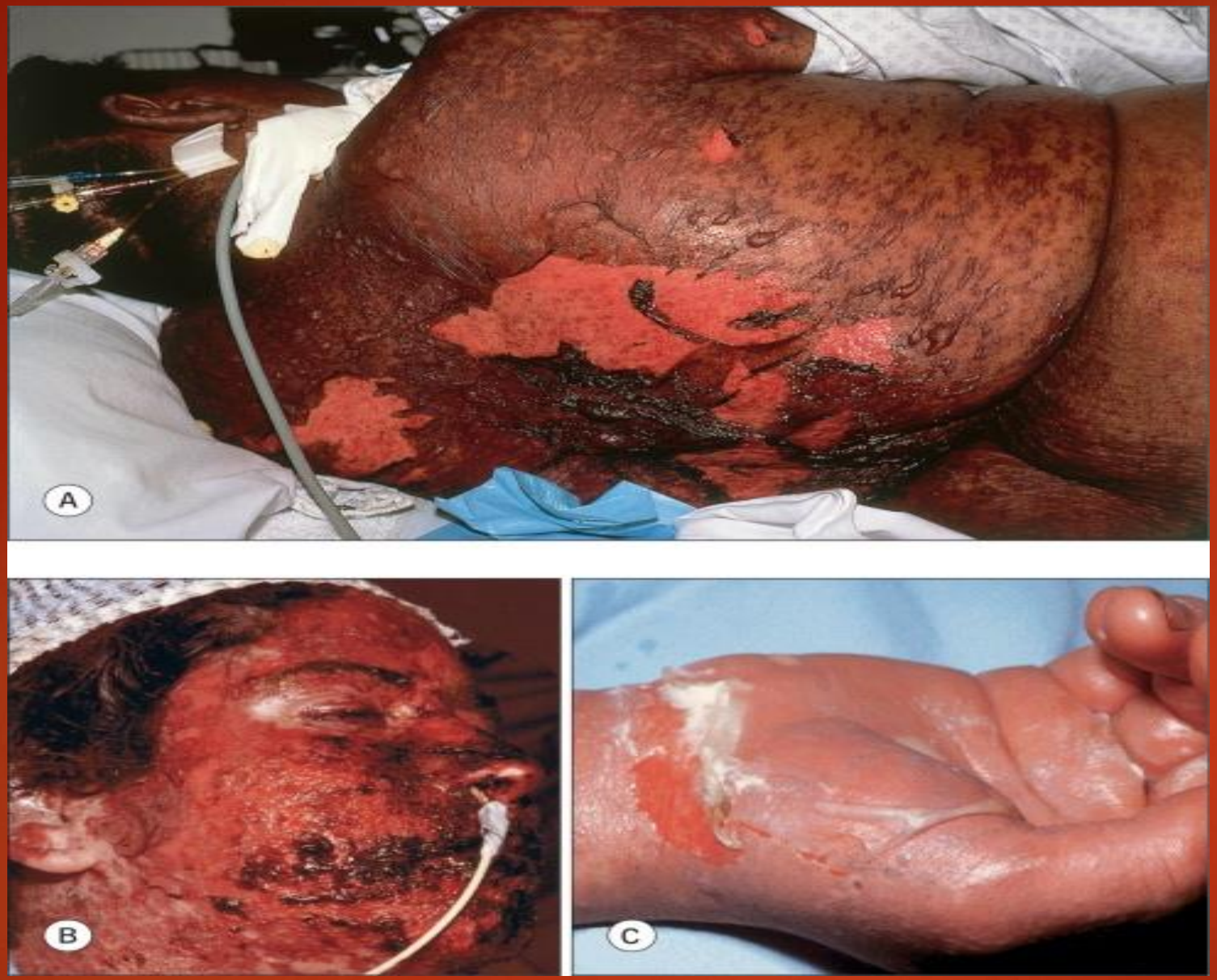
Toxic Epidermal Necrolysis



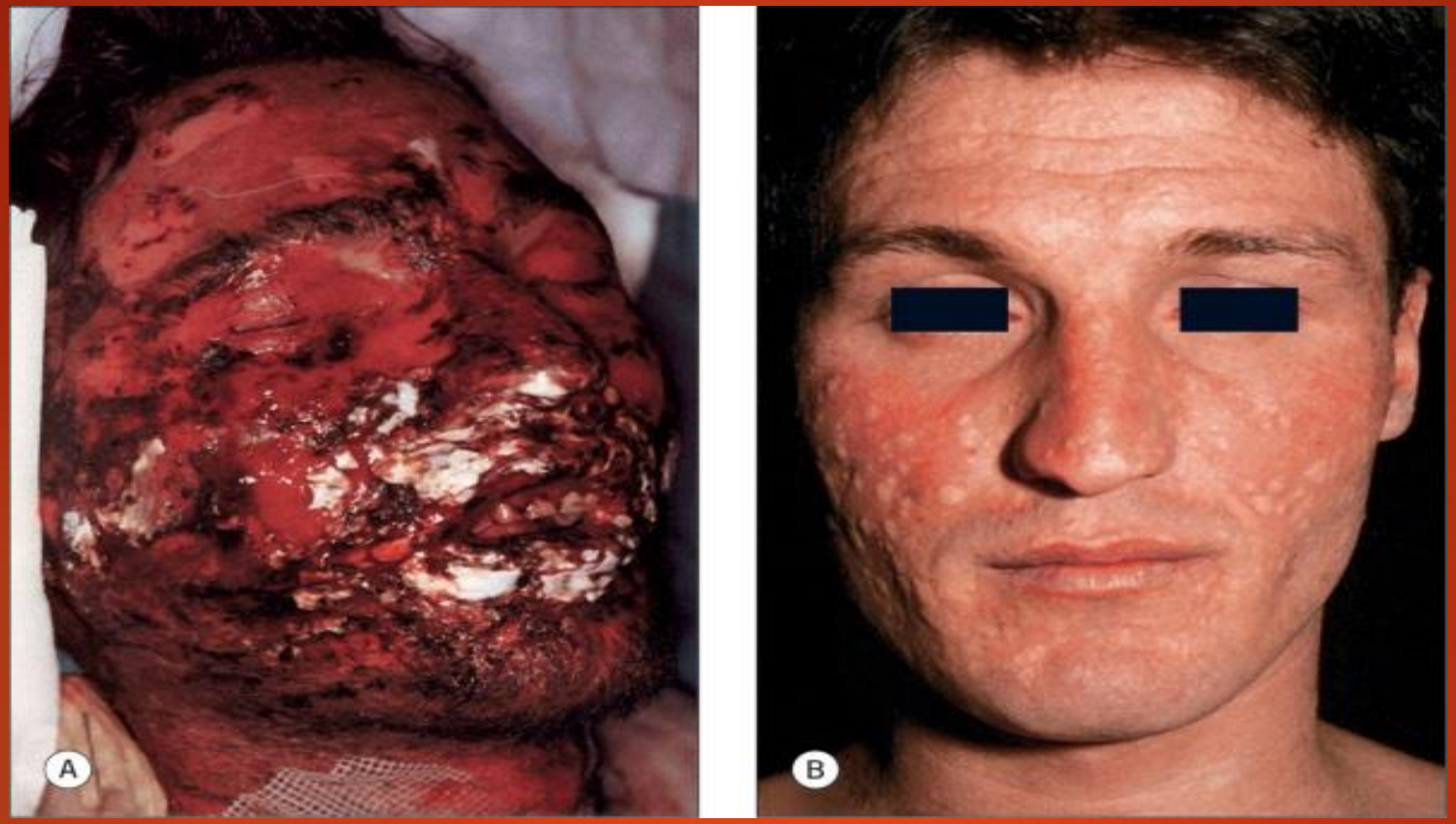




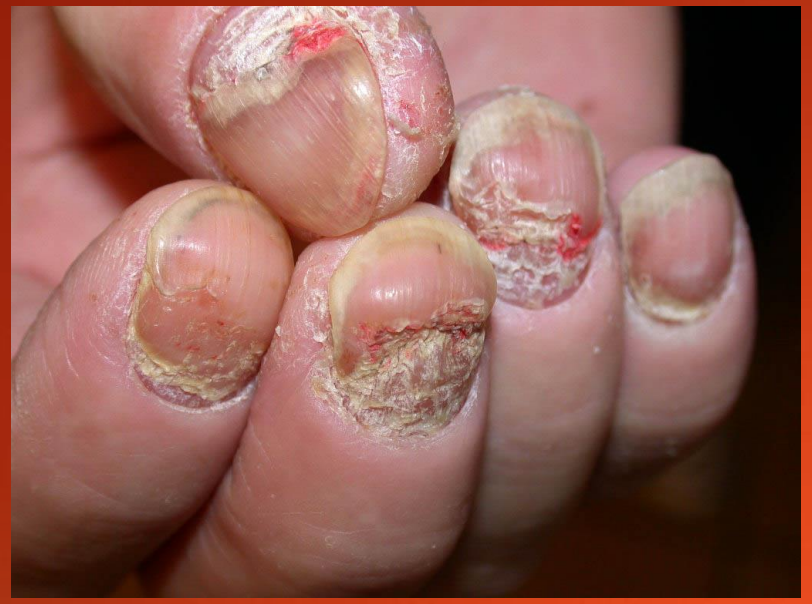
HEALTH SCIENCES



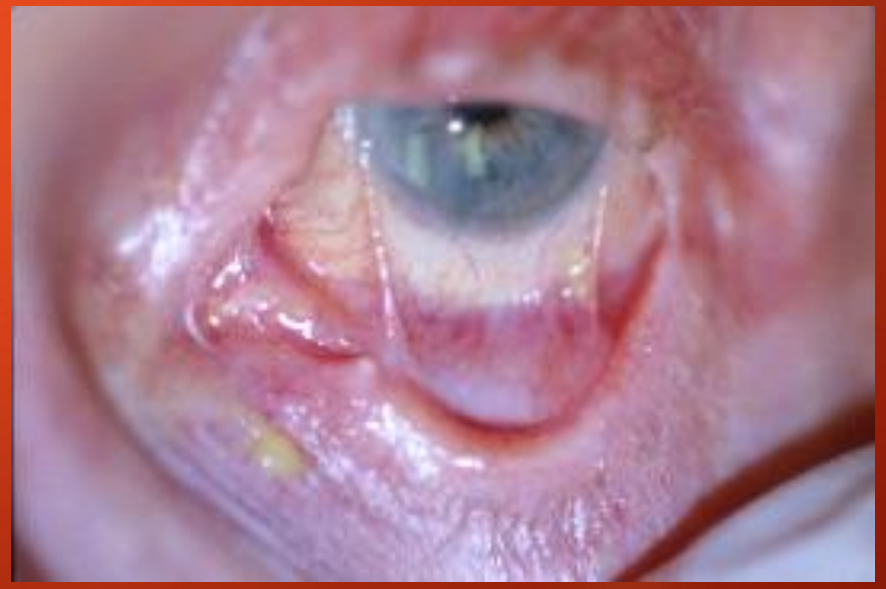
Clinical features of toxic epidermal necrolysis (TEN). A Detachment of large sheets of necrolytic epidermis (>30% body surface area), leading to extensive areas of denuded skin. A few intact bullae are still present. **B** Hemorrhagic crusts with mucosal involvement. **C** Epidermal detachment of palmar skin.



Treatment of toxic epidermal necrolysis (TEN). Facial involvement of a patient with TEN (50% body surface area involvement) before (**A**) and 3 weeks after (**B**) treatment with IVIg (0.75 g/kg/day for 4 days)



Onychomadesis - spontaneous separation of the nail plate from the matrix area and is associated with arrest of nail growth. Onychomadesis has been reported in patients with bullous dermatoses, febrile illnesses, psoriasis, and cutaneous drug eruptions particularly Stevens-Jophnson syndrome and toxic epidermal necrolysis.



Symblepharon

TEN: Predisposing Factors

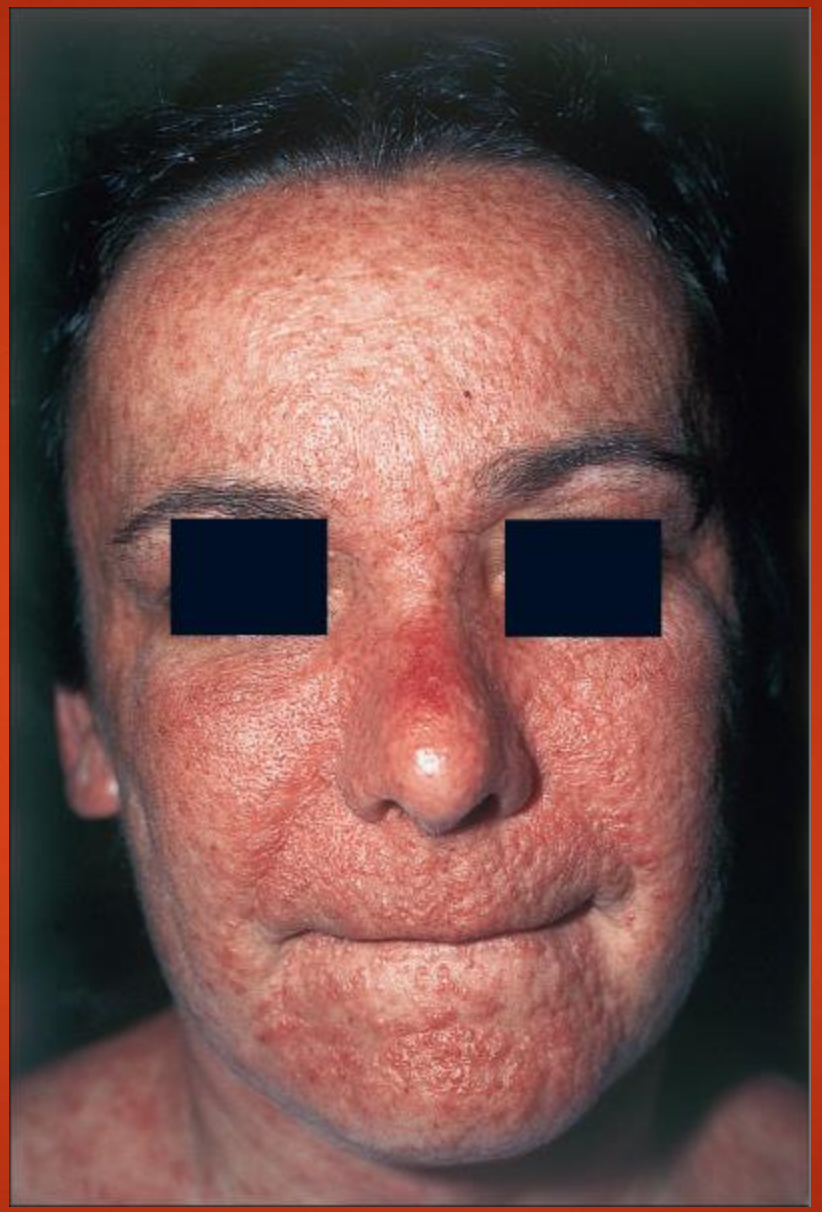
- HIV
- Genetic factors
  - HLA types
  - Polymorphisms in CYP2C19 gene
- Malignancy
- High doses and rapid induction of medications
- Systemic lupus erythematosus
- Physical stimuli, e.g. UV light or radiation therapy

Drugs Associated with SJS/TEN

- Allopurinol
- Aromatic anticonvulsants
- Antibacterial sulfonamides
- Lamotrigine
- Nevirapine
- Oxicam NSAIDs

Case # 2

- CC: facial swelling and rash
- History : 34 year old woman with a 1 week history of a non-painful rash which is located on trunk, extremities and complains of swelling and redness of her face. Feels unwell and has persistent fever. No other family members ill. Started Lamictal 4 weeks ago for a seizure.
- PH/FH/SH: unremarkable
- PE: (-) mucous membrane involvement; erythematous macules, papules, vesicles, bullae; facial erythema, edema, pinpoint pustules; adenopathy
- Lab: peripheral eosinophilia, + atypical lymphocytsis, and abnl LFTs

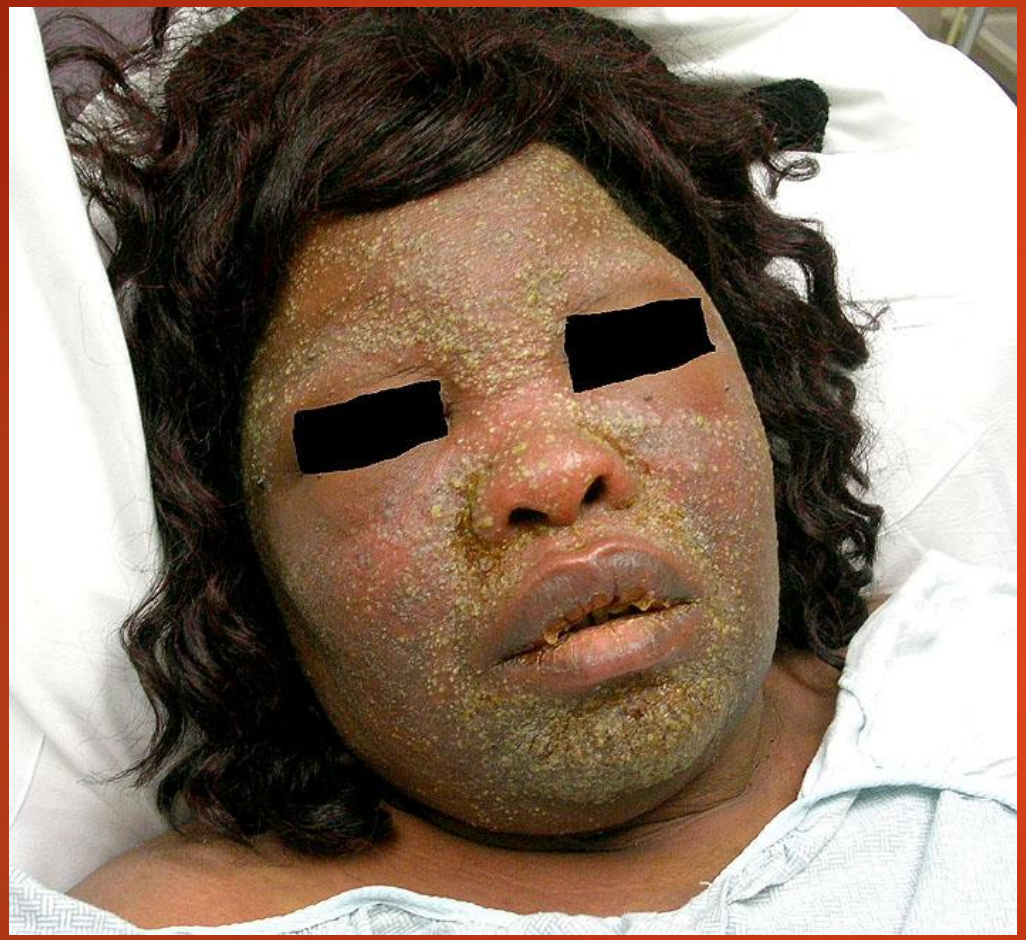


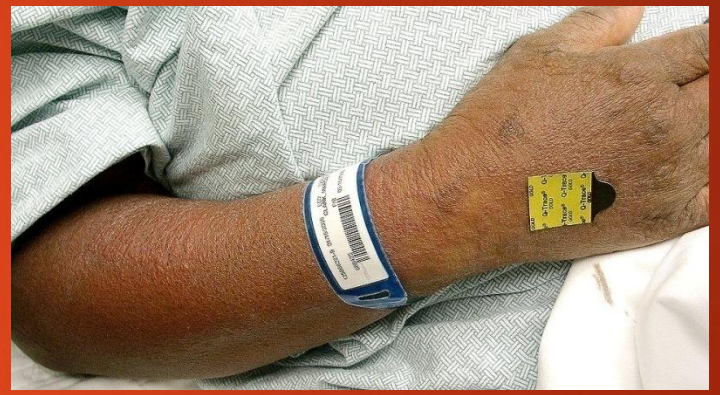
DRESS

- Drug reaction with eosinophilia and systemic symptoms
- The broad spectrum of clinical features and long latency period in DRESS often results in diagnostic delay
- Typically, patients present with fever, rash, lymphadenopathy, lymphocytosis (atypical lymphocytes) and abnormal liver tests
- Skin Biopsy: Superficial perivascular lymphocytes, eosinophils; ± dyskeratotic keratinocytes; ± variable lichenoid inflammation

Finding	Incidence (%)
Fever	90-100
Rash	87-90
Lymphadenopathy	70
Hepatitis	50-60
Hematologic abnormalities (leukocytosis, **eosinophilia**, hypogammaglobulinemia)	23-50
Periorbital or orofacial edema	25
Myalgias, arthralgias	20
Nephritis	11
Pharyngitis, conjunctivitis	10
Pulmonary manifestations	9

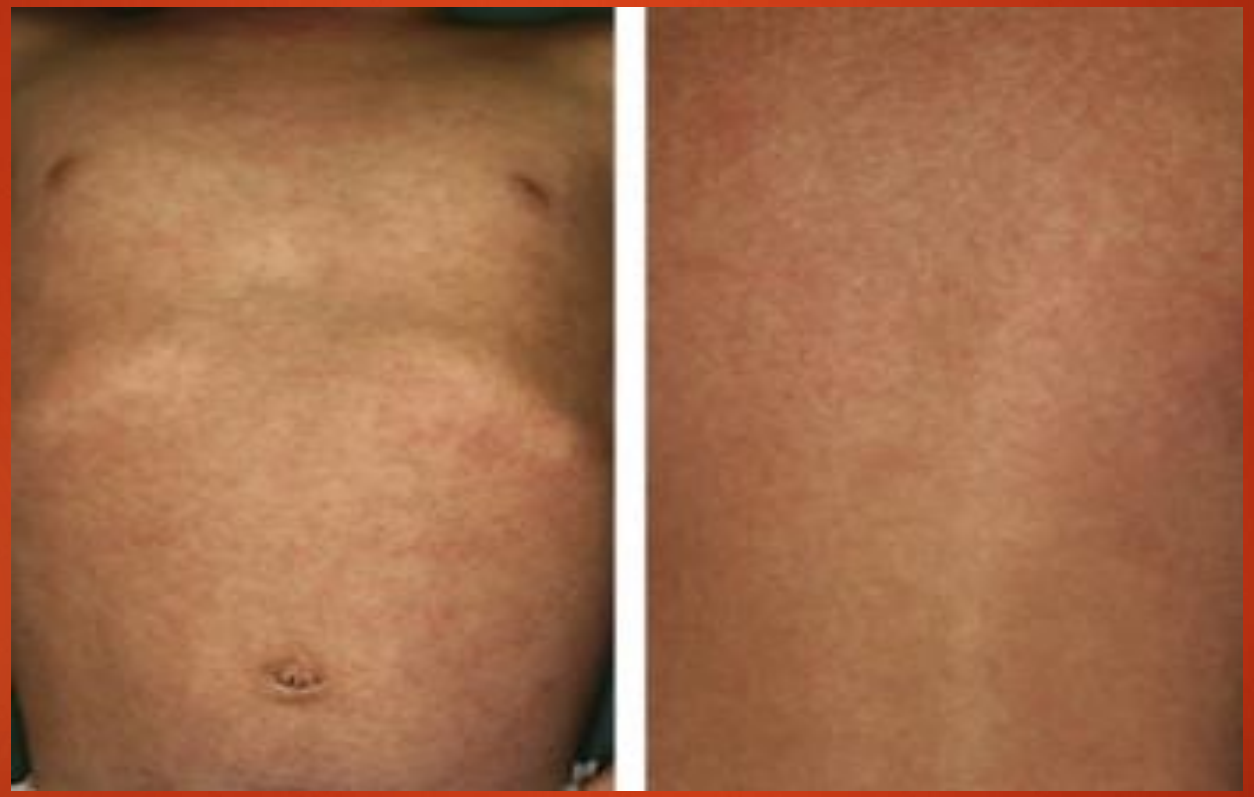
Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: report of four cases and brief review .



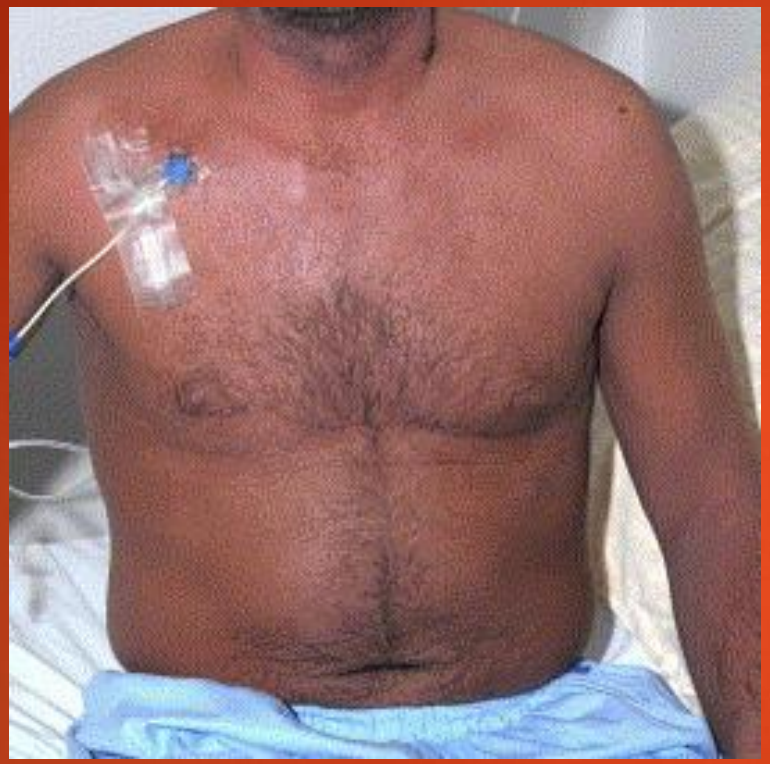


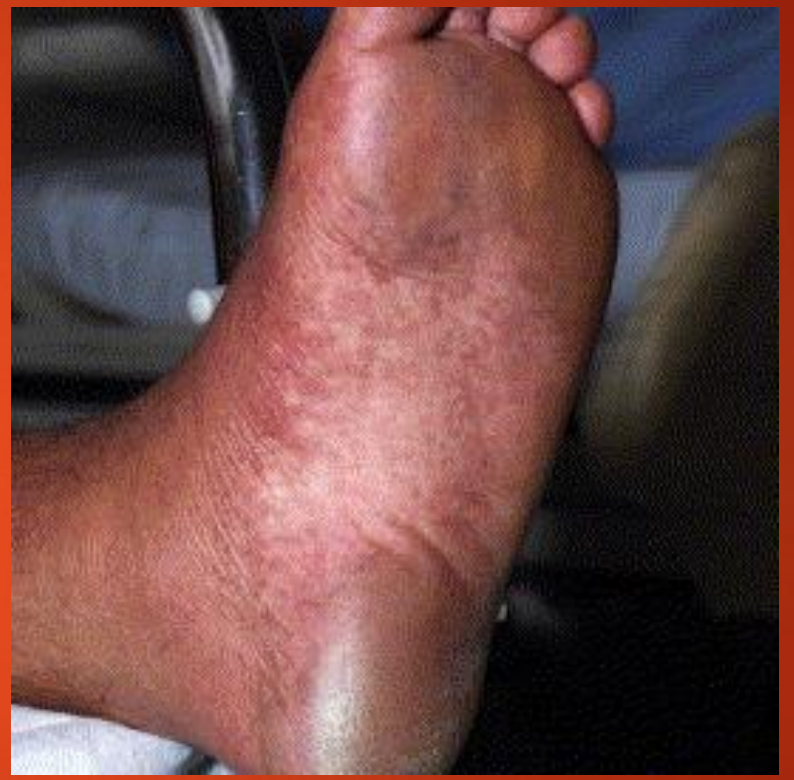
DRESS

Drug-induced hypersensitivity syndrome: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome induced by aspirin treatment of Kawasaki disease

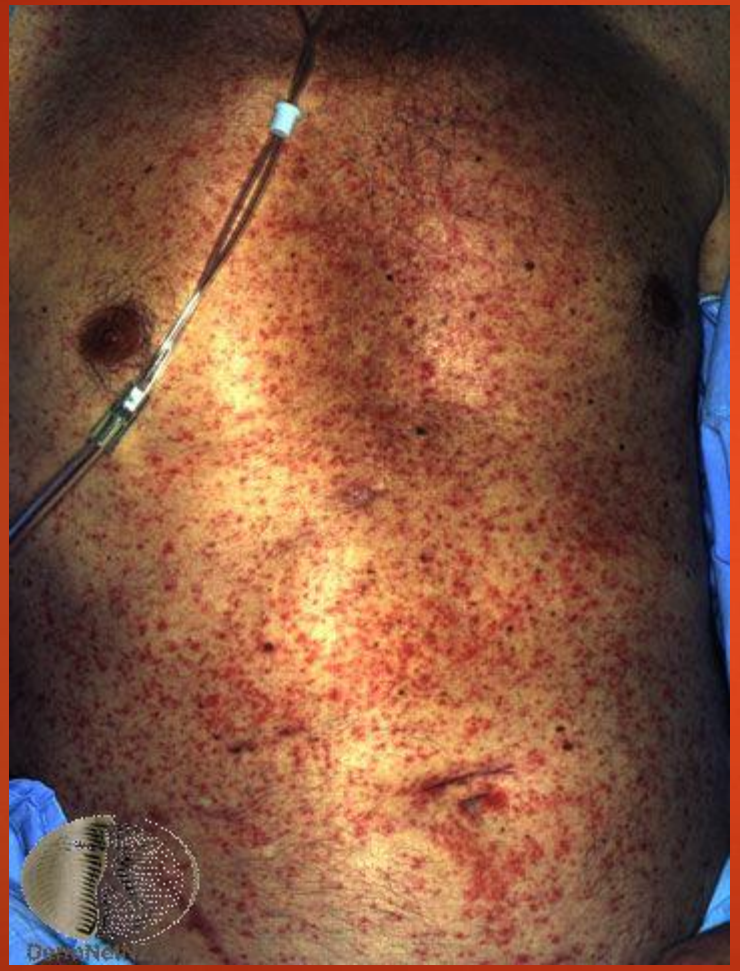


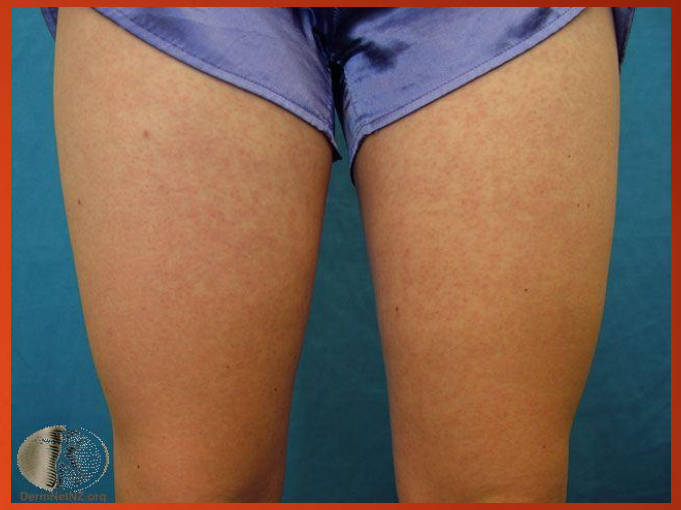
Generalized maculopapular eruption on patient's trunk

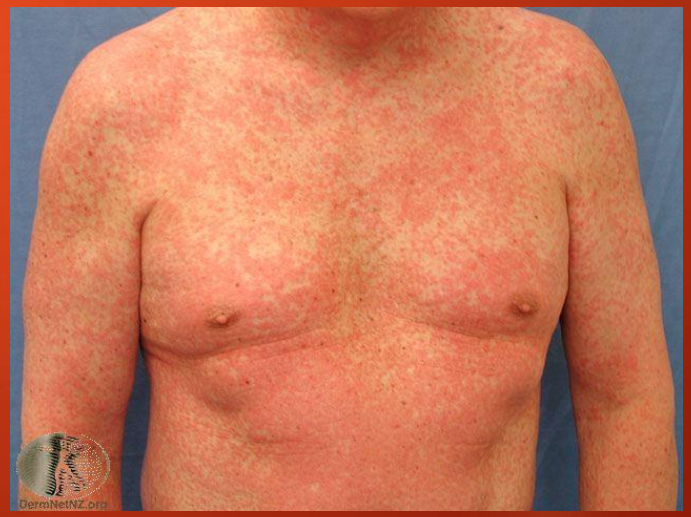




DRESS – Drug Reaction with Eosinophilia and Systemic Symptoms







Other Concerns:

- Liver involvement is the most common visceral manifestation and can lead to fulminant hepatic failure and death.
- Myocarditis which may progress to acute necrotizing eosinophilic myocarditis (ANEM), interstitial nephritis, pneumonitis, and thyroiditis are other possible complications that require long-term close monitoring.

Viruses associated with DRESS

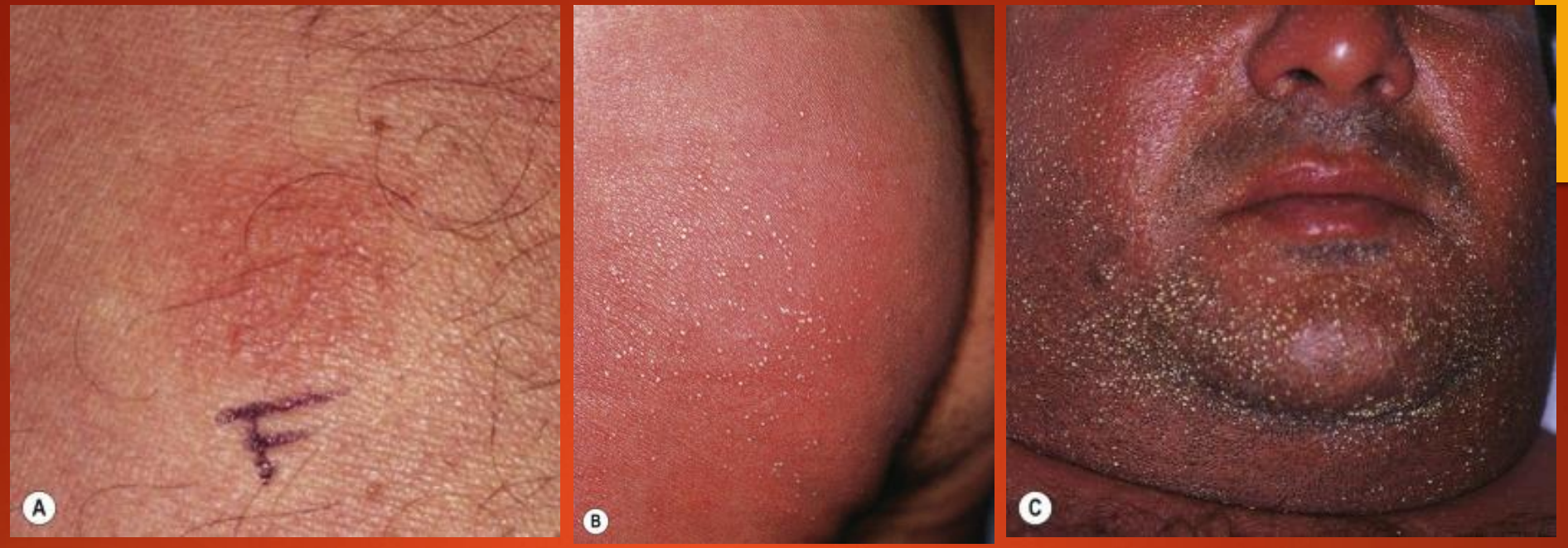
- Herpesviruses
  - Human herpesvirus 6 (HHV6)
  - Human herpesvirus 7 (HHV7)
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
- Paramyxoviruses
  - Mumps
  - Parainfluenza

Drugs Associated with DRESS

- Anticonvulsants
- Antidepressants
- Sulfones and Sulfonamides
- NSAIDs
- Anti-infectives
- Ace-inhibitors
- Beta blockers
- Allopurinol and others

Case # 3

- CC: face and hands are swollen and rash
- History : 54 year old man with a 1 day history of rash which started on body fold and face and rapidly spread. The symptoms are itch and burning. Notes swelling on his hands and face. Has fever but otherwise well. No other family members ill. Started amoxicillin 2 days ago for a sore throat. And is complaining of some trouble catching his breath.
- PH/FH/SH: unremarkable
- PE: + oral mucosal erosions, diffuse pin head pustules with flexural accentuation, edema of face and hands, a few scattered vesicles and bullae
- Lab: leukocytosis with neutrophilia, mild abnormalities in LFTs, Bun/Cr



Acute generalized exanthematous pustulosis (AGEP). A A positive patch test result 4 days following the application of 0.75% metronidazole in a patient with a previous pustular drug eruption to that medication. Diffuse erythema of the buttock (due to cephalosporin, B) and face (due to metronidazole, C) studded with sterile pustules.

Acute Generalized Exanthematous Pustulosis

- Rare, acute eruption characterized by the development of numerous nonfollicular sterile pustules on a background of edematous erythema
- Fever and peripheral blood leukocytosis are usually present.
- In approximately 90 percent of cases, AGEP is caused by drugs, most often antibiotics (aminopenicillins and macrolides), the calcium channel blocker diltiazem, and antimalarials.
- The eruption develops within hours or days of drug exposure and resolves spontaneously in one to two weeks after drug discontinuation.

Timeline for Drug Reactions

- AGEP: less that 4 days
- DRESS: 1-8 weeks
- SJS/TEN: 1 day to 3 weeks

Mortality Incidence

- SJS 1-5%
- TEN 25-35%
- DRESS ~10%
- AGEP 2-4%

Objectives

- To become familiar with the most common drugs causing immune reactions
- To be able to suspect a drug reaction based on clinical and lab findings
- To recognize the patient characteristics that put them at risk of a drug reaction
- To be aware of the characteristics of the 3 most Serious Cutaneous Adverse Reactions (SCARs)

Approach to the patient with a suspected drug eruption

- Testing: CBC with diff, LFTs, kidney function, TFTs, ECHO, BIOPSY
- Discontinuation of medication
- Treatment:
  - Topical steroids and antihistamines if mild
  - Steroids for DRESS
  - Cyclosporine (and in some cases IVIG) for SJS/TEN
  - Supportive treatment of AGEP

WITH THANKS