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Severe Cutaneous Adverse Drug Reactions: Current Concepts

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Objectives

- Review the types of Severe Cutaneous Adverse Drug Reactions (SCAR)
- Discuss clinical features that distinguish between the types of SCAR and facilitate diagnosis
- Review updated therapy options

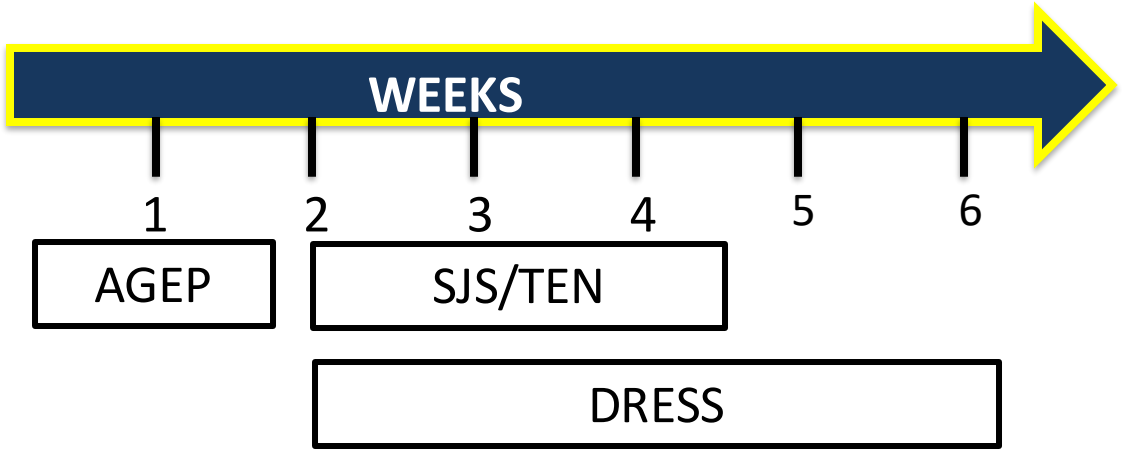

SUN BUM
SUN BUM
30
Broad Spectrum SPF 30
Water Resistant (80 Minutes)
Premium Sunscreen Face Stick
Broad Spectrum SPF 30 Sunscreen
Water Resistant (80 Minutes)
Net Wt. 0.45 OZ / 13 g
30

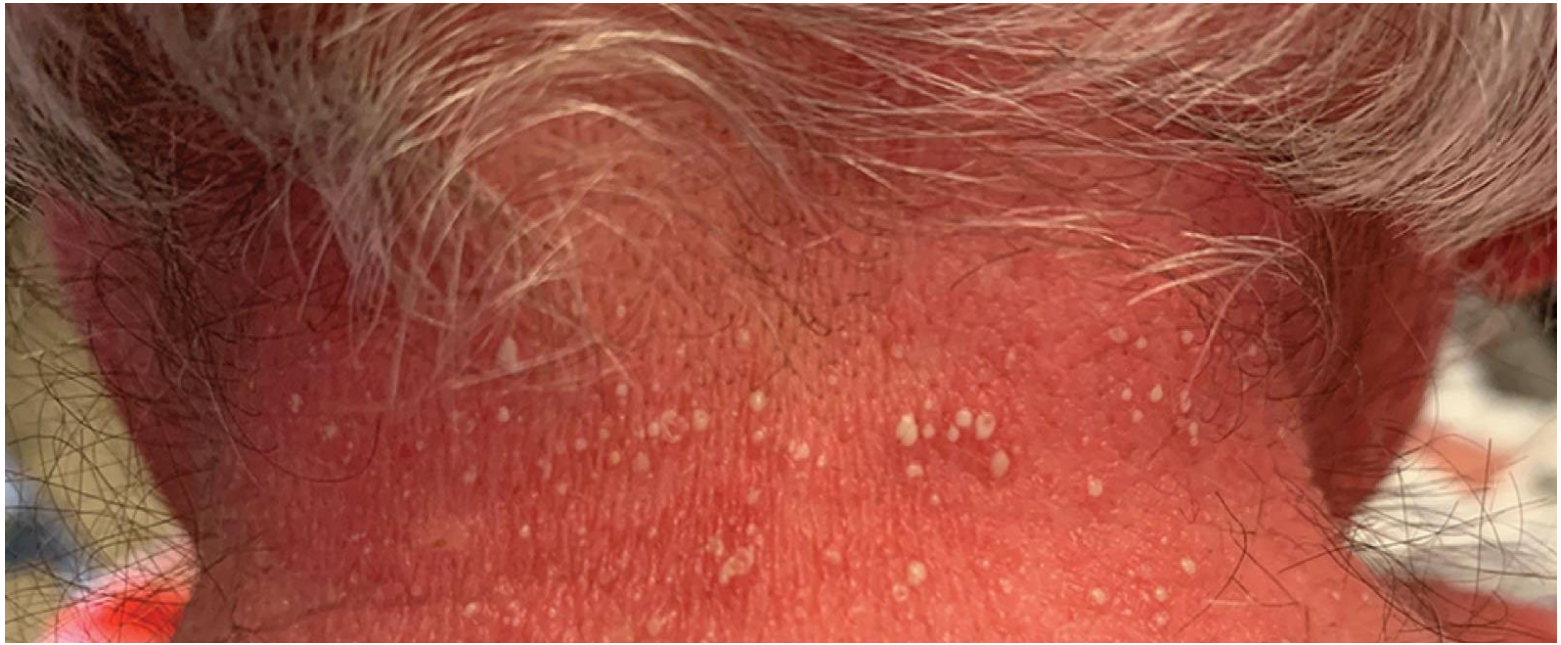
Severe Cutaneous Adverse Drug Reactions (SCAR)

SEVERE SCAR	SCAR
DRESS	AGEP
SJS	GBFDE
SJS-TEN Overlap	
TEN	

SCAR

Typical duration of drug exposure to initiation of reaction



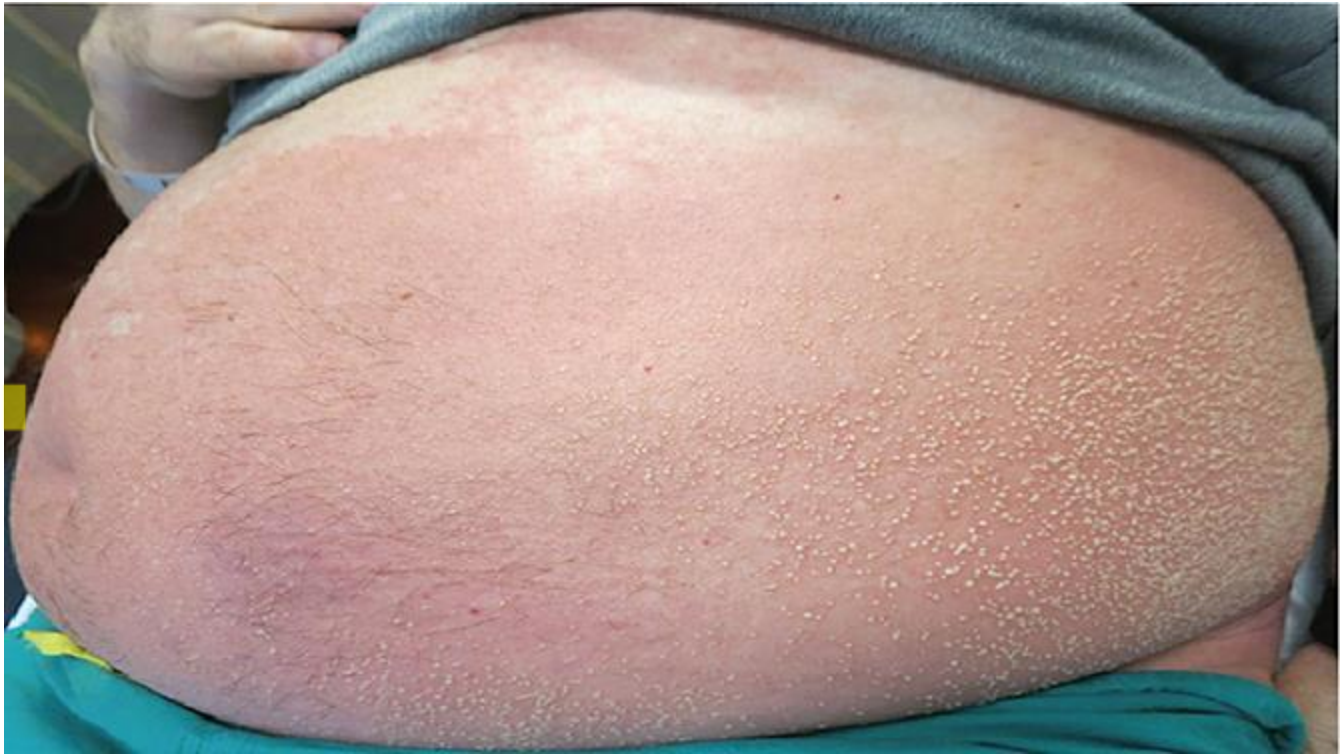


- **AGEP**- erythema with non-follicular pustules

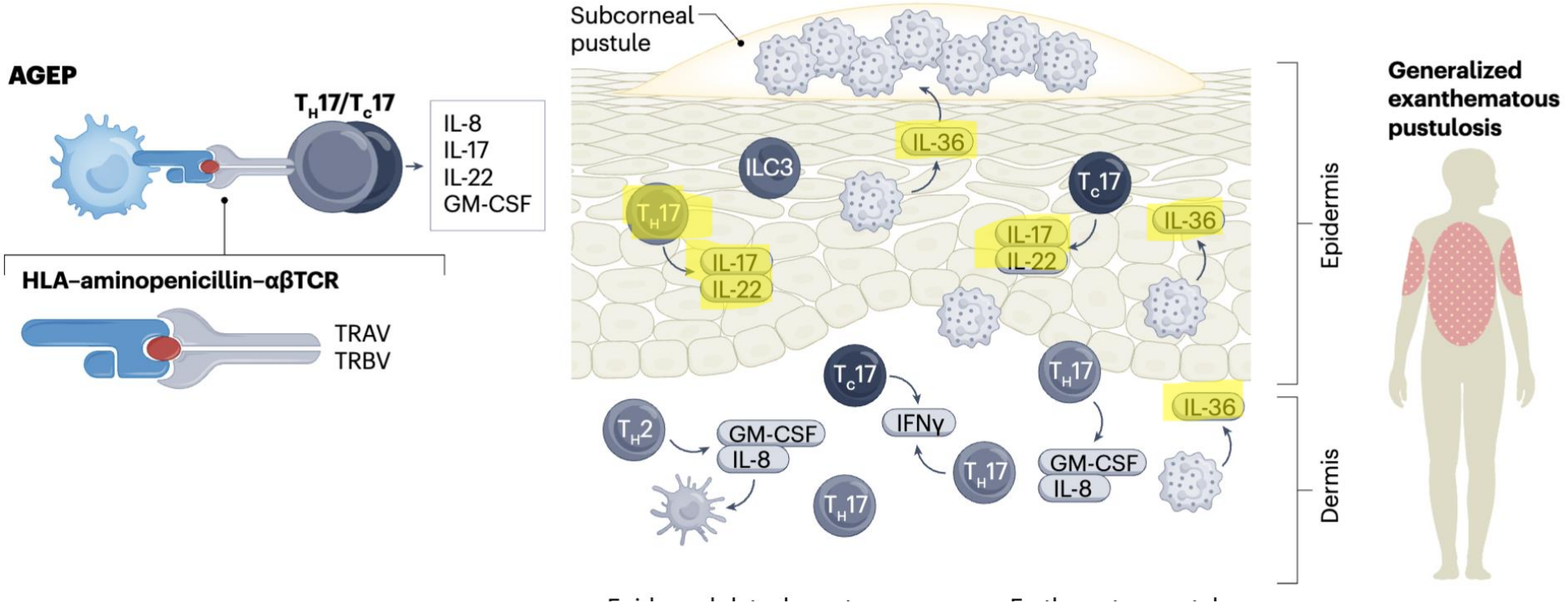
Acute Generalized Exanthematous Pustulosis (AGEP)

- Fast onset related to culprit drug (days)
- Initially intertriginous erythema with non-follicular pustules
- Rapid evolution spreading to torso
- RARE mucosal lesions
- May have fever 38.0 C (< DRESS)
- Laboratory findings: Leukocytosis with neutrophilia, rare transaminitis

Parisi et al. Am J Clin Dermatol 2023. 4(24)



Andrews Clinical Atlas of the Skin. 2023



Hung, SL et al. Nature Reviews Disease Primers 2024. 10:30

AGEP: Associated Drugs

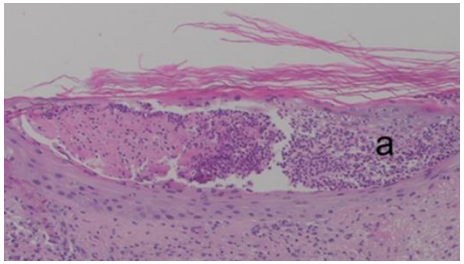
- Beta lactams
- Quinolones
- Hydroxychloroquine
- Targeted therapies
- Terbinafine
- Diltiazem
- Macrolides
- Vaccinations

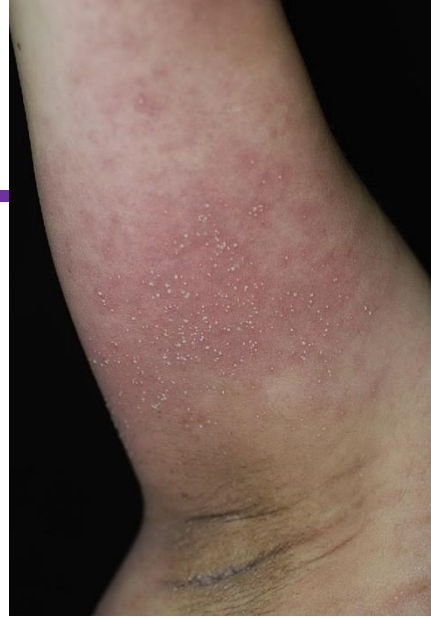
Parisi et al. Am J Clin Dermatol 2023. 4(24)

AGEP EuroSCAR Criteria

Key features:

- Typical pustules +2
- Typical erythema +2
- Typical distribution +2
- Mucosal involvement –2
- Acute onset within 10 days NO –2
- Resolution within 15 days NO –4
- Histology very important
- Subcorneal pustule with papillary edema +3



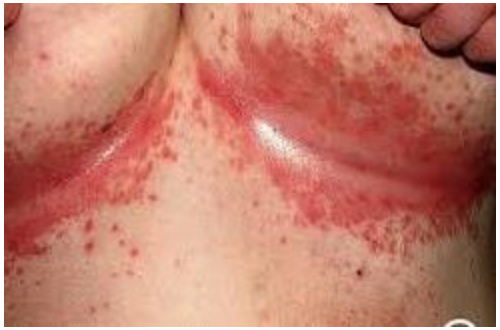


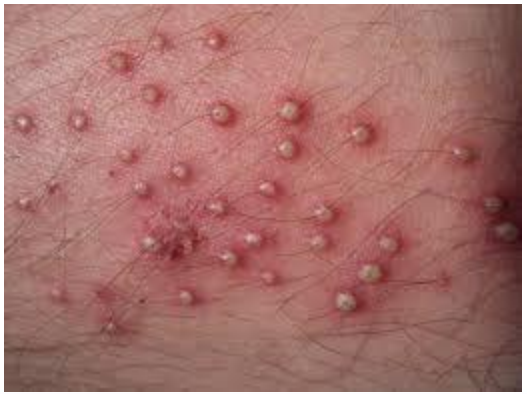
Score interpretation:

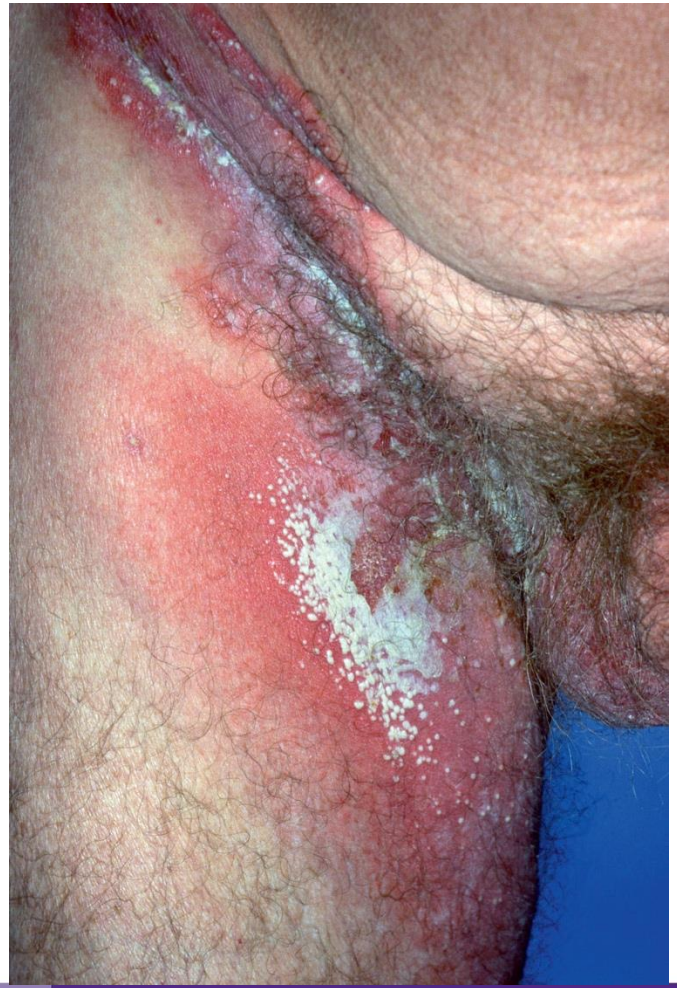
- ≤0 = not AGEP
- 1–4 = possible AGEP
- 5–7 = probable AGEP
- 8–12 = definitive AGEP

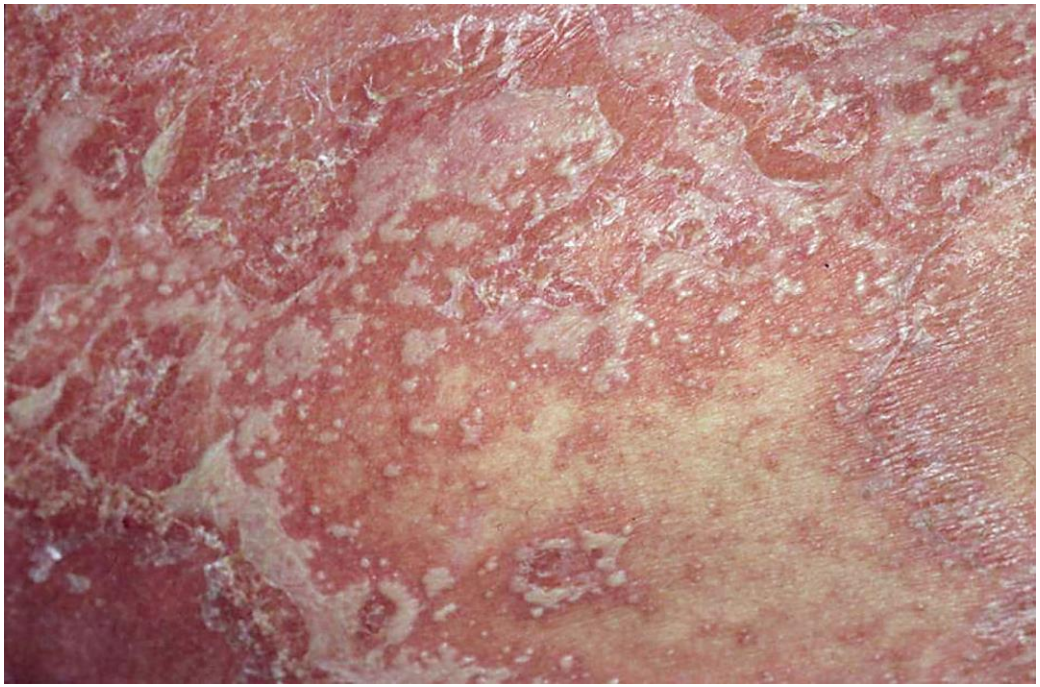
AGEP DDX

- Candidiasis
- Bacterial folliculitis
- Pustular psoriasis
- Subcorneal pustular dermatosis
- DRESS syndrome









Treatment of AGEP

- Drug cessation
- **Topical steroids**
  - Oral corticosteroids in severe eruptions
- Evolving options
  - Anti-IL36 (spesolimab)[1]
  - Anti-IL17 (secukinumab, ixekizumab)[2]
  - Anti-TNF (adalimumab)[3]

1. Jama Dermatol. 2024.160(9):1009-1012
2. J Eur Acad Dermatol Venereol. Published online Feb 24, 2024
3. Clin Cosmet Investig Dermatol. 2023. 16:9-15

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Also referred to as Drug-induced hypersensitivity syndrome (DIHS), Anticonvulsant Hypersensitivity Syndrome (AHS), DReSS, and Pseudolymphoma
- Represents up to one fifth of inpatient drug eruptions
- Mortality rate 5% (1.6-6.2%)

Wei, BM et al 2024. J AmAcad Dermatol 90 (5)

DRESS Clinical Features

- Longest latency: 2-6 weeks (up to 8)
- Fever >38.5C (highest)
- Extensive rash >50% TBSA
- Organ involvement

Krochinsky, D et al. NEJM 2024; 391: 2242-54

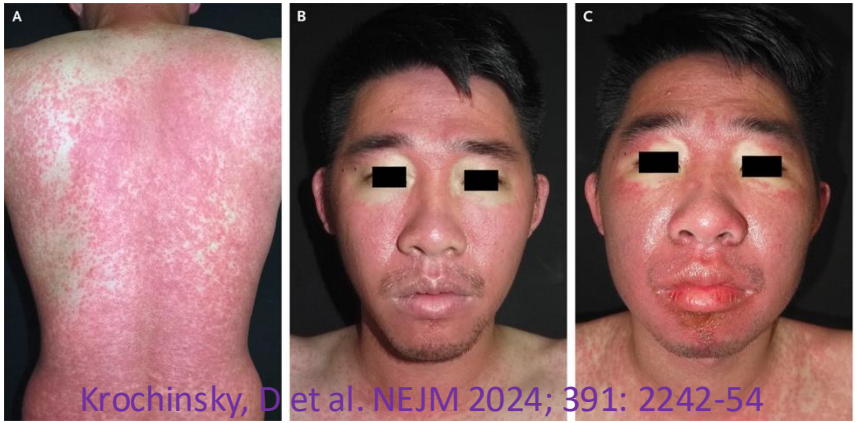
DRESS Clinical Features

- Longest latency: 2-6 weeks (up to 8)
- Fever >38.5C (highest)
- Extensive rash >50% TBSA
- Organ involvement
- Lymphadenopathy 50%
- Purpura (poor prognostic sign)
- Mucosal involvement (milder)
- Relapsing course
- Facial edema/earlobe crease

Krochinsky, D et al. NEJM 2024; 391: 2242-54

DRESS: Skin Findings

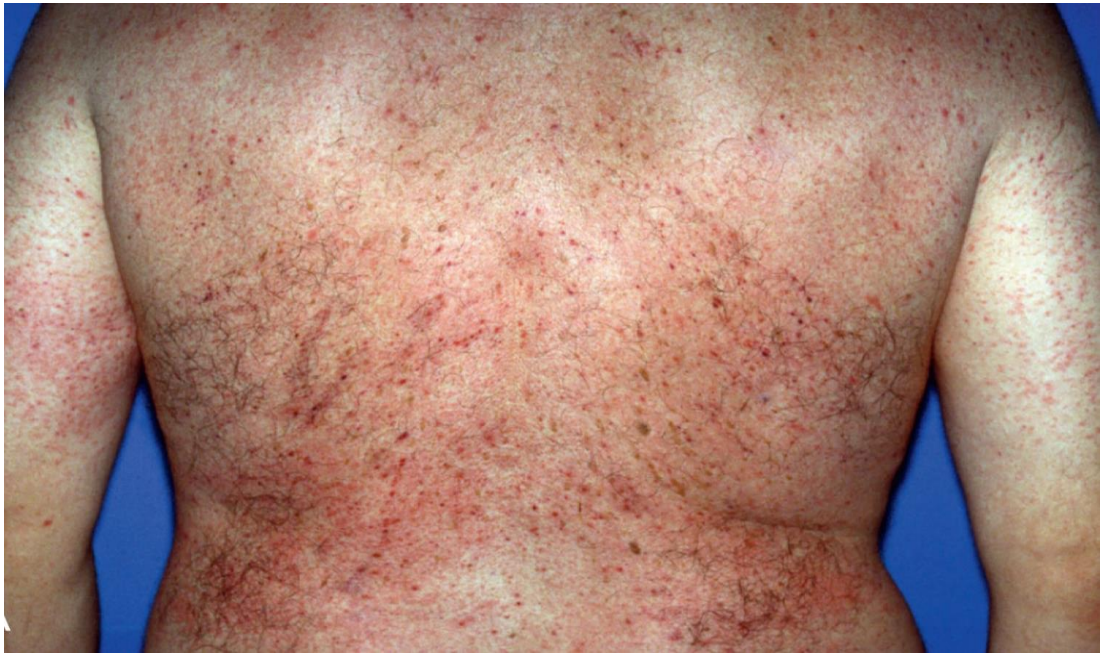
- Skin findings (73-100%)
  - Maculopapular (MPR) (81%)
  - Erythroderma
  - Urticarial
  - Vesiculobullous
  - Pustular
  - Purpura (poor prognostic feature)
  - Facial edema
  - Mucositis



Krochinsky, D et al. NEJM 2024; 391: 2242-54

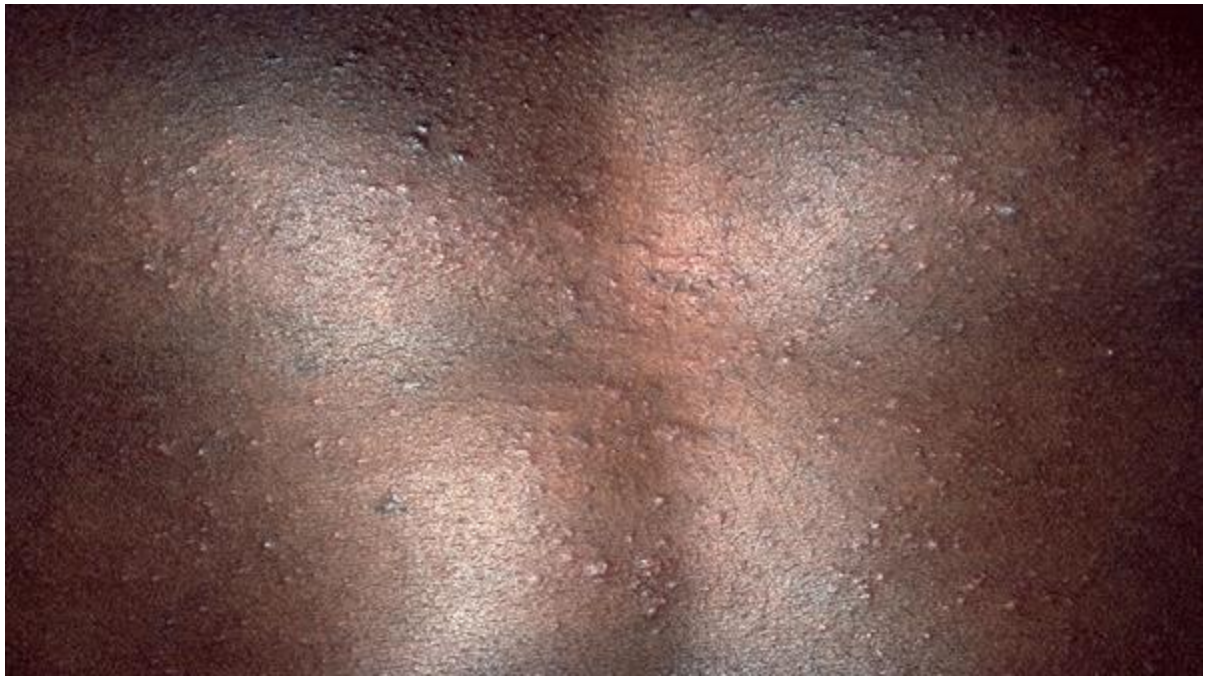
Chen et al. Dermatologica Sinica. 2013

Drug Rash with Eosinophilia and Systemic Symptoms



Andrews Clinical Atlas of the Skin. 2023

Drug Rash with Eosinophilia and Systemic Symptoms



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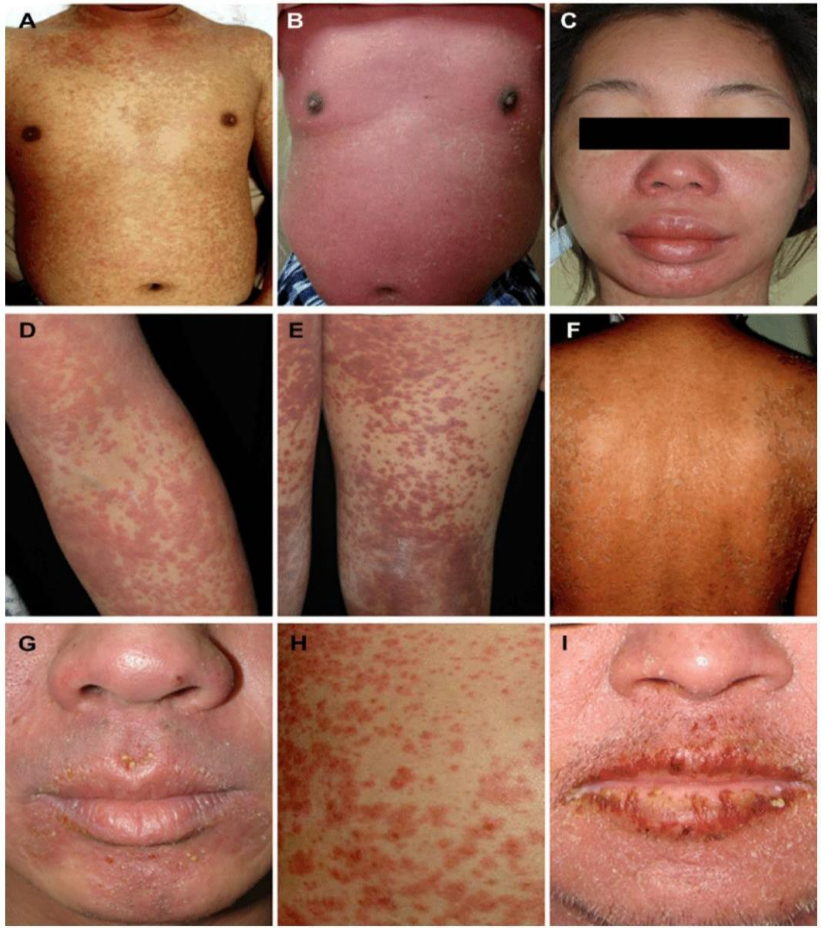
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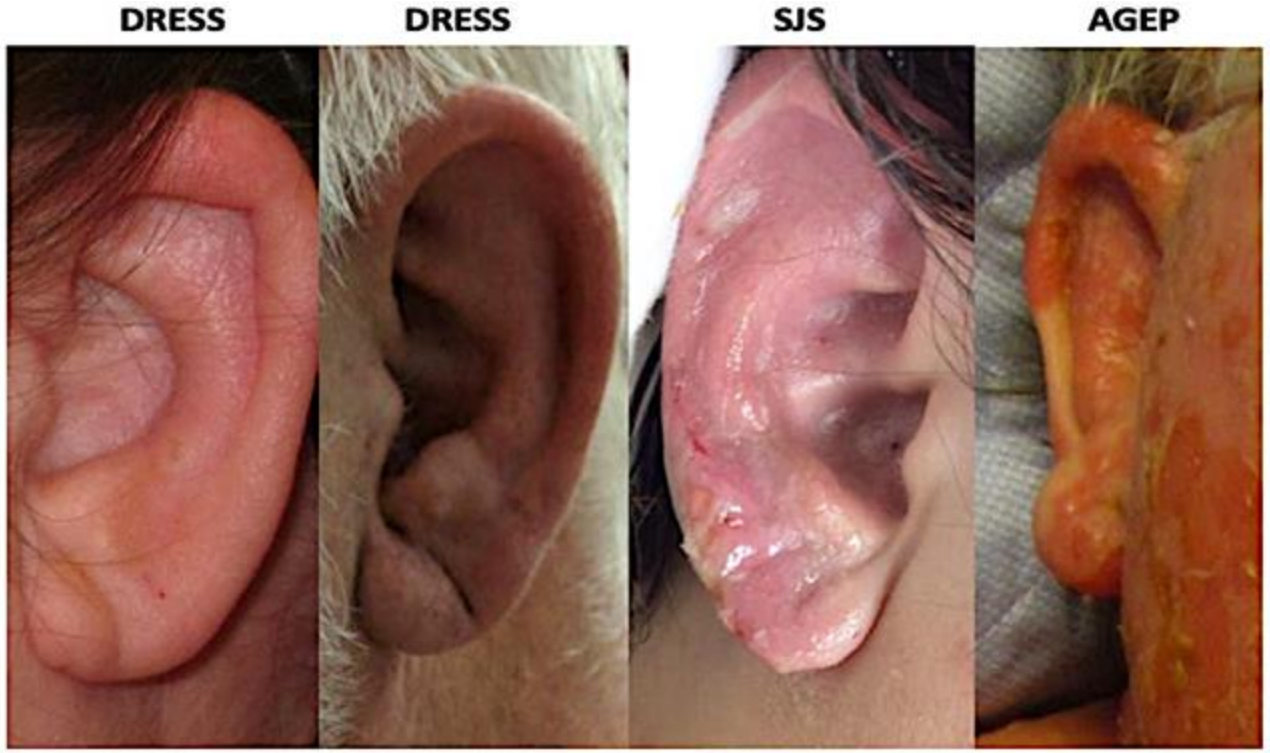
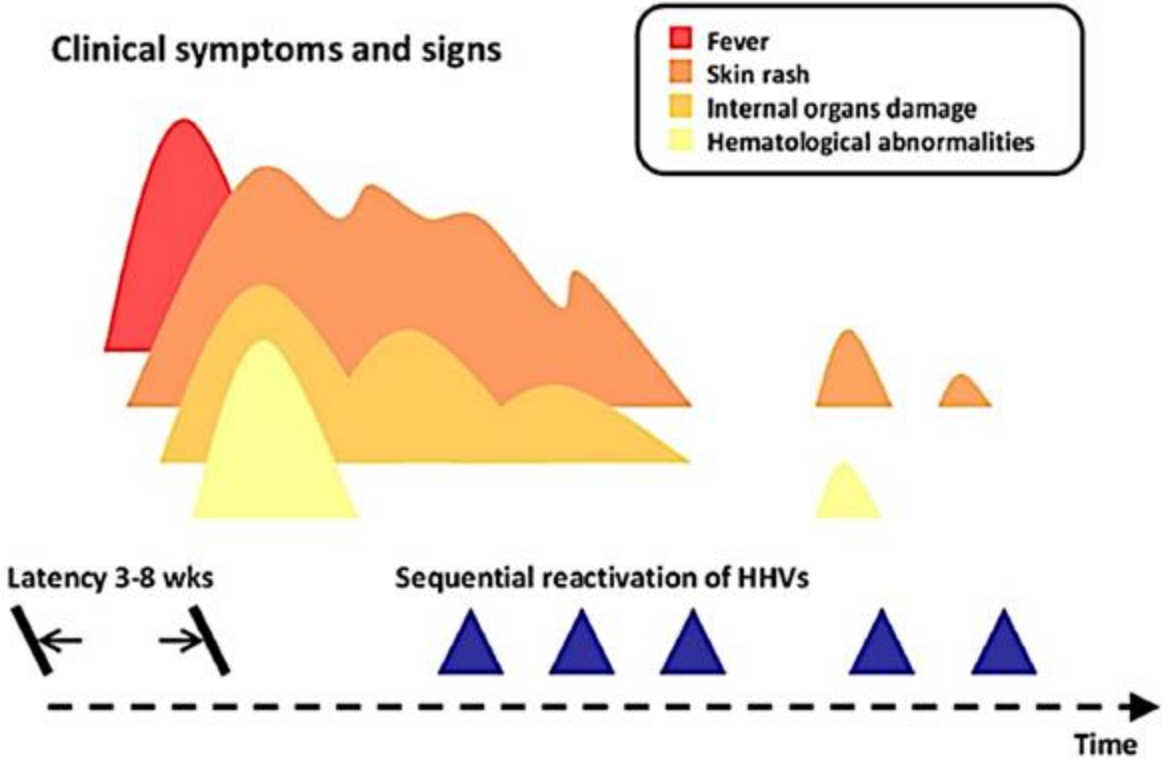
Oblique Earlobe Crease in SCAR

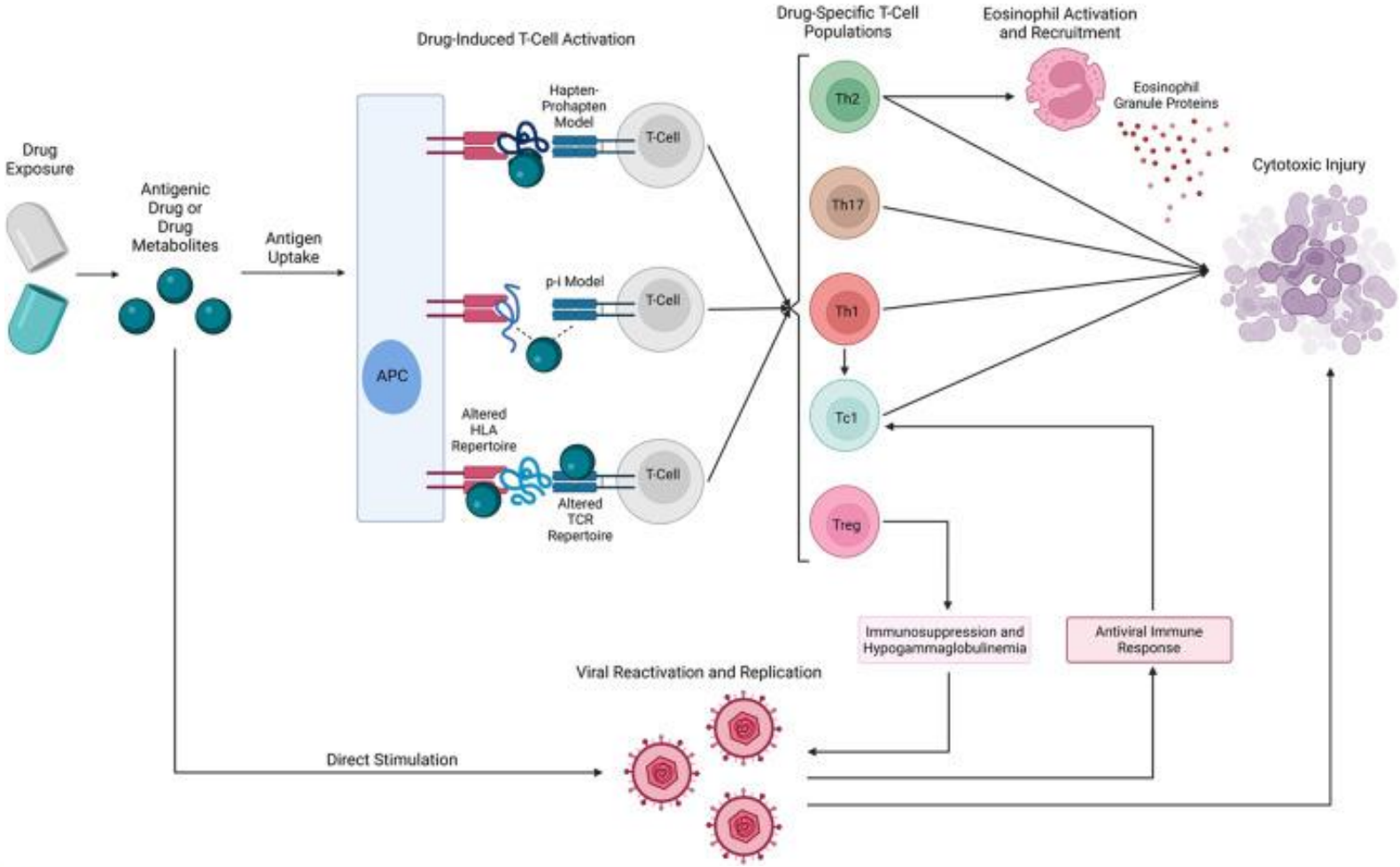


Gilkey et al. Journal of the European Academy of Dermatology and Venereology 2022

Clinical Course of DRESS



Wedell Arch Derm Res 2024. 316:644



JAAD 2024. 90(5): 885-908

Top 5 Causes of DRESS

- Vancomycin
- Trimethoprim Sulfamethoxazole
- Carbamazepine
- Lamotrigine
- Allopurinol

Hung, SL et al. Nature Reviews Disease Primers 2024. 10:30

High Risk Drugs in DRESS

- Allopurinol (8.2%)
- Antiepileptic drugs (37.6%)
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Lamotrigine
  - Oxcarbazepine
- Antibiotics (24.8%)
  - Sulfonamides:
    - Sulfasalazine
    - Dapsone
    - Trimethoprim-sulfamethoxazole
  - Vancomycin
  - Minocycline
  - Aminopenicillins
- Nevirapine/Abacavir (5.6%)
- Anti TB drugs
  - Rifampin
  - Ethambutol
  - INH
  - Pyrazinamide
- Immune Checkpoint Inhibitors
  - Ipilumumab
  - Nivolumab

Drugs and Specific Organs

Medication	Clinical abnormality
Allopurinol	Renal
Ampicillin	Cardiac
Carbamazepine	Renal
Dapsone	Hepatic and renal
Minocycline	Hepatic, pulmonary, and cardiac
Phenytoin	Hepatic

Husain JAAD 2013. 68:693-e1

DRESS: Laboratory Findings

- CBC Abnormalities
  - Leukocytosis with mild to extreme eosinophilia
  - Atypical lymphocytes
- Liver enzyme elevations
- Elevated creatinine, hematuria, proteinuria
- Cardiac troponins
- HHV-6 serologies (reactivation): incidence ranges from 46% to 100%
- ANA negative

Criteria to Diagnose DRESS

RegiSCAR

Bocquet et al[4]	[72]	J-SCAR[73*]
Cutaneous drug eruption	Acute rash[†]	Maculopapular rash developing >3 weeks after starting offending drug
Hematologic abnormalities	Reaction suspected to be drug-related[†]	Prolonged clinical symptoms after discontinuation of the causative drug
Eosinophils $\geq 1.5 \times 10^9$/L	Hospitalization[†]	Fever >38°C
Presence of atypical lymphocytes	Fever >38°C[‡]	Liver abnormalities (ALT >100 U/L) or other organ involvement
Systemic involvement	Enlarged lymph nodes involving ≥ 2 sites[‡]	Leukocyte abnormalities (≥ 1)
Adenopathy: lymph nodes ≥ 2 cm in diameter	Involvement of ≥ 1 internal organ[‡]	Leukocytosis ($>11 \times 10^9$/L)
Hepatitis with liver transaminases ≥ 2 times normal	Blood count abnormalities[‡]	Atypical lymphocytes (>5%)
Interstitial nephritis	Lymphocytes above or below normal limits	Eosinophilia ($>1.5 \times 10^9$/L)
Interstitial pneumonitis	Eosinophils over laboratory limits	Lymphadenopathy
Carditis	Platelets under laboratory limits	HHV-6 reactivation

[†]Necessary criteria for diagnosis according to RegiSCAR.
[‡]Three of these 4 criteria required for diagnosis according to RegiSCAR.

Husain JAAD 2013;68:693-e1

DRESS Scoring Based on RegiSCAR

Clinical parameters	Score			Comments
	−1	0	1	
Fever ≥101.3°F (38.5°C)	No/unknown	Yes		
Lymphadenopathy		No/unknown	Yes	>1 cm, at least 2 sites
Eosinophilia ≥0.7 × 10^9 or ≥10% if leucopenia		No/unknown	Yes	Score 2 points of ≥1.5 × 10^9
Atypical lymphocytes		No/unknown	Yes	
Skin rash				
▪ Rash suggestive of DRESS	No	Unknown	Yes	Suggestive features: ≥2 facial edemas, purpura, infiltration, desquamation
▪ Extent ≥50% of BSA		No/unknown	Yes	
Skin biopsy suggestive of DRESS	No	Yes/unknown		
Organ involvement		No	Yes	1 point for each organ involvement, maximum score: 2
Disease duration ≥15 days	No/unknown	Yes		
Exclusion of other causes		No/unknown	Yes	1 point if 3 of the following tests are performed and are negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture

- <2: Excluded
- 2-3: Possible
- 4-5: Probable
- ≥6: Definite

UpToDate 2023

Evaluation for Suspected DRESS

- Skin biopsy
- CBC with diff, smear
- Comprehensive metabolic panel, UA
- ESR/CRP
- HHV6, HHV7, CMV, EBV serologies
- Troponin
- ECG, Echo, LN biopsy, CT scan

DRESS

- Symptoms and lab abnormalities may persist weeks to months even after discontinuing causative medication
- Relapses even after discontinuation of drug (58.7%)
  - Viral reactivation may drive this
- Autoimmune complications post recovery: 3.8%
  - SLE, RA, DM, hepatitis, thyroiditis, hemolytic anemia

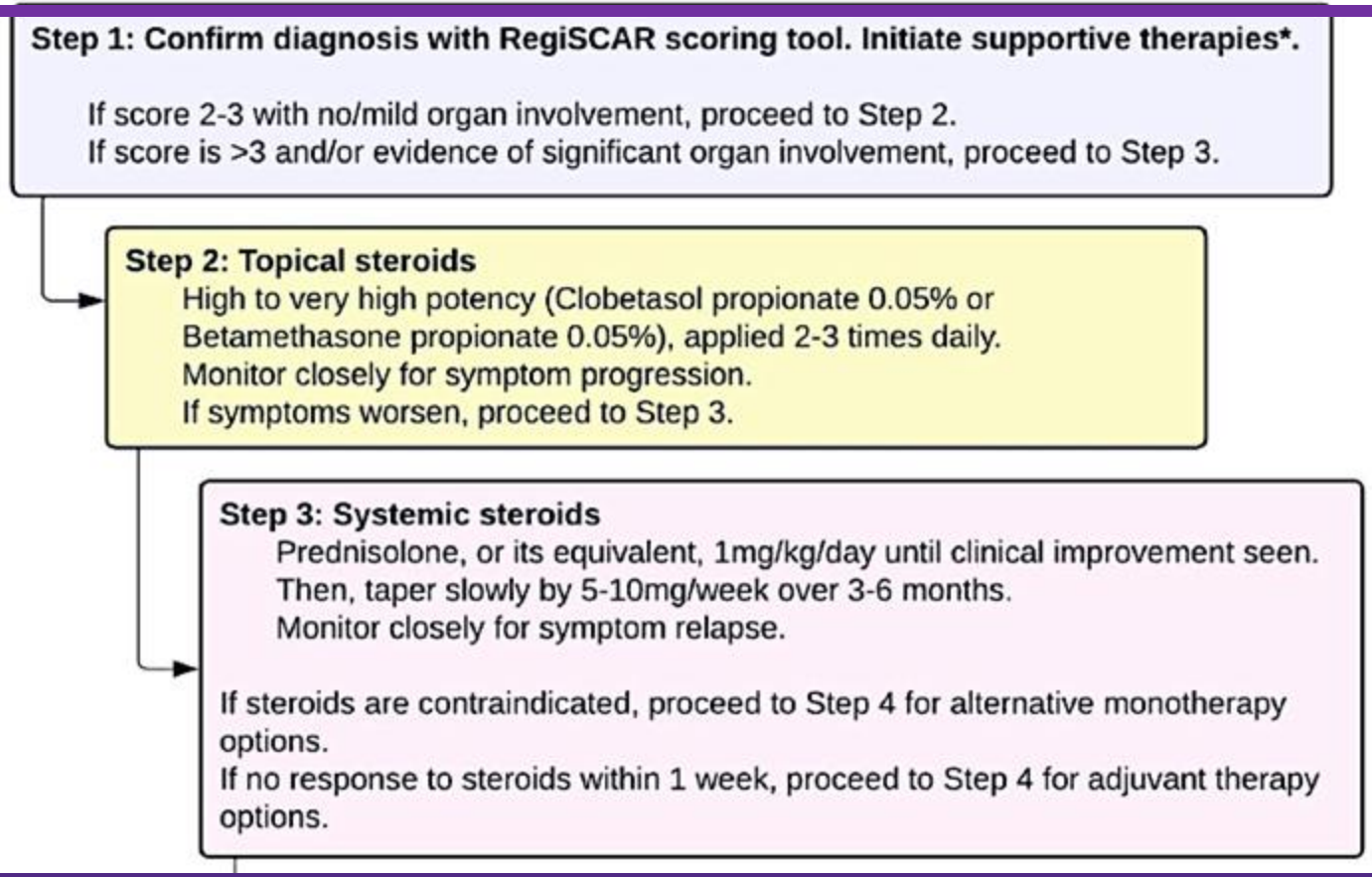
Pavlos JACI Pract 2014;2:21

DRESS: Therapy

- Systemic corticosteroids
- Cyclosporine
- Anti-IL5
- IVIG
- JAKi

Wei, BM et al 2024.J AmAcad Dermatol 90 (5)

DRESS Treatment



Wedell Arch Derm Res 2024;316:644

Alternative and Mono Therapy

Cyclosporine:
1.73-5mg/kg/day for 7 days
Taper by 50mg/day over 1-6 weeks

*May be used as mono- or adjuvant therapy.

IVIG:
2-5g/kg/day for 3-5 days

*Adjuvant therapy only

N-acetylcysteine:
Loading dose of 150mg/kg over 1hr, followed by 100mg/kg over 16hrs.
For use in acute phase only.

*Adjuvant therapy only.

Plasmapheresis:

*Adjuvant therapy only

Targeted therapy:
Tofacitinib 10mg daily or BID
Benralizumab 30mg SC, repeat monthly as needed.
Mepolizumab 300mg SC, or 100mg SC monthly as needed.
Etanercept 50mg SC, followed by 25mg SC every 3 days, as needed.

*May be used as mono- or adjuvant therapy.

Wedell Arch Derm Res 2024;316:644

Mepolizumab for DRESS

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome successfully treated with mepolizumab

Nikhita Ange, MBBCh[a], Sonia Alley, MBBS[a,b], Suran L. Fernando, MBBS, PhD[a,c,d], Luke Coyle, MBBS[b,d,e], and James Yun, MBBS, PhD[a,d]

Clinical Implications

- The anti–IL-5 mAb mepolizumab shows promise as a novel therapy in the treatment of relapsing/refractory drug reaction with eosinophilia and systemic symptoms syndrome.

JACI in Practice 2018

Successful mepolizumab treatment for DRESS-induced refractory eosinophilic myocarditis and concurrent thyroiditis

Kelvin Truong [1,2] Shane Kelly,[3] Angela Bayly,[4] Annika Smith[1,2]

BMJ Case Report 2021

Treatment with IL5-/IL-5 receptor antagonists in drug reaction with eosinophilia and systemic symptoms (DRESS)

Anna Gschwend · Arthur Helbling · Laurence Feldmeyer · Ulrich Mani-Weber · Cordula Meincke · Kristine Heidemeyer · Simon Bossart · Lukas Jörg

Allergo J Int 2023

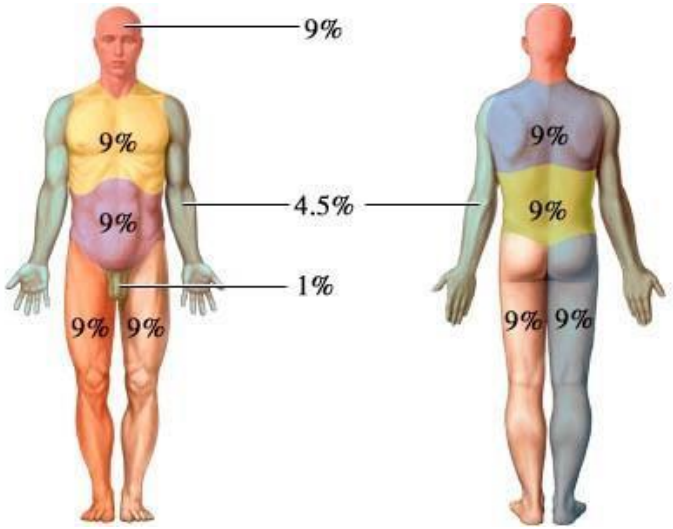
Dupilumab for DRESS

- Dupilumab may be a safe and effective therapy option
  - 2 cases of DRESS successfully treated with Dupilumab

J Allergy Clin Immunol Pract. 2023 :11(12):3789-3791

SJS/TEN

- SJS v TEN:
  - Incidence v DRESS lower
  - Variants of the same condition
  - % body surface area (BSA) involvement
    - SJS: <10%
    - SJS/TEN overlap: 10-30%
    - TEN: >30% of BSA
    - New proposal: SJS<10% and TEN>10%[1]



https://www.health.state.mn.us/communities/ep/surge/burn/tbsa.html

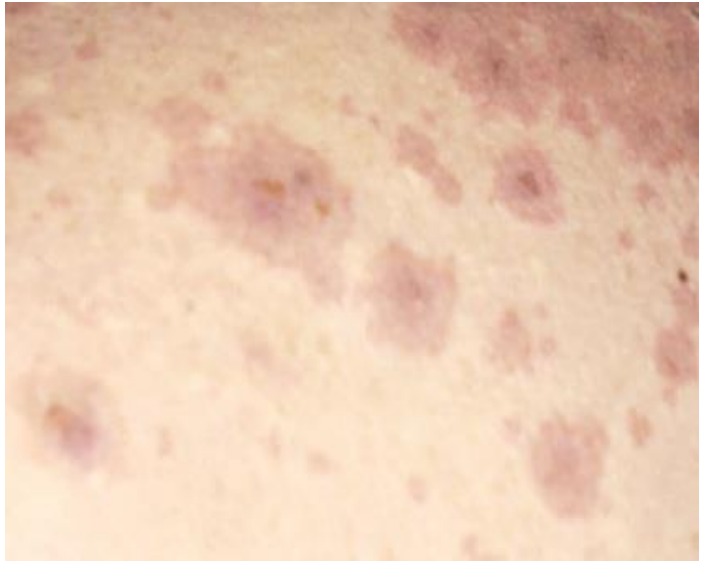
1. Br J Dermatol 2025. 192: 9-18

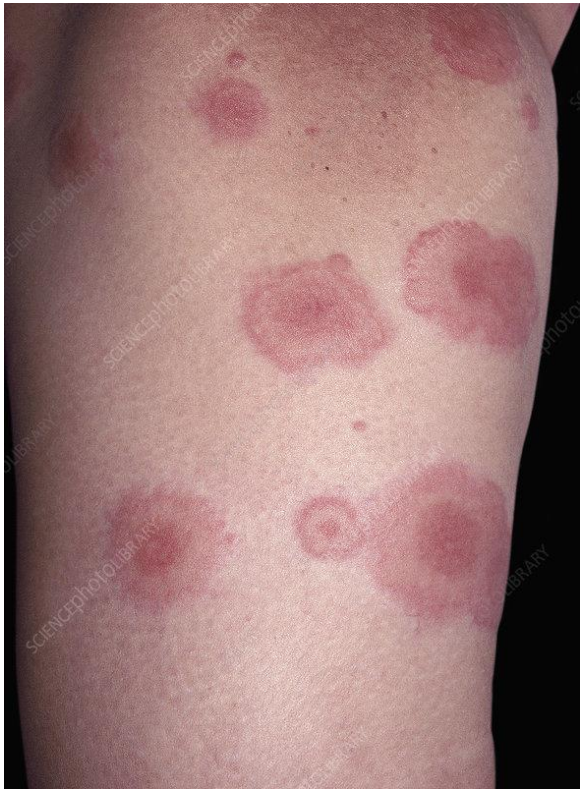
SJS/TEN

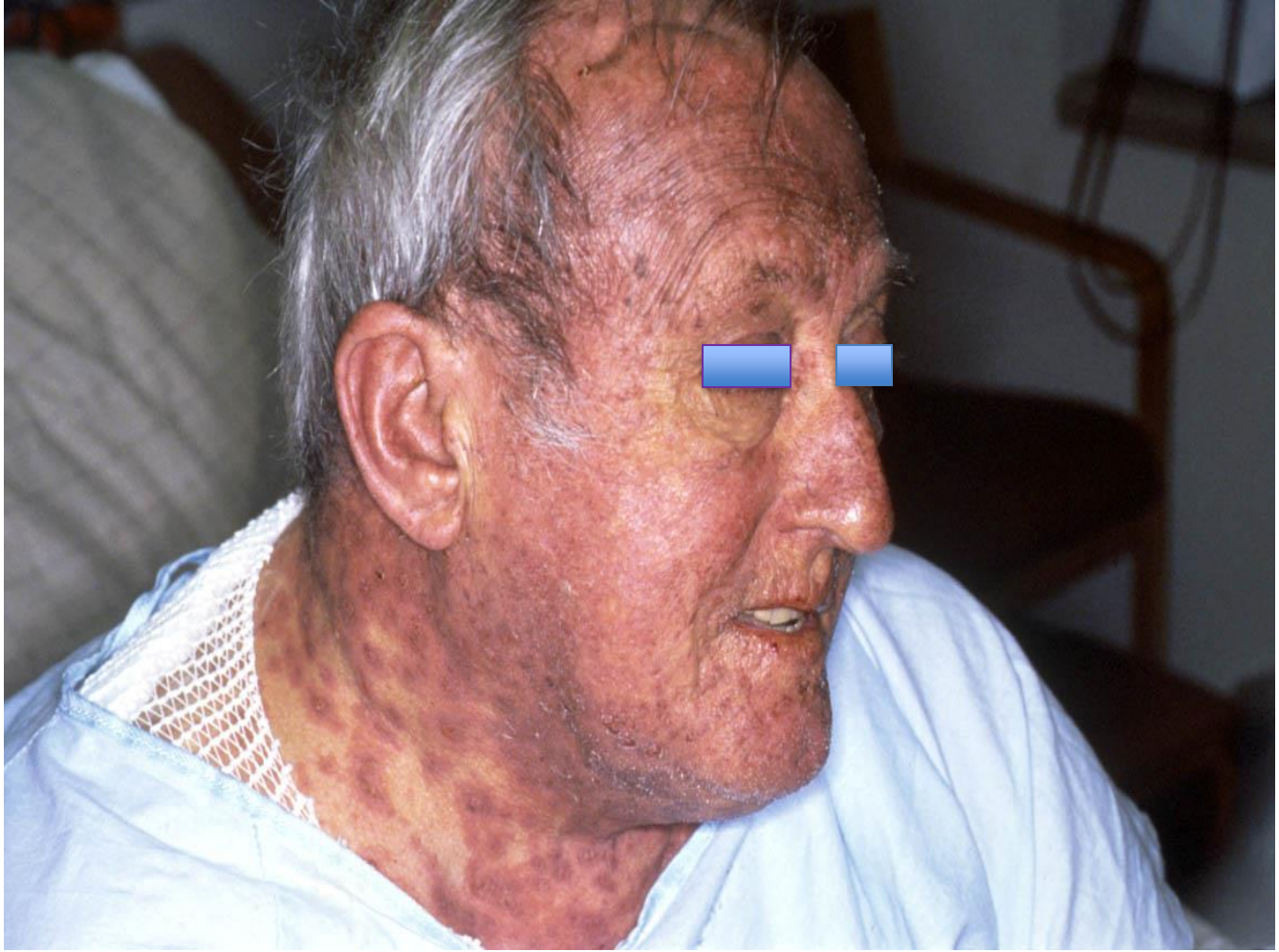
- Risk Factors
  - HIV (100x increase risk)
  - Underlying malignancy (lymphoma)
  - SLE
  - Race (African American, Asian)
  - Gender (female>male)
  - Introduction of new medication at high dose
  - No links to ETOH, tobacco, BMI

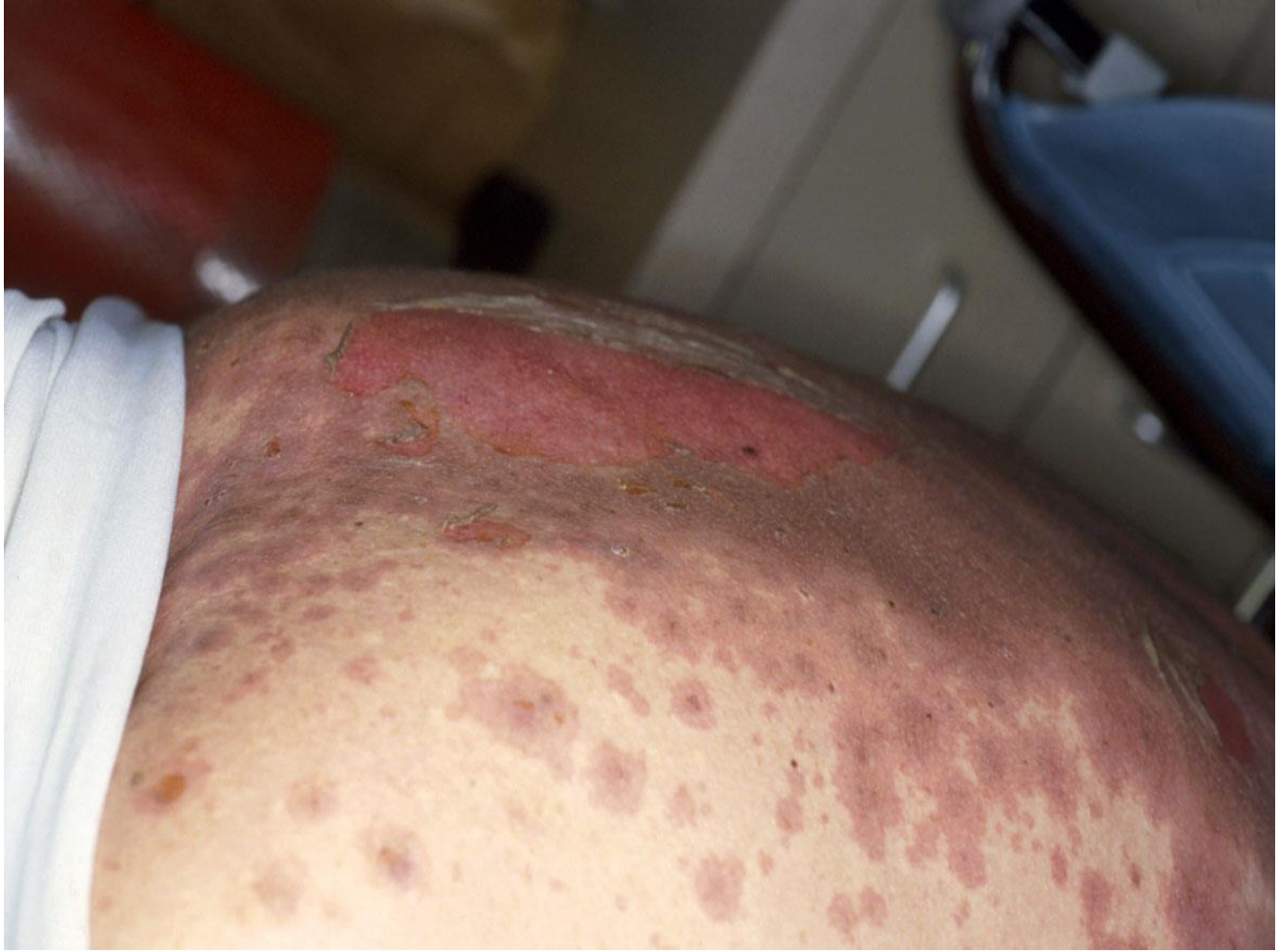
SJS/TEN Clinical Findings

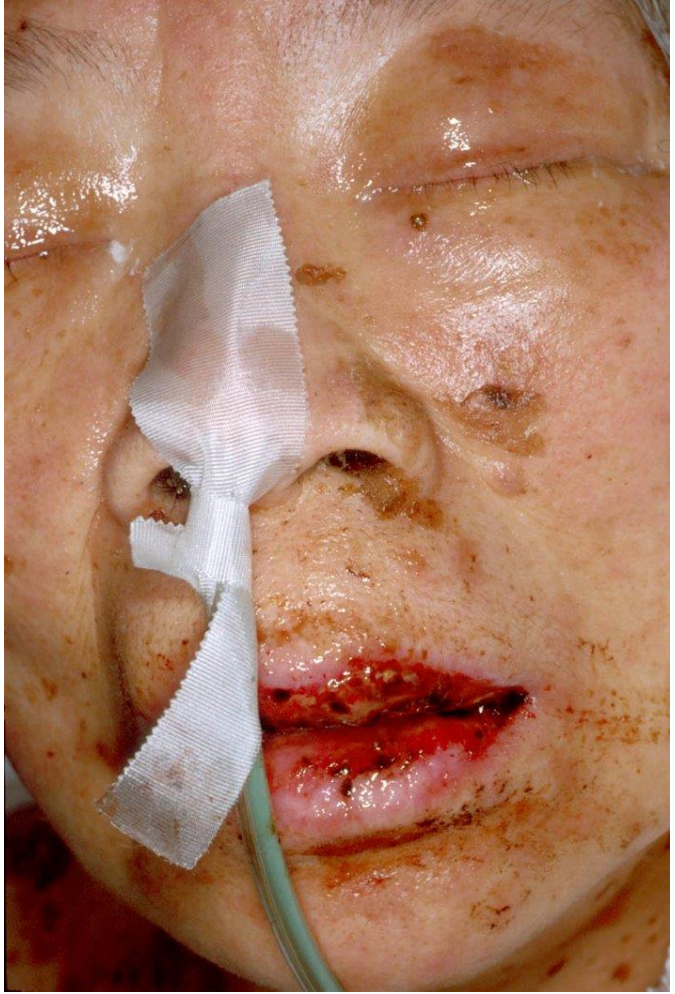
- Painful macules
- Flat, atypical targets
    - Truncal > acral
- POSITIVE Nikolsky sign, desquamation
- Mucosal erosions >90%
    - Prodrome: fever and sore throat then rash follows
- Causative medication: within previous 2-4 weeks
- Labs: non-specific
- Fever may be present, not as severe as DRESS

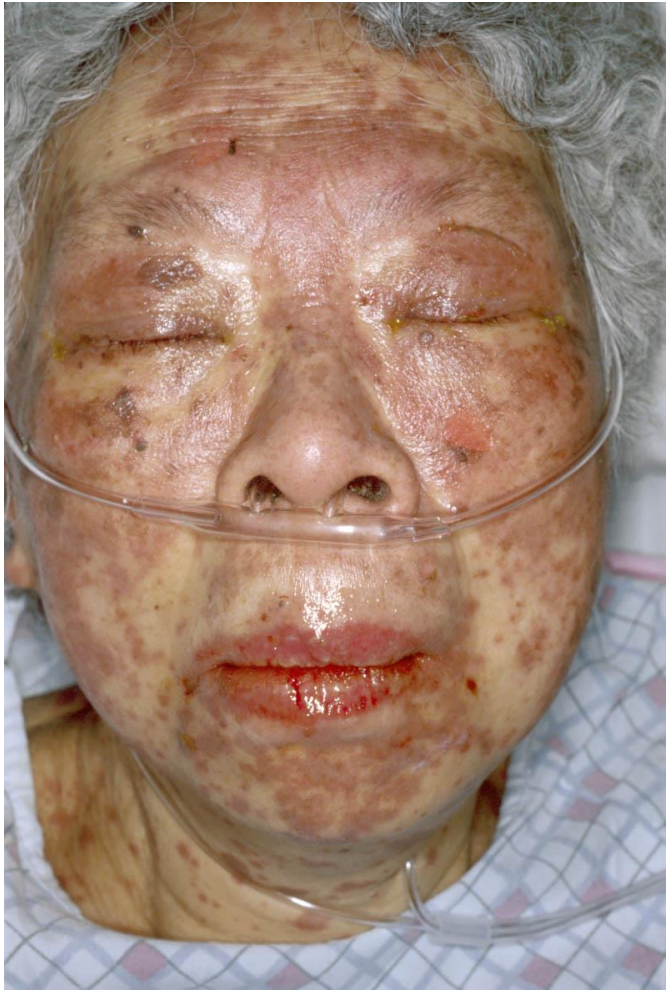


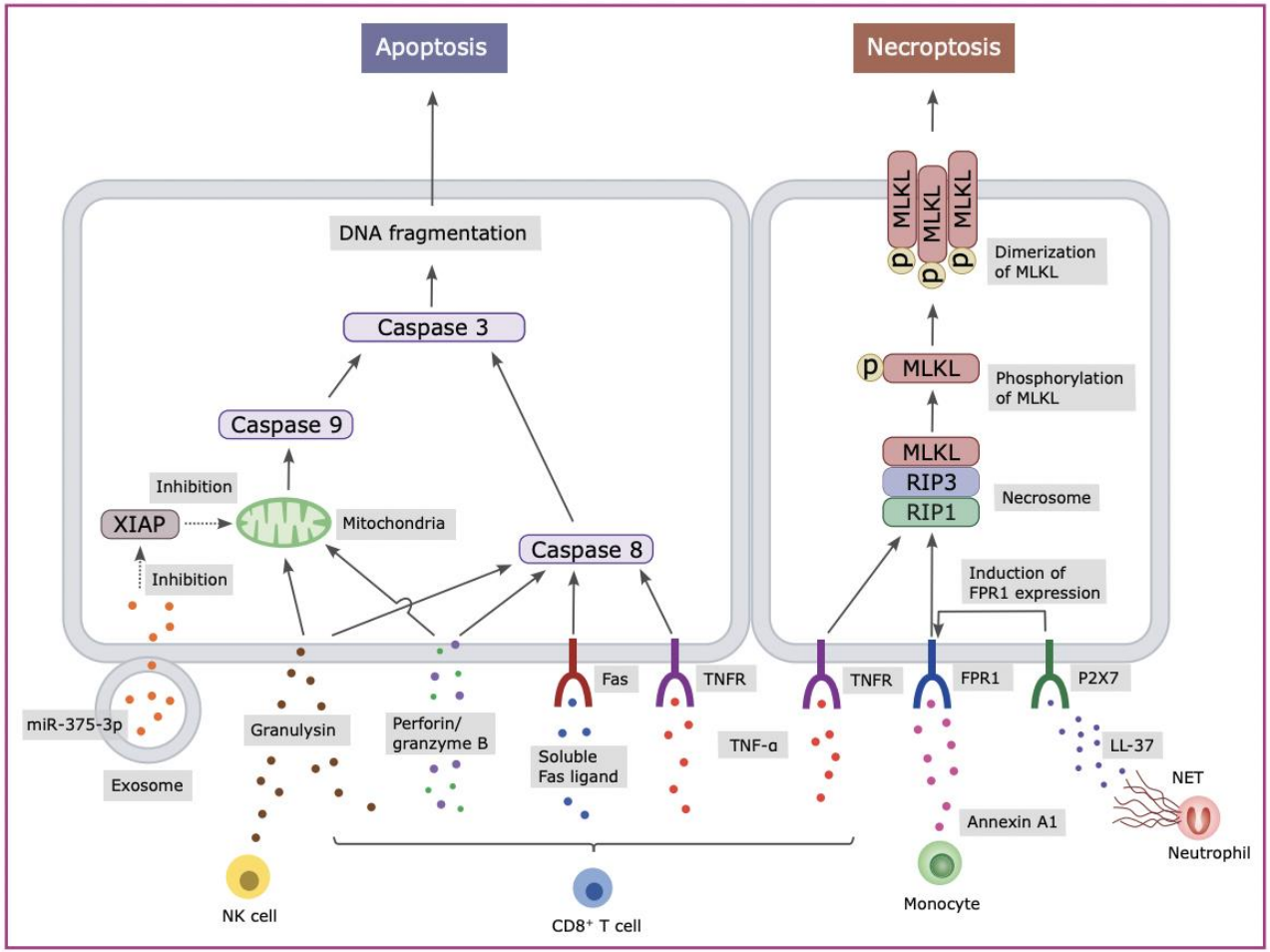











Apoptosis
Necroptosis
DNA fragmentation
Caspase 3
Caspase 9
Caspase 8
Inhibition
XIAP
Mitochondria
Inhibition
miR-375-3p
Exosome
Granulysin
Perforin/
granzyme B
Fas
TNFR
Soluble
Fas ligand
TNF-α
NK cell
CD8⁺ T cell
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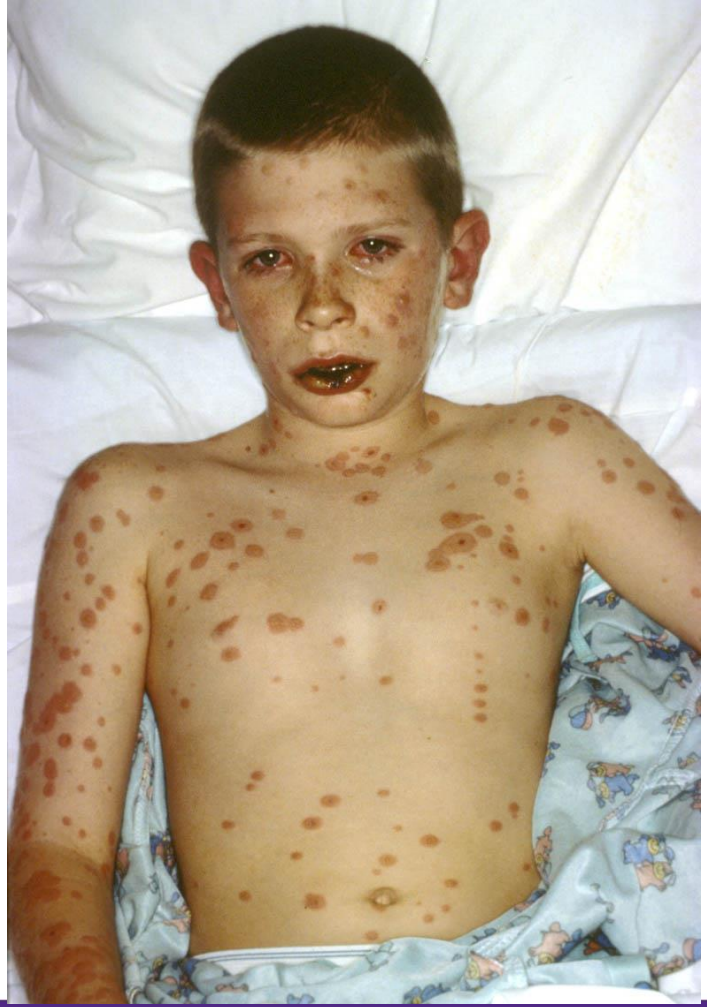
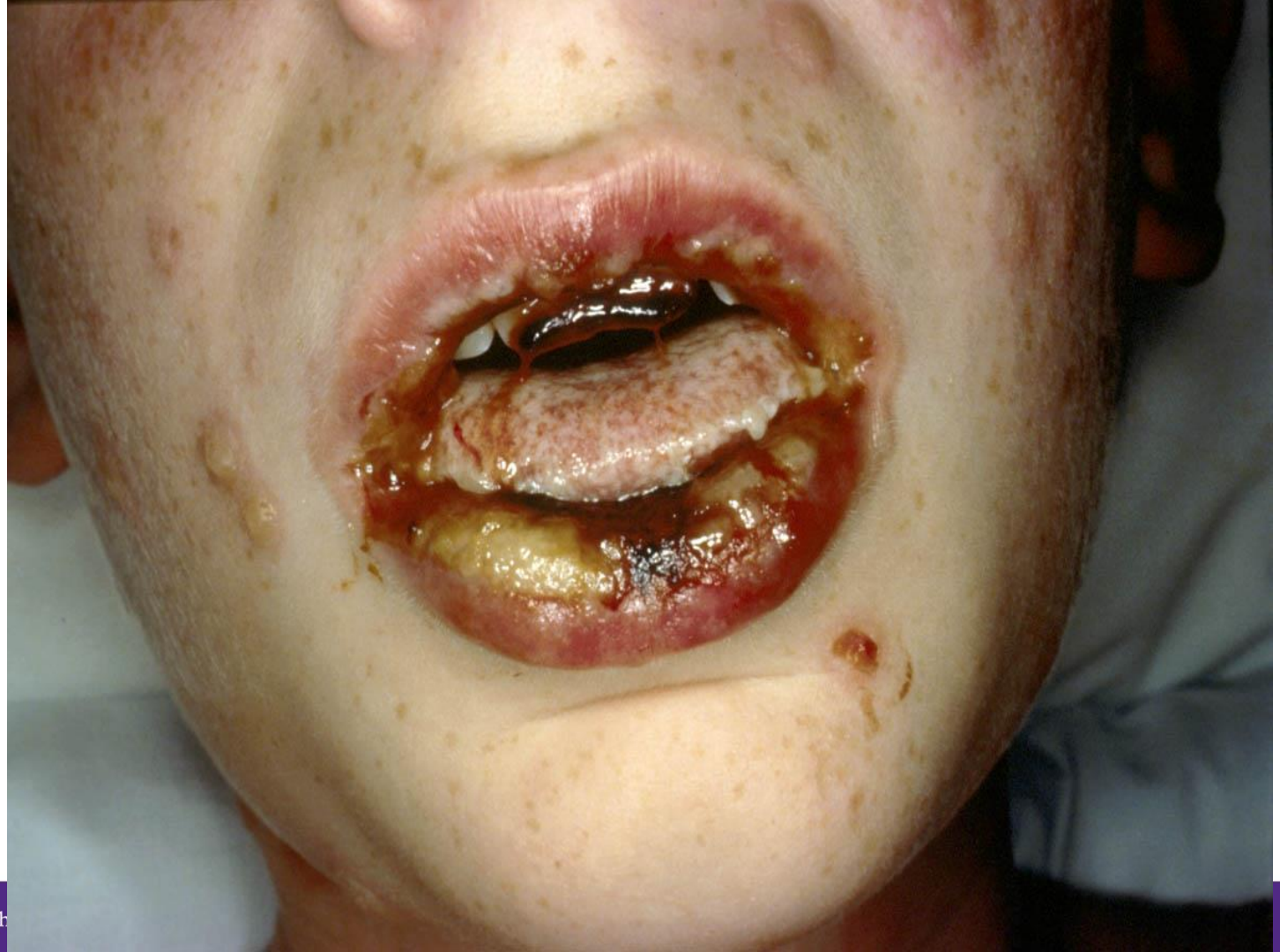
RIP3
RIP1
Necrosome
Induction of
FPR1 expression
TNFR
FPR1
P2X7
LL-37
NET
Neutrophil
Annexin A1
Monocyte

Stevens-Johnson Syndrome

- Etiology
    - Drugs
    - Infections (*Mycoplasma pneumoniae*)
- Skin biopsy: confirm dx and exclude other diseases such as blistering disorders
    - DIF negative
- Mortality 5%





Toxic Epidermal Necrolysis

- Most severe adverse drug reaction
- Drugs implicated in 90%
- 25-35% mortality
- Extensive mucosal and visceral involvement
- Epidermal detachment > 10 (or >30%) of TBSA
- Skin biopsy and DIF:
    - full thickness epidermal necrosis of keratinocytes
    - DIF negative

EuroSCAR Study: Drugs associated with SJS/TEN

- Allopurinol
- Carbamazepine
- Cotrimoxazole
- Phenobarbital
- Phenytoin
- Sulfonamides
- NSAIDs
- Lamotrigine
- Nevirapine
- Sertraline
- Pantoprazole
- Tramadol

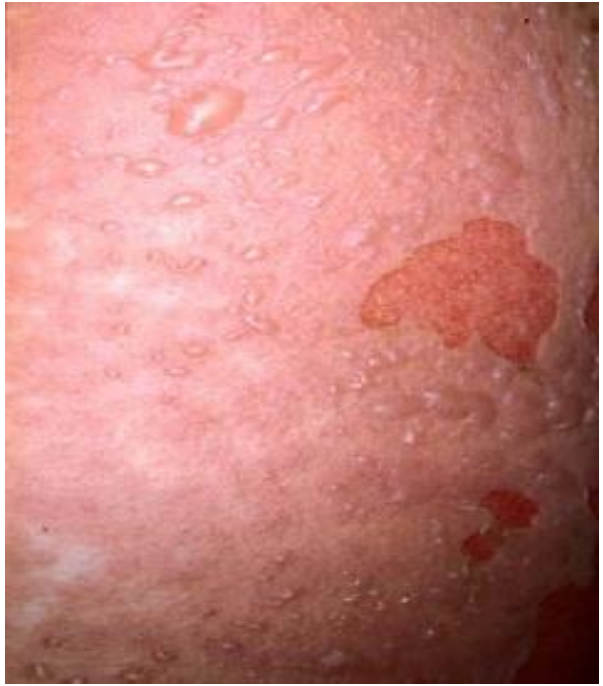
Mockenhaupt et al. J Inv Dermatol 2008

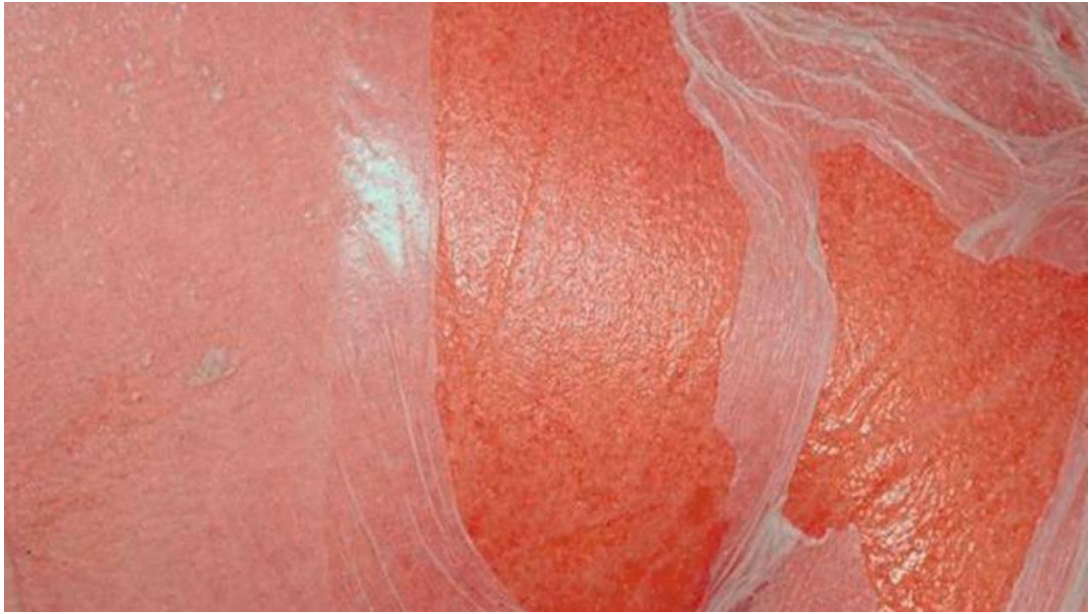
SJS/TEN: CAUSES

- MOST COMMON CAUSE: ALLOPURINOL (associated with a 20-fold increased risk)
- Recent meta-analysis: Sulfonamides, penicillins, cephalosporins, quinolones and macrolides, were reported to account for 28% of SJS/TEN
- Risk period to induce SJS/TEN: 4 days- 4 weeks
  - up to 8 weeks for medications with a long half-life
    - allopurinol, phenytoin, carbamazepine or lamotrigine

Severe cutaneous adverse reactions. *Nat Rev Dis Primers* 2024. **10(30)**

TEN



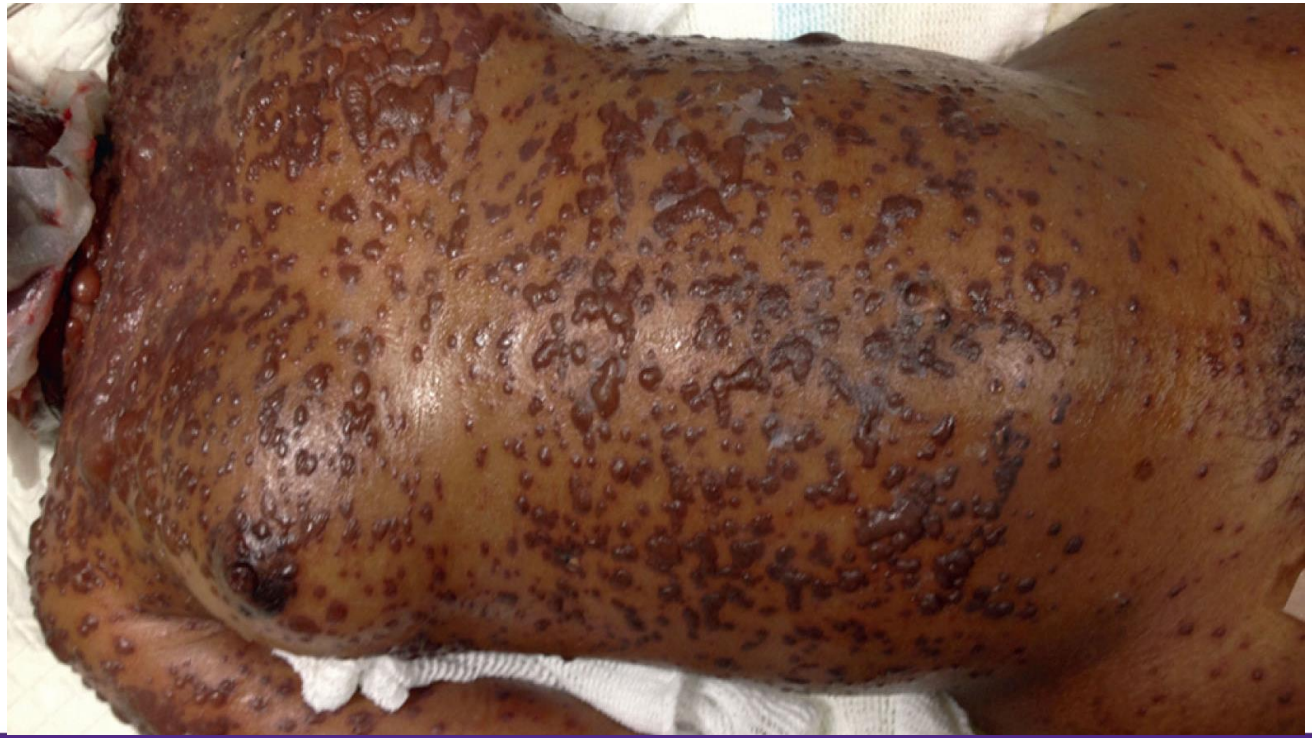


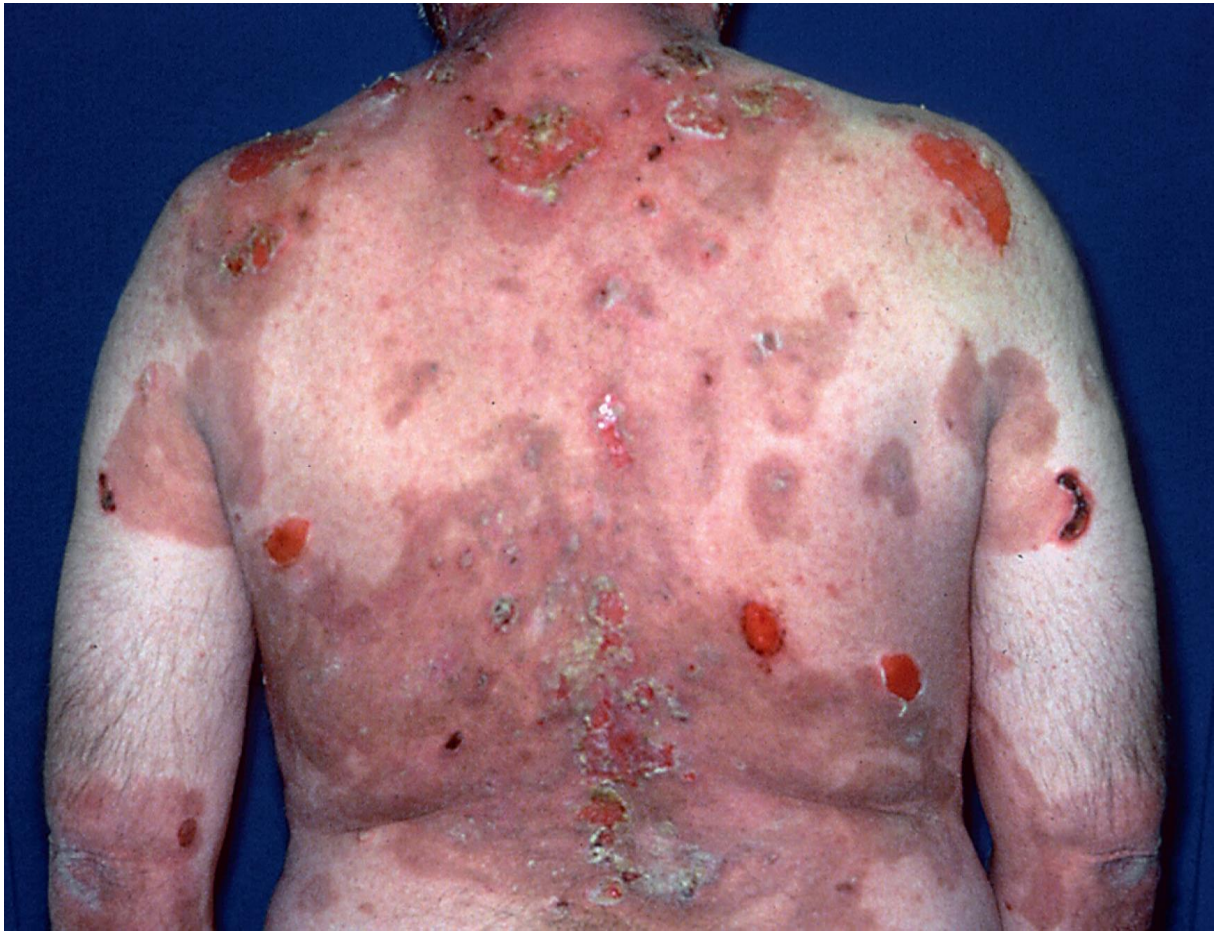
SJS/TEN

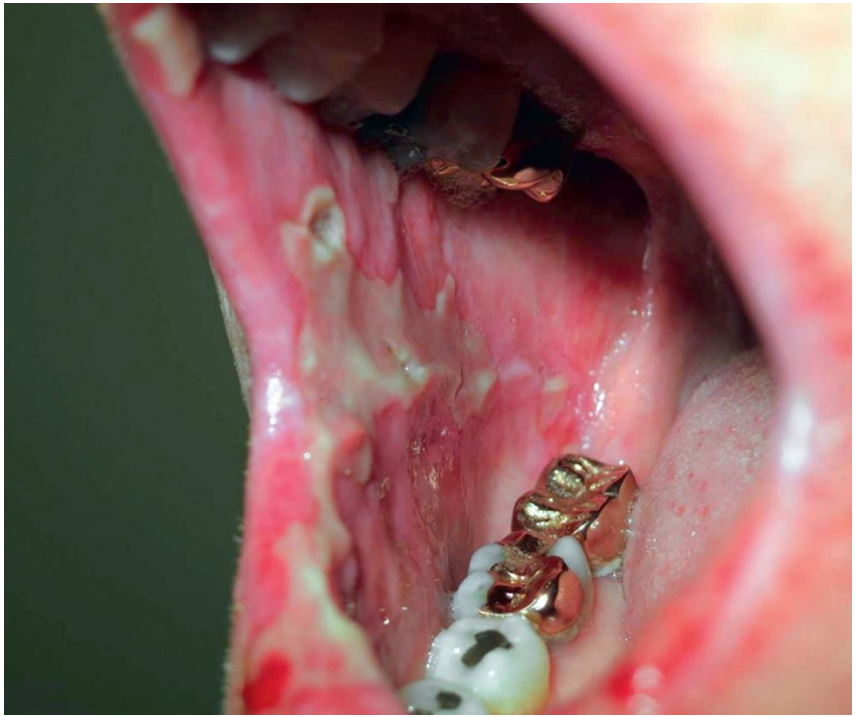
- DDx
  - GBFDE
  - SSSS
  - TSS
  - Paraneoplastic pemphigus
  - Pemphigus/pemphigoid
  - SLE (bullous), SLE/EM Overlap
  - Acute GVHD

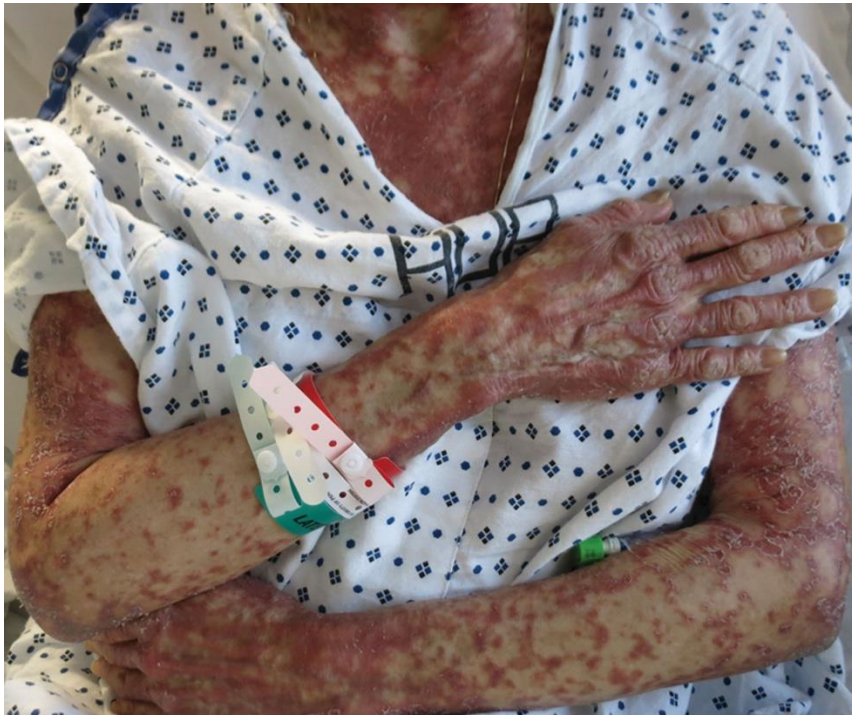
- Biopsy for routine histology and DIF: Full thickness epidermal necrosis with negative DIF supports SJS/TEN

TEN v GBFDE









SJS/TEN: Acronym Overload

- ALDEN
- SCORTEN
- ABCD-10
- CRISTEN
- RegiSCAR
- Niigata Criteria

ALDEN Score: Algorithm for Assessment of Drug Causality

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	−3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely −1	>56 Days	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present	
	Excluded −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar[c] drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative −2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case–control studies[d]	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case–control studies[d]	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[c]	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score	−1
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	

Score: -12 to 10

<0: Very unlikely

0-1: Unlikely

2-3: Possible

4-5: Probable

>6: Very probable

Sassolas Clin Pharmacol Ther 2010;88:60

SCORTEN

SCORTEN (2000)

- Validated 7-point system to measure the severity of illness
  - Age older than 40
  - Presence of underlying malignancy
  - > 10% skin detachment
  - Tachycardia
  - Elevated BUN, Glucose, bicarbonate

SCORTEN on days 1 and 3 predicts mortality

- If ≤ 2 mortality < 10%
- **If ≥ 4 mortality > 75%**

- **ABCD-10 (2015)**
  - Shares 4/5 features with SCORTEN
  - Inferior to SCORTEN in predicting mortality

Guegan et al. J Invest Dermatol 2006 126:272

Clinical Risk Score for TEN (CRISTEN)

- Clinical-based risk assessment
  - Novel scoring system to predict mortality SJS/TEN
  - No laboratory values included
  - Focuses on 10 clinical factors
    - Age>65
    - Epidermal detachment >10%
    - Culprit drug antibiotics
    - On therapy for diabetes
    - History of renal impairment
    - Malignancy
    - Bacterial Infection
    - Cardiac disease
    - 3 mucous membranes affected
    - On systemic corticosteroids before onset

J Allergy Clin Immunol Pract 2023.11(10): 3161-3168

Clinical Risk Score for TEN (CRISTEN)

Mortality rates in 449 cases in Japan

Mortality	# of Risk Factors
0%	0
1.2%	1
3.4%	2
13.2%	3
20.8%	4
50%	5
61.1%	6
66.7%	7
100%	8

J Allergy Clin Immunol Pract 2023.11(10): 3161-3168

SJS/TEN: Treatment

- Insufficient evidence and lack of consensus regarding systemic therapy[1]
- Best setting for care: ICU or specialized Burn Unit [2]
- Collaborative multidisciplinary approach
    - Ophthalmologic
    - Allergy Immunology
    - Dermatology

1. Br J Dermatol 2025; 192:9–18
2. *Arch Dermatol 1987;123:1160*

SJS/TEN Treatment

- Discontinue causative agent
    - Early discontinuation improves outcomes*
- Aggressive fluid and electrolyte replacement
- Infection precautions
- Specialized skin care (Petrolatum or Silicone dressings)

Garcia et al. Arch Dermatol 2000;136:323

SJS/TEN: Systemic Therapy

- First Line
  - Corticosteroids
  - Cyclosporine
  - Etanercept

SJS/TEN: Systemic Therapy

- Second Line
  - IVIG- mixed results, slight benefit when used with systemic corticosteroids (JAAD, 2021.(84) 390-7)
  - Plasmapheresis: retrospective cohort study showed no benefit v IVIG (JAMA Dermatol, 2023. (159) 481-7

SJS/TEN: Systemic Therapy

- Developing therapeutic targets
  - Tofacitinib (JAK/STAT)
  - Daratumumab (anti-CD38+ antibody)

Systemic Corticosteroids in SJS

- Controversial, disparate indications and discordant doses in studies
- Northwestern experience
  - 67 patients with SJS
  - No mortality associated with SJS
  - Oral prednisone or methylprednisolone 1 – 3 mg/kg
  - Slow reduction in dose over 3 – 4 weeks

Tripathi et al. Allergy and Asthma Proc 2000;21:101-105

SCAR PREVENTION

- HLA PRECREENS
  - HLA-B*57:01 : abacavir DRESS
  - HLA-B*15:02: carbamazepine SJS TEN (Taiwan, South Asia)
  - HLA-B*58:01: Allopurinol induced SCAR (Taiwan) - less predictive in non-SE Asian populations

- NNT 200-1000 to prevent 1 SCAR
  - Is price of testing reasonable? Accurate?
  - Are alternative drug options available?

SCAR: Key Clinical Features

- AGEP- intertriginous erythema with pustules
- SJS/TEN- prominent mucosal involvement, atypical targets, desquamation
- DRESS- high fever, morbilliform or maculopapular eruption (MPR), lymphadenopathy, less mucosal involvement

Conclusions

- Recognizing key clinical features of SCAR facilitates diagnosis
- Improved understanding of pathogenesis offers expanding potential treatment options
- A multidisciplinary approach to therapy is warranted

Mahalo!