How to Diagnose, Assess and Adress Severe Cutaneous Adverse Reactions (SCARs) based on the available level of evidence.

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INTRODUCTION

- The skin eruptions are observed in 0.1–1% of patients and skin eruptions are affecting 2-3% of hospitalized patients.
- The incidence of fatalities due to systemic and cutaneous drug reactions among inpatients is estimated at between 0.1% and 0.3%.
- Drug eruptions are usually not characteristic for any specific drug or group of drugs, but certain clinical pictures commonly follow the use of certain drugs.
- It can be stated almost without exception that any drug administered systemically is capable of causing a skin eruption.

Today:

We have to make decisions based on weak evidences and non defined cases;

Confusion between Case definition and causality assessment :

Case definition must be clearly differentiate from causality assessment. Except for SJS/TEN, there is no causality assessment methods specifically dedicated to the SCARs. For the other SCARs , generalist methods can be used;

The information in the SmPCs is unclear and not really helpful for HCP and patients (SmPCs is for regulators ….).

But……..

We know how to diagnose SCARs (Strong criteria and scoring);

Regulators MUST make a decision on definite or very probable cases of SCARs whatever the causality assessment.

Maculopapular Eruptions or Drug-induced exanthema.

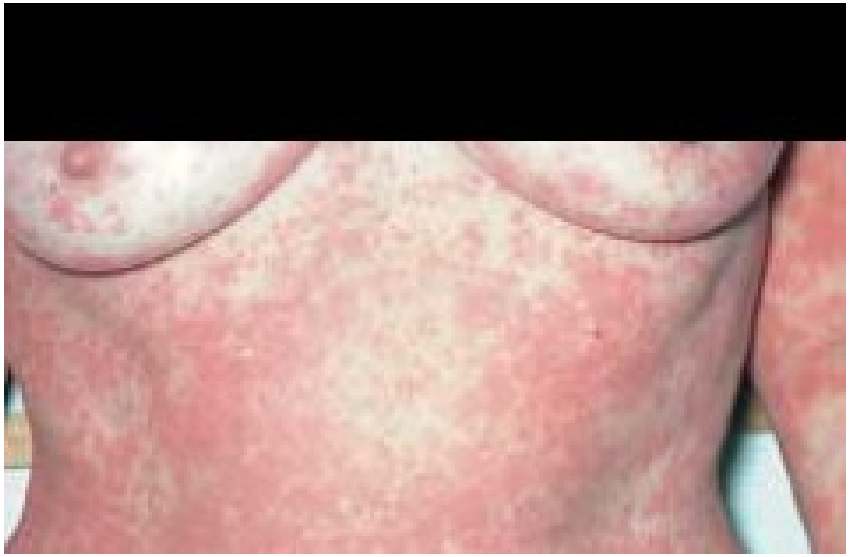
- The most common adverse drug reactions affecting the skin, being responsible for approximately 90% of all drug rashes;
- It usually occurs between 4 and 14 days after a patient begins taking a new medication, but it can develop sooner, especially in case of re-challenge;
- Pruritus and low-grade fever are often associated with the eruption, which usually disappears in a few days.

The main Diagnosis criteria are:

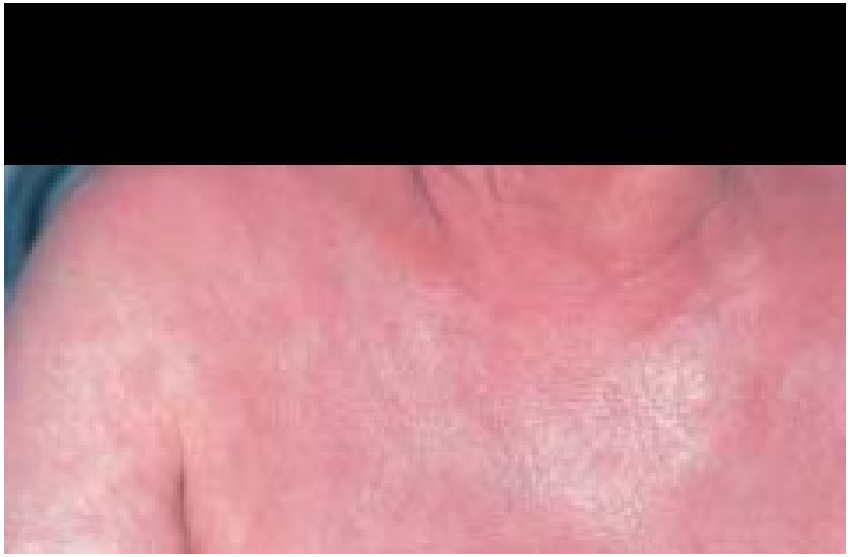
(1) Exanthematous or morbilliform (measles-like) eruption, with erythematous macules or papules, which are often symmetric. They begin on the trunk and upper extremities, and progressively become confluent.

(2) No mucous membranes involved.

(3) No skin blister/detachment.



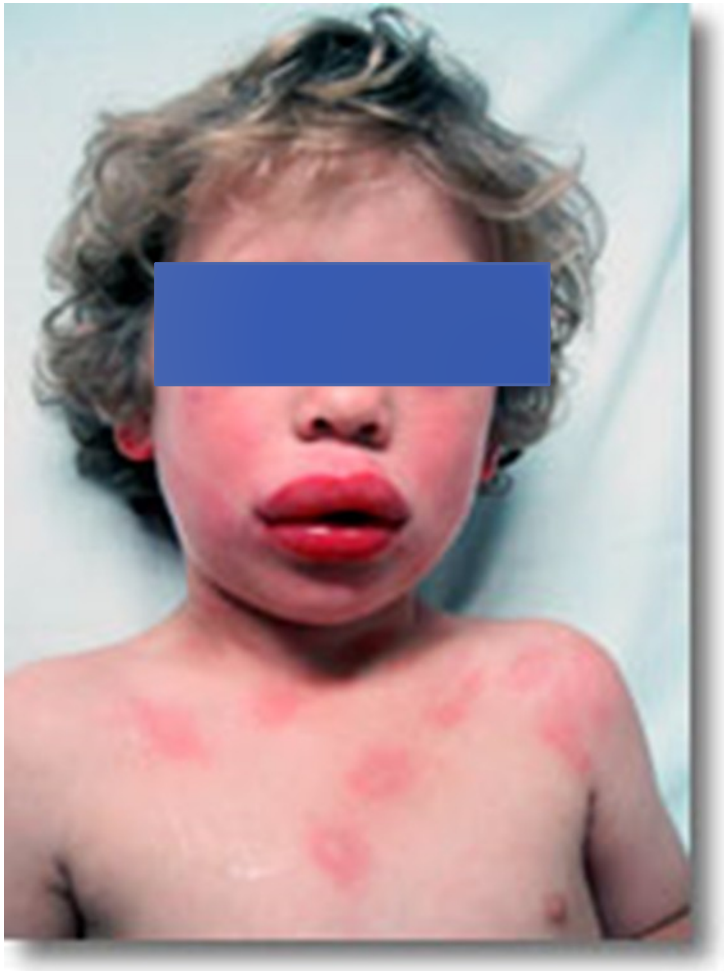
measles-like rash



Scarlatiniform like rash

ANAPHYLAXIS

- Anaphylaxis usually results from a type I hypersensitivity reaction mediated by IgE antibodies through the release of histamine or other mediators of inflammation. It is much more often related to insect stings and drugs are the second most common cause of anaphylaxis.
- Sudden onset of pruritus, urticaria, angioedema, laryngeal edema, wheezing, nausea, vomiting, tachycardia, sense of impending doom, and occasionally shock usually begins a few minutes to a few hours after drug administration.



A child with bee sting came to Emergency Department
He has Facial Edema, urticaria and wheezing.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) - 1

- The most severe drug-induced skin reactions.
- The incidence of TEN is estimated to be 0.4–1.2 cases/million person-years, and the incidence of SJS 1–6 cases/million person-years.
- SJS and TEN are considered to be severity variants of the same drug-induced disease and drugs are responsible for at least 70% of cases. The risk of developing SJS or TEN is increased in HIV-infected patients.
- Patients with SJS or TEN may have high fever. Severe erosions of mucous membranes are found. Systemic manifestations include elevation of hepatic enzymes, intestinal and pulmonary manifestations (with sloughing of epithelia similar to what happens to the skin). Death occurs in 10% of patients with SJS and above 30% of patients with TEN, principally from sepsis.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) - 2

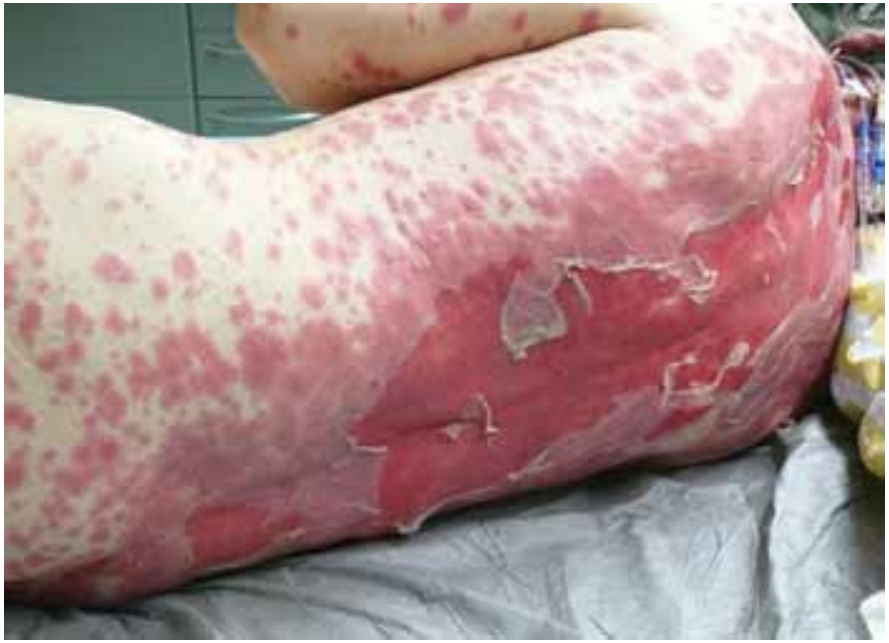
The main Diagnosis criteria are:

(1) Epidermal necrosis/blister/detachment: lesions affect less than 10 percent of the body surface in SJS and greater than 30 percent of the body surface in TEN. Cases with detachment between 10 and 30% are labeled SJS/TEN overlap. SJS is characterized by a tendency to affect the trunk or generalized dissemination of rather atypical target lesions and maculae.

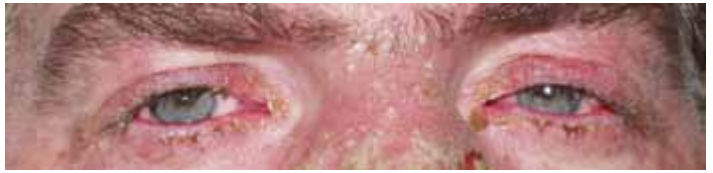
(2) Mucous membranes erosions/ulcers (at least 2 mucosal sites).

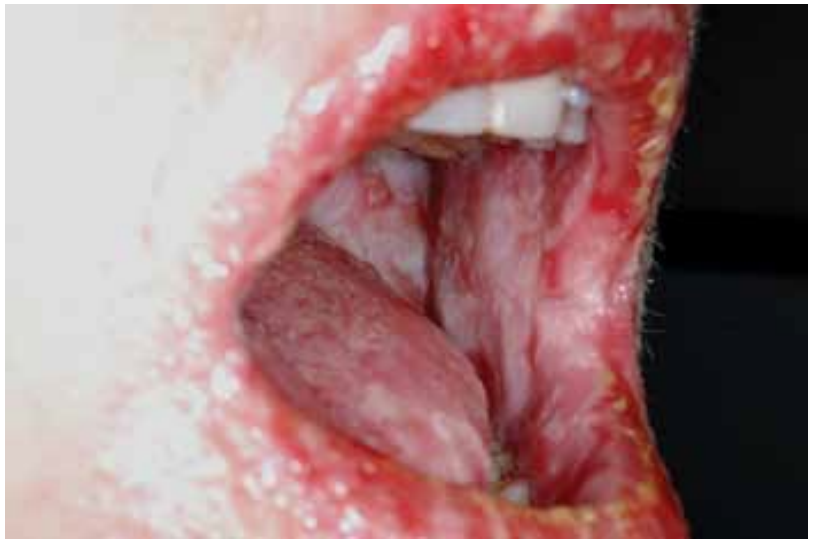
(3) Positive Nikolsky sign and detachment of large epidermal sheets on the body surface area.

(4) Skin pathology showed keratinocyte apoptosis (dyskeratosis) with large sheet of necrosis. It is essential to differentiate SJS/TEN with other autoimmune blistering diseases like paranéoplastic pemphigus (10% of cases) or GBFDE.



Detachment of large epidermal sheets in SJS/TEN overlap; atypical target lesions can still be seen.





Hemorrhagic erosions of mucosal membranes (eyes, mouth) in SJS/TEN

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS/TEN are the only SCARS with a Causality assessment method

(*Not Diagnosis criteria*)

ALgoritm of **D**rug causality for **E**pidermal **N**ecrolysis

ALDEN

Table 5 Details of the algorithm of drug causality for epidermal necrolysis (ALDEN)

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)	
Final score −12 to 10			

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) -1

- DRESS, or drug-induced hypersensitivity syndrome (DiHS), is a severe adverse drug reaction characterized by fever, generalized skin eruption, lymphadenopathies, eosinophilia, and visceral organ involvement.
- The incidence of DRESS is estimated to be 1–5 cases/million person-years, and the mortality around 10%.
- DRESS symptoms typically occur 2 to 6 weeks after the initiation of the offending medication; however, reactions may not develop until 3 months later, especially when the syndrome is induced by allopurinol.
- The diagnosis of DRESS is complicated, and a detailed scoring system for diagnosis has been proposed by an international expert group.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) -2

The main Diagnosis criteria are:

(1) Fever (usually above 38°C);

(2) Rash: The rash usually begins as a nonspecific morbilliform eruption, which is indistinguishable from other drug reactions, but can progress to a generalized form or even to erythrodermia. Extent > 50% body surface area. The cutaneous eruption later becomes confluent and infiltrated with purpuric changes. As the rash resolves, the end stage involves large sheet desquamation;

(3) Cervical, axillary, and inguinal lymphadenopathies;

(4) Facial edema with periorbital accentuation;

(5) Atypical lymphocytes;

(6) Hypereosinophilia;

(7) Visceral organ involvement: the liver (80%) and the kidney are the two most frequently involved organs;

(8) Prolonged course of more than 14 days;

(9) Skin pathology showed spongiotic dermatitis, keratinocyte apoptosis (dyskeratosis), interface dermatitis, dense superficial perivascular infiltration or vasculopathy; Only for exclusion.

Assessment/ Score	-1	0	1	Comment
Fever ≥ 38.5º C	No/U	Yes		Acute episodes
Enlarged lymph nodes		No/U	Yes	>1cm, ≥ 2 different areas (right side plus left side is not adequate)
Eosinophilia ˙Eosinophils≧700/μL or ˙≥10% if leukocyte <4000/μL		No/U	Yes	Score 2 for extreme eosinophilia ˙Eosinophils ≥1500/μL or ˙≥20% if leukocyte <4000/μL
Atypical lymphocytes		No/U	Yes	
Skin rash				Onset < 21 days before hospitalization
˙Extent > 50% body surface area		No/U	Yes	
˙Rash suggesting DRESS	No	U	Yes	≥2 symptoms: purpuric change, facial edema, infiltration, psoriasiform desquamation
˙Biopsy suggesting DRESS	No	Yes/U		Score -1 if results fit any other specific dermatopathologic diagnosis
Organ involvement				Excluding other causes, score max. of 2
˙Liver: any one criterion		No/U	Yes	˙ALT>2*UNL, twice on successive dates ˙D-bil.>2*UNL, twice on successive dates ˙AST, T-bil., ALP all>2*UNL, once
˙Kidney: any one criterion			Yes	˙Creatinine>1.5* patient's baseline ˙Proteinuria above 1g/day
˙Lung: any one criterion			Yes	˙Evidence of interstitial lung (CT, x-ray) ˙Abnormal bronchoalveolar lavage, blood gases
˙Muscle/Heart: any one criterion			Yes	˙Raised creatine kinase; Raised troponin T; Abnormalities in the echocardiogram
˙Pancreas			Yes	Amylase >2* UNL
˙Other organs			Yes	Central nervous system, splenomegaly
Rash resolution ≥ 15 days	No/U	Yes		
Excluding other causes		No/U	Yes	Score 1 if ≥ 3 tests are performed and negative
˙Hepatitis A, B, C				At least 2 tests are negative and 1 unknown: negative
˙Mycoplasma/Chlamydia				At least 1 test is negative and 1 unknown: negative
˙Antinuclear antibody				

Table. 1 The RegiSCAR-Group Diagnosis Score for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

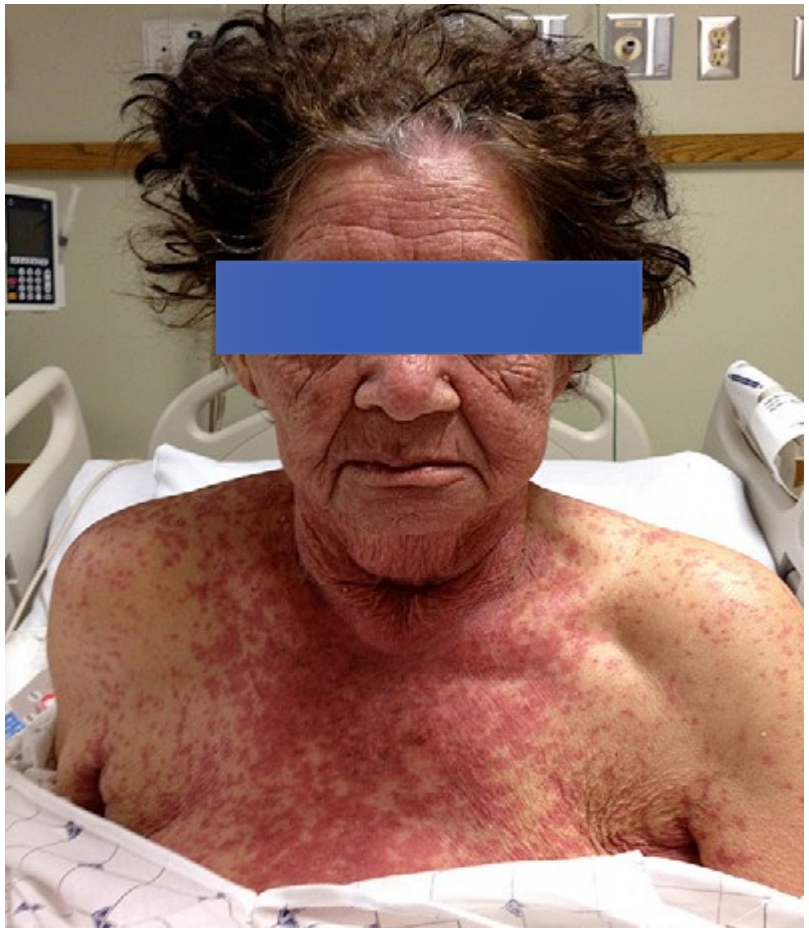
	NO	YES	UNKNOWN
Fever (≥ 38.5 °C)	- 1	0	-1
Enlarged lymph nodes (≥ 2 sites, > 1cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
700-1499 or 10-19.9		1	
≥ 1500 or ≥ 20%		2	
Skin rash	0		0
extent > 50%	0	1	0
at least 2 of: edema, infiltration, purpura, scaling	-1	1	0
biopsy suggesting DRESS	-1	0	0
Internal organ involved	0		0
One		1	
2 or more		2	
Resolution in > 15 days	-1	0	-1
At least 3 biological investigations done and negative to exclude alternative diagnosis	0	1	0

Final score: < 2 no case; 2-3 possible case; 4-5 probable case, > 5 definite case

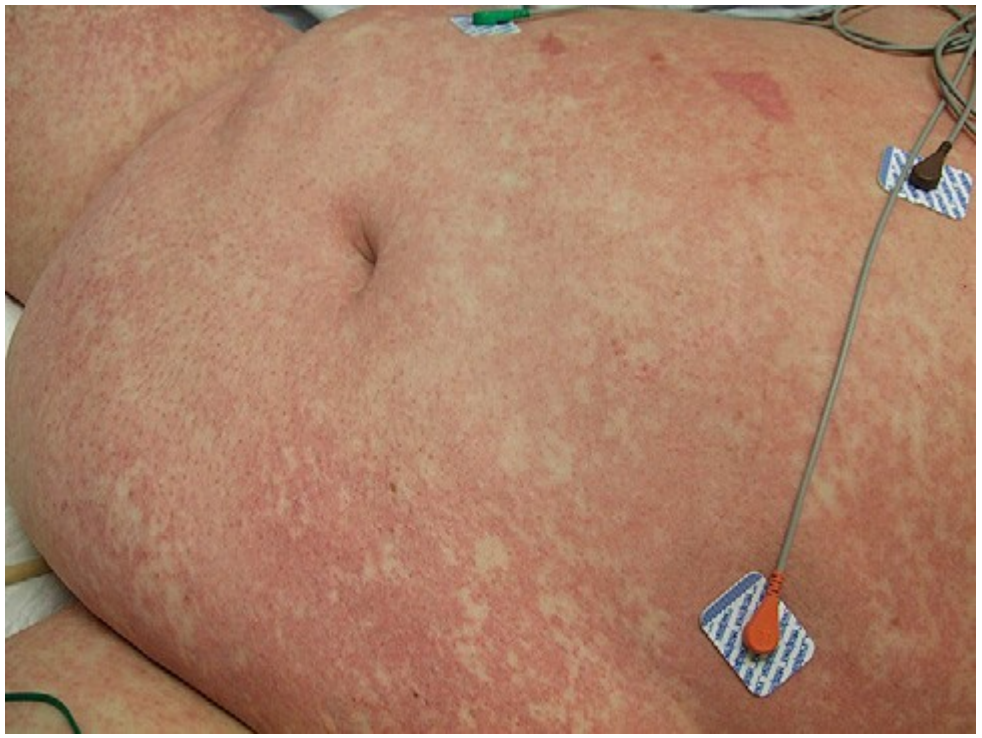
Scoring System of RegiSCAR for Diagnosing DRESS.

Final scores:

<2: excluded
2-3: possible
4-5: probable
>5: definite



Patient with vemurafenib-induced DRESS. Prominent facial edema and morbillform eruption. *(Courtesy of Michael Y. Cashman, MD, and Dominique C. Pichard, MD.)*



Patient with piperacillin-tazobactame induced DRESS. Morbilliform eruption on the abdomen. *(Courtesy of Naurin E. Ahmad, MD.)*

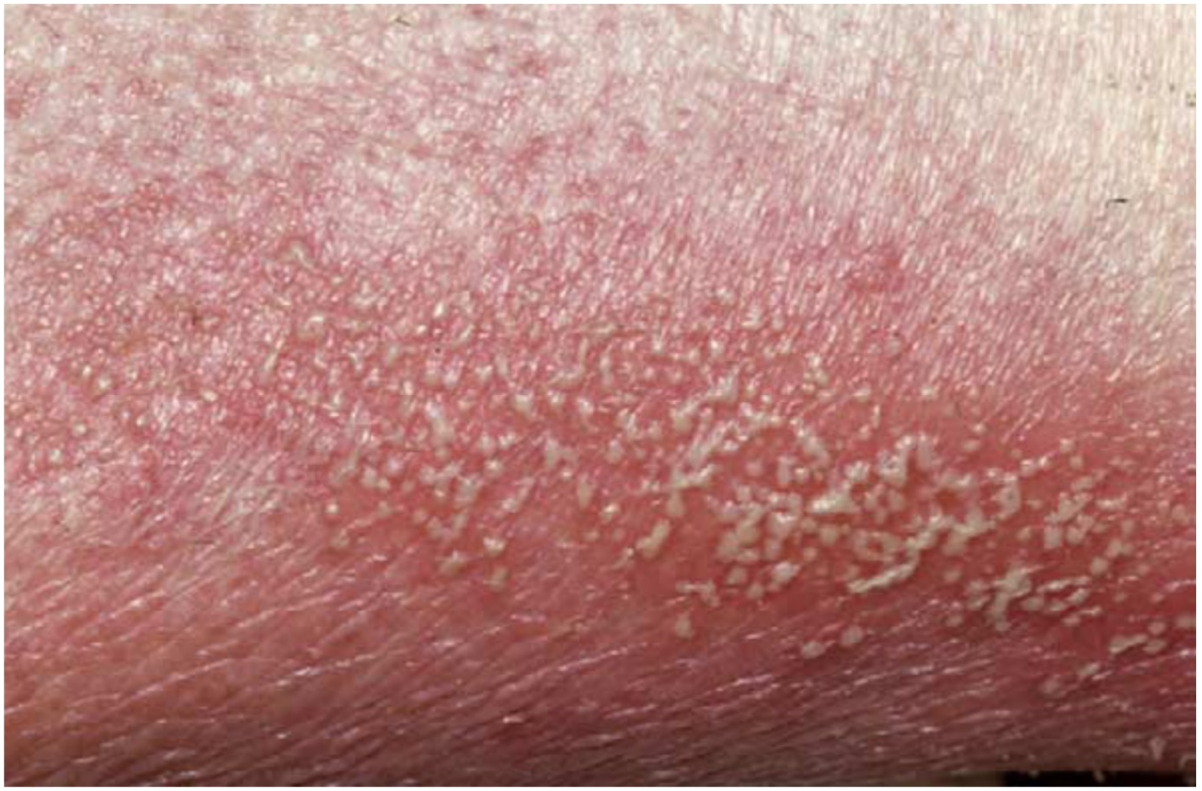
Acute Generalized Exanthematous Pustulosis (AGEP) - 1

- AGEP is an acute pustular eruption that must be differentiated from pustular psoriasis.
- Its incidence is estimated to be 1–5 cases/million/year and the mortality between 3-5%
- More than 90% of AGEP cases are drug-induced. Antibiotics (particularly aminopenicillins) and diltiazem are thought to be the main drugs implicated in AGEP.
- A few cases have been reported to be related to viral infection (enterovirus or parvovirus B19) or hypersensitivity to mercury.

Acute Generalized Exanthematous Pustulosis (AGEP) - 2

The main Diagnosis criteria are:

(1) Short time to onset (less than 48 hours) after the administration of the suspected drug.
(2) Fever of >38°C.
(3) Numerous, small, mostly nonfollicular pustules arising on a widespread edematous erythema and mainly localized on the skin folds, trunk, and upper extremities.
(4) Leukocytosis with elevated neutrophil count.
(5) Rapid resolution: less than 2 weeks and followed by a superficial desquamation.
(6) Skin pathology showed subcorneal pustulosis without other features of psoriasis. Essential to differentiate from psoriasis



AGEP.
Dozens of non-follicular pustules arising on disseminated erythema.

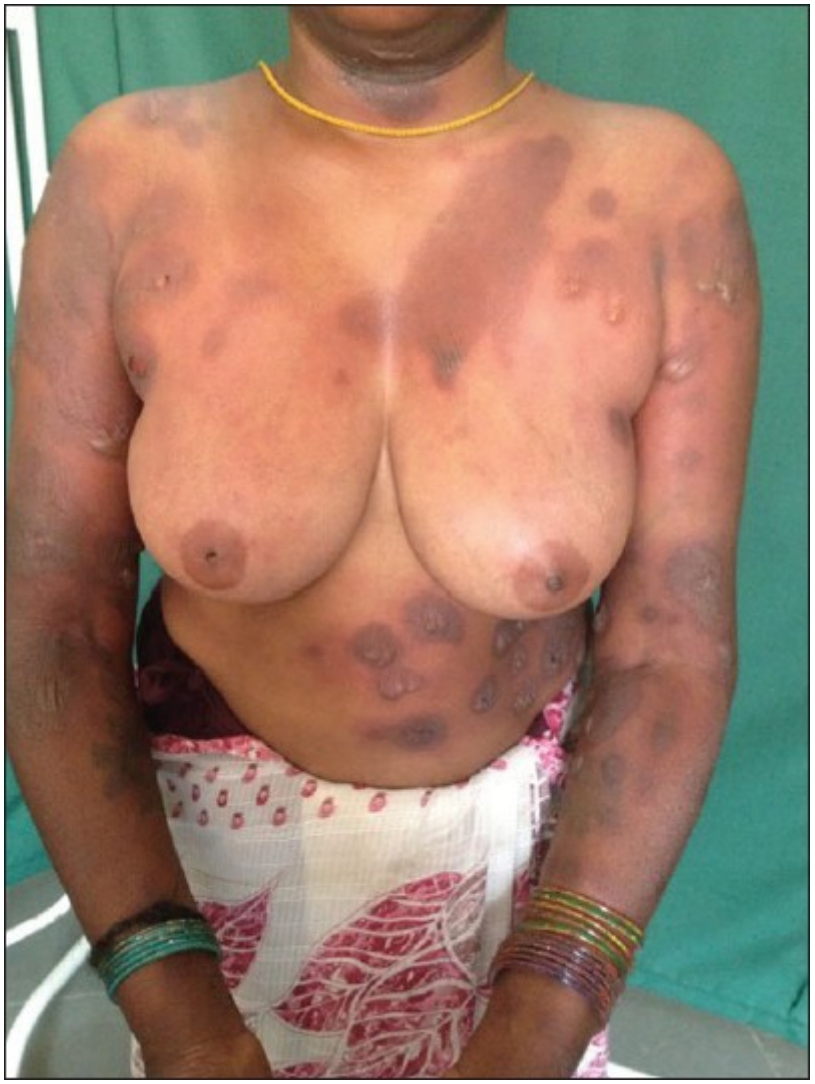
Generalized bullous Fixed Drug Eruption (GBFDE) - 1

- Patients with GBFDE can be misdiagnosed as having SJS/TEN, but mucosal involvement is usually absent or mild in GBFDE, and the clinical course is favorable, with rapid resolution in 7 to 14 days after drug discontinuation.
- Mortality around 20%.
- Underreporting.

Generalized bullous Fixed Drug Eruption (GBFDE) - 2

The main Diagnosis criteria are:

(1) The lesions usually develop less than 2 days after the drug intake.
(2) Many round, sharply demarcated, geographically distributed, erythematous and edematous plaques, sometimes with large detachment of skin. The mouth (lips and tongue), genitalia, face, and acral areas are commonly involved sites.
(3) Postinflammatory hyperpigmentation.
(4) Recurrence of lesions at exactly the same sites with drug re-exposure.
(5) No or few mucosal involvement.
(6) Rapid resolution in 14 days after drug discontinuation.
(7) Skin pathology showed keratinocyte apoptosis (dyskeratosis), interface dermatitis with dense superficial and deep perivascular infiltration, pigment incontinence, mixed inflammation with eosinophils.



Multiple well-defined hyperpigmented macules with surrounding erythema and few vesicles, bullae, and eroded areas present all over the body.

Comparison of clinical and pathologic features between GBFDE and TEN

	GBFDE	TEN
Clinical features		
Age	Usually older	**All age groups**
Previous events	Usually yes	**None**
Conjunctival involvement	None	**Almost all**
Constitutional symptoms	Rare	**Frequent**
Latency of disease onset to drug intake	Short (<3 days)	**Long (10-14 days)**
Blister lesions	Well demarcated dusky-red patches with blisters/erosions	**Symmetrically distributed confluent blisters/erosions**
Immuno-Pathologic features		
Superficial and deep perivascular inflammation	Often	**None**
Eosinophil infiltration	Often	**Usually none**
Pigment incontinence	Frequent	**Infrequent**
Intra-epidermal CD56 cells	Less	**More**
intra-epidermal granulysin+ cells	Less	**More**
Serum granulysin level	Lower	**High**
Dermal Foxp3^{+} cells	More	**Less**

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