

DRUG-INDUCED SKIN REACTIONS



Prof. Ahmed Bouhamidi

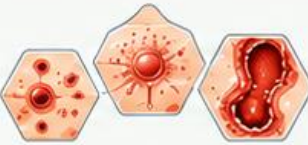


Learning objectives

At the end of this training, you will be able to:

1  Define a drug-induced skin reaction (toxidermia) and understand its **classification** 

2  Understand the **immunological mechanisms** (Gell & Coombs, type I-IV hypersensitivity) 

3  Identify the main benign and severe **clinical forms** 

4  Assess **severity** and recognize dermatological **emergencies** 

5  Conduct a structured and reasoned **diagnostic approach** 

6  Use **causality assessment** tools (ALDEN, RegiSCAR, EuroSCAR, Naranjo scores) 

7  Prescribe appropriate **complementary tests** 

8  Implement **management** in accordance with current recommendations 

 **Understand** the mechanisms |  **Recognize** clinical forms |  **Assess** severity |  **Diagnose** in a structured way |  **Use validated** tools |  **Prescribe** appropriate tests |  **Manage** effectively

Course outline



INTRODUCTION

01



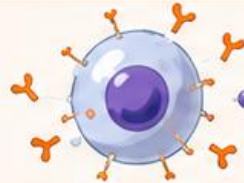
Introduction & epidemiology



02



Immuno-allergic pathophysiology



03



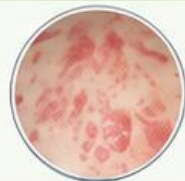
Classification of toxicodermias



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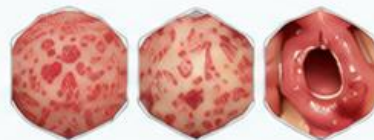
Benign clinical forms



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Severe toxicodermias (DRESS, AGEP, SJS/TEN)



06



Other forms & high-risk drugs



07



Diagnostic approach & imputability



08



Management & prevention



09



Interactive clinical cases



10



Key messages & summary



Definition and history



INTRODUCTION



Toxidermia: any cutaneous, mucosal, or phaneral reaction induced by the systemic administration of a drug.



A term distinct from **contact dermatoses** (local application).



First systematic descriptions date back to the **19th century** with the advent of modern pharmacopoeia.



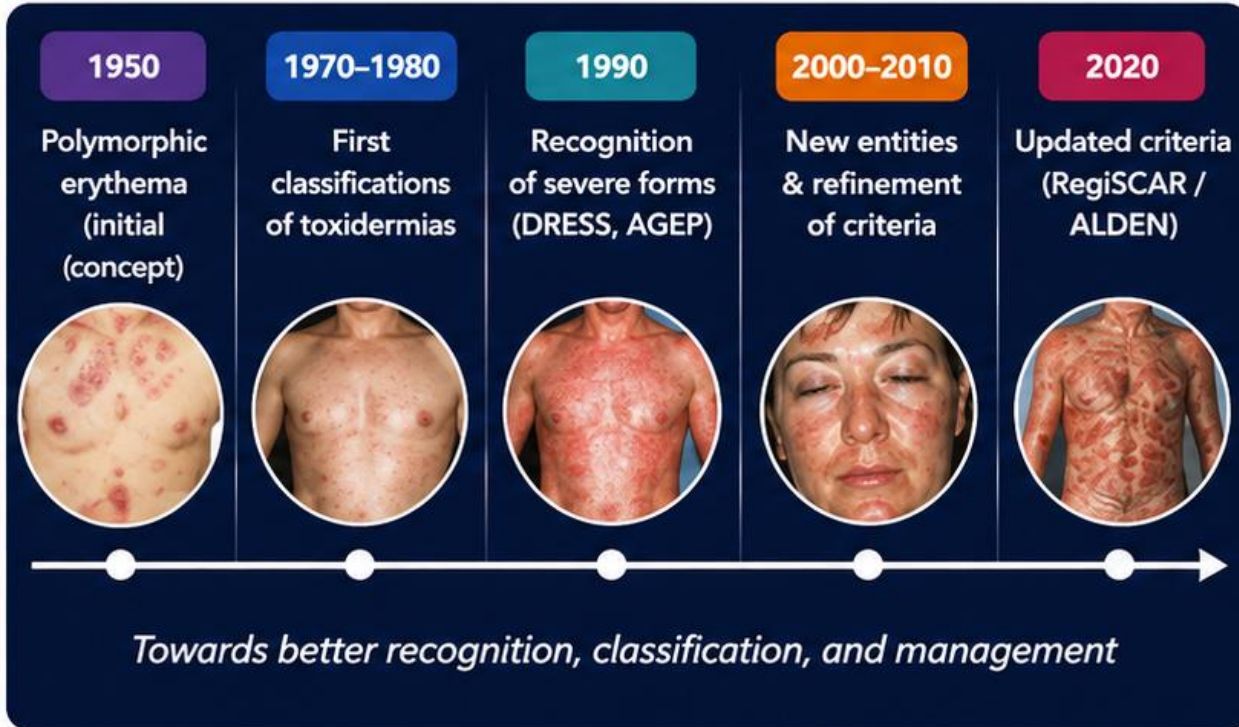
Major broadening of the spectrum since the 1990s (**DRESS, AGEP**) and then in 2010 (immunotherapies).



Concerns **2 to 3%** of hospitalized patients receiving a drug treatment.



Very wide clinical spectrum: from benign exanthema to epidermal necrolysis, engaging vital prognosis.



KEY MESSAGE

A toxidermia is not a single disease but a clinical spectrum ranging from benign to potentially life-threatening.



General Classification and Epidemiology



 Criterion	 Mild Forms	 Severe Forms
 Frequency	~90% of drug eruptions 	<5%, but high mortality 
 Examples	Exanthema, urticaria, fixed drug eruption	DRESS, AGEP, SJS, TEN
 Time to onset	Variable, often 4–14 days	DRESS : 2–8 weeks ; SJS/TEN : 4–28 days
 Mucosal involvement	Absent or minimal 	Frequent and severe (SJS/TEN) 
 Mortality	Virtually none 	DRESS ~10% ; TEN 20–30% 
 Management	Outpatient management 	Specialized hospitalization 



KEY MESSAGE

Early distinction between **mild** and **severe** forms is the central challenge in every consultation for a suspected drug eruption.



Overview of immuno-allergic reactions



Two major mechanisms: **immunological** (allergic) and **non-immunological** (direct pharmacological)



Immunological reactions follow the classification of **Gell and Coombs** (types I to IV)



The drug or its metabolite acts as a **hapten**, binding to a **carrier protein**



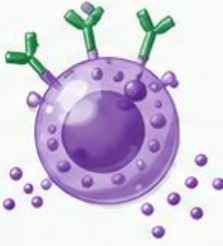
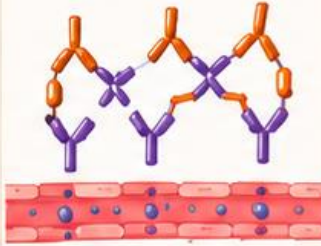
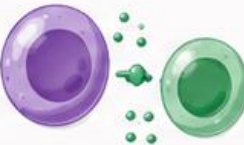
Recognition by the **adaptive immune system**: lymphocytes T and/or B, antibodies



The **p-i** (pharmacological interaction) theory explains reactions without classical sensitization



The **genetic background (HLA)** strongly influences individual risk

TYPE I IMMEDIATE	TYPE II CYTOTOXIC	TYPE III IMMUNE COMPLEXES	TYPE IV CELL-MEDIATED
< 1 hour	1 – 24 hours	1 – 3 weeks	48 – 72 hours to several days
			
Mast cell IgE	IgG/IgM antibodies + complement	Immune complexes deposited in vessels	T lymphocyte (Th1/Th17/CD8+)
Example Urticaria, anaphylaxis	Example Hemolytic anemia due to drugs	Example Vasculitis, serum sickness	Example Contact dermatitis, DRESS



KEY MESSAGE

Understanding the **underlying mechanism** helps to anticipate the **delay**, the **potential severity** and the **risk of recurrence**.



Types I and II of Gell and Coombs



Type I — Immediate hypersensitivity



Mediated by specific **IgE**



Mast cell and basophil **degranulation**



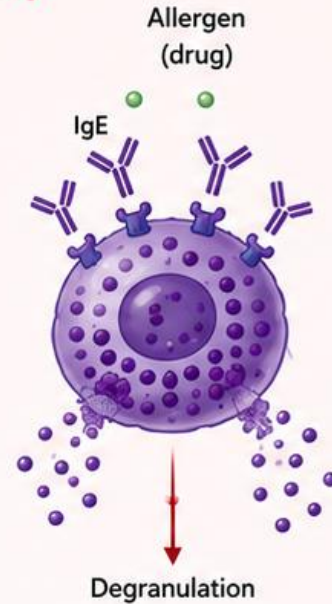
Onset: **minutes to a few hours**



Clinical features: **urticaria, angioedema, anaphylaxis**



Examples: **β -lactam** antibiotics, curare, contrast media



Clinical examples



Urticaria



Angioedema



Anaphylaxis



Type II — Cytotoxic



IgG/IgM antibodies directed against a cell-surface antigen



Activation of **complement** and cytotoxicity



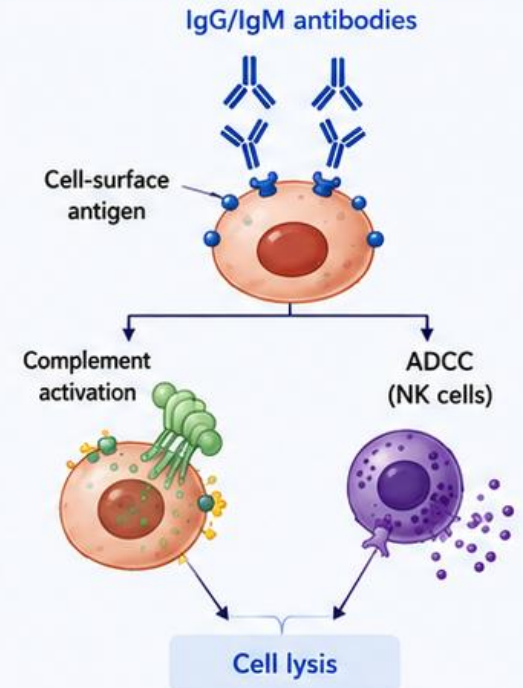
Target cells are usually **blood cells** or **skin cells**



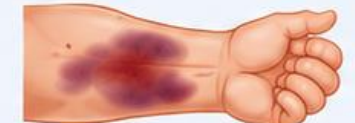
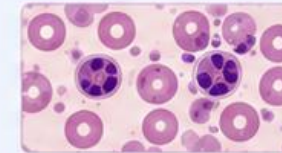
Example of damage: **vascular purpura** due to cytotoxicity



Examples: **penicillins, quinine** (cytopenias)



Clinical examples



KEY MESSAGE

Type I explains the immediate allergic emergency;
type II is rare and is usually the first consideration in pure dermatology.



Type III and overview of Type IV



Type III — Immune complex-mediated



Formation of **circulating** antigen-antibody **complexes**



Vascular deposition and activation of **complement**



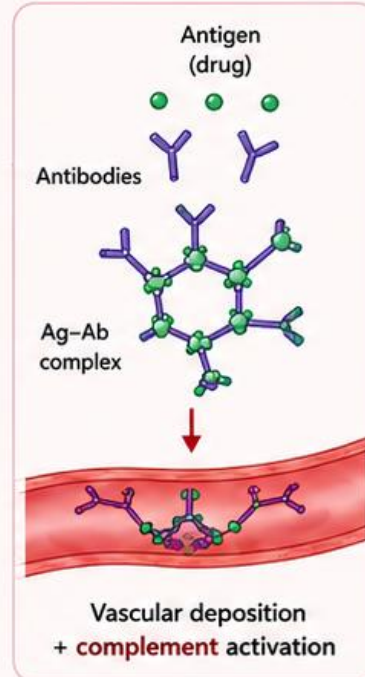
Onset: **1 to 3 weeks** (serum sickness)



Clinical features: **vasculitis**, **urticaria**, prolonged **angioedema**, **arthralgias**



Examples: sera, certain **antibiotics**



Clinical examples



Urticaria



Angioedema



Anaphylaxis



Type IV — Delayed hypersensitivity



Mediated by **T lymphocytes** (no antibodies)



Major mechanism of **severe drug eruptions**



Onset: **several days** to **several weeks**



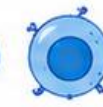
Subdivided into **4 subtypes** (IVa to IVd) based on effector cell



Pathophysiological basis of **DRESS**, **SJS/TEN** and **AGEP**

Subtypes of delayed hypersensitivity (Gell & Coombs)

IVa



Th1 / Macrophages (IFN- γ)
Example: allergic contact dermatitis

IVb



Th2 / Eosinophils (IL-4, IL-5)
Example: DRESS

IVc



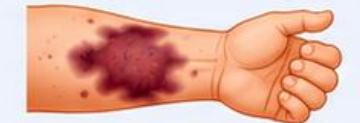
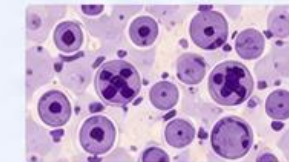
CTL (CD8+)
Direct cytotoxicity
Example: SJS / TEN

IVd



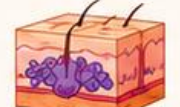
Neutrophils (IL-17, CXCL8)
Example: AGEP

Clinical examples



KEY MESSAGE

Type IV is the **central mechanism** of **severe** drug eruptions: it justifies a **separate and in-depth development**.



HLA, genetic susceptibility and p-i theory



Certain class I HLA alleles strongly increase the risk of severe drug eruption



HLA-B*15:02: major risk of SJS/TEN with carbamazepine (Southeast Asian populations)



HLA-B*58:01: risk of DRESS/SJS/TEN with allopurinol



HLA-A*31:01: risk of DRESS with carbamazepine (European populations)

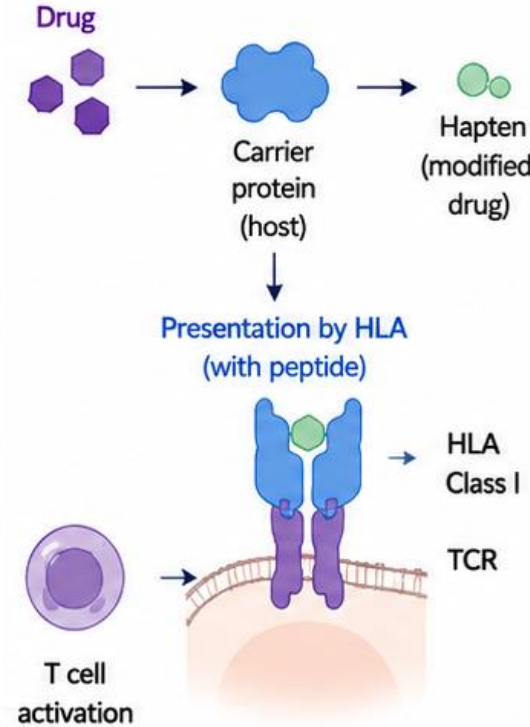


p-i theory (pharmacological interaction): non-covalent, direct and reversible binding of the drug to the T cell receptor (TCR) or to the HLA molecule, without the need for metabolism or haptens

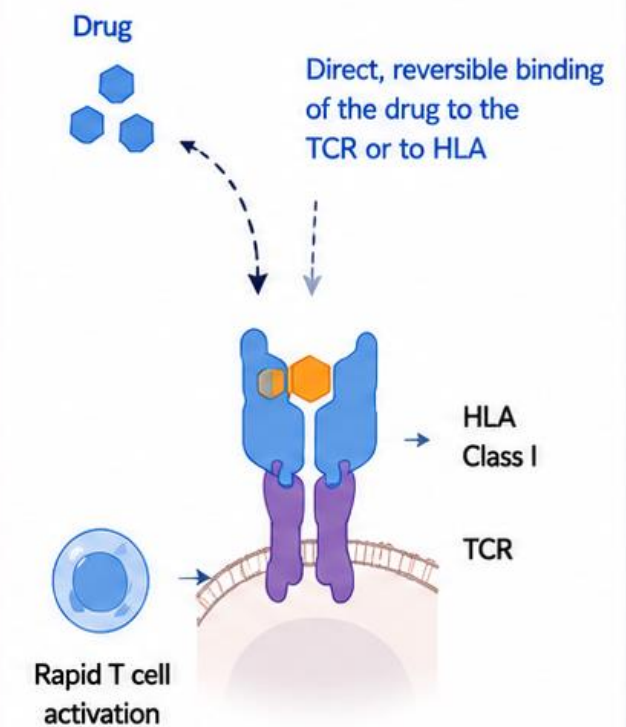


The p-i theory explains the rapid occurrence of some reactions after the first exposure

CLASSICAL HAPTEN MODEL



p-i MODEL (PHARMACOLOGICAL INTERACTION)



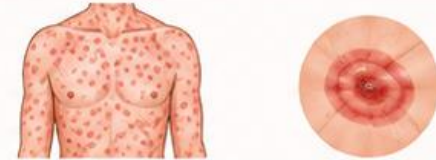
KEY MESSAGE

HLA screening before introducing **abacavir**, or **carbamazepine** or **allopurinol** in at-risk populations is a **validated prevention strategy**.

Clinical classification of drug eruptions



CLASSIFICATION

CATEGORY	TYPICAL ONSET	EXAMPLES
 Immediate reactions (< 1 hour)	 Minutes to 1 hour 	Urticaria, angioedema, anaphylaxis 
 Benign delayed reactions	 4 to 14 days 	Maculopapular exanthem, fixed drug eruption 
 Severe delayed reactions	 1 to 8 weeks 	DRESS, SJS, TEN 
 Acute pustular reactions	 1 to 2 days (very brief) 	AGEP 
 Chronic / recurrent reactions	 Weeks to months 	Drug-induced lupus, photosensitivity, lichenoid eruptions 



KEY MESSAGE

The delay from drug introduction to onset of symptoms is the first key element for diagnostic orientation.



Drug-induced maculopapular exanthem



CLINICAL FORMS



Most frequent form of drug eruption (up to **90%** of cases)



Mechanism: **delayed hypersensitivity** mediated by T lymphocytes (type IVa/IVb)



Clinical features: **maculopapular eruption**, symmetrical, pruritic, starting on the trunk



Onset: **4 to 14 days** after drug introduction (longer with re-exposure)



Diagnosis: clinical, based on **signs of severity** (high fever, facial edema, mucosal involvement, peeling)



Treatment: **immediate withdrawal** of the suspected drug, emollients, antihistamines, topical corticosteroids if needed



Prognosis: excellent, resolution in **1 to 2 weeks** with possible desquamation



CLINICAL COURSE AND TYPICAL FEATURES



Drug introduction



4 to 14 days



Maculopapular eruption starting on the trunk



Symmetrical spread



Regression in **1 to 2 weeks**



KEY MESSAGE

Any **high fever, facial edema or lymphadenopathy** associated with a maculopapular exanthem should prompt consideration of a diagnosis of early **DRESS**.



Drug-induced urticaria and angioedema



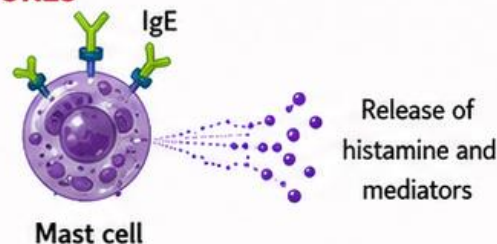
CLINICAL FORMS



MECHANISMS AND CLINICAL FEATURES



IgE-mediated (type I) or pharmacologic (AINS, contrast media)



Edematous wheals (**erythematous, pruritic**, migratory)



Possible angioedema (**airway obstruction risk** if laryngeal)



Onset: **minutes to a few hours** after intake



Drug intake



Minutes



Hours



DIAGNOSIS AND MANAGEMENT



Clinical diagnosis: look for **signs of anaphylaxis**



Allergy work-up at distance if recurrent or severe



Treatment: antihistamines **anti-H1 and H2 2nd generation**

ANTI-H1
2nd generation



Systemic corticosteroids and **adrenaline** if severe angioedema/anaphylaxis



Withdrawal of the suspected drug and issue of an allergy card



KEY MESSAGE

Facial or laryngeal angioedema associated with drug-induced urticaria is an **immediate vital emergency**.



Fixed Drug Eruption



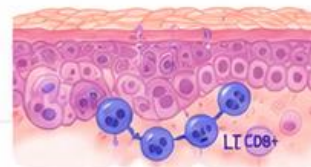
CLINICAL FORMS



Very characteristic form: recurs at the same site each time the drug is reintroduced



Mechanism: CD8+ T lymphocytes, resident epidermal memory (localized type IVc)



Epidermal resident cells



Clinical: round or oval erythematous-violaceous patch(es), sometimes with central blistering



Preferred locations: genitalia, lips, hands, trunk



Evolution: heals with residual brown-gray pigmentation characteristic



Generalized bullous form possible, may mimic localized SJS/TEN



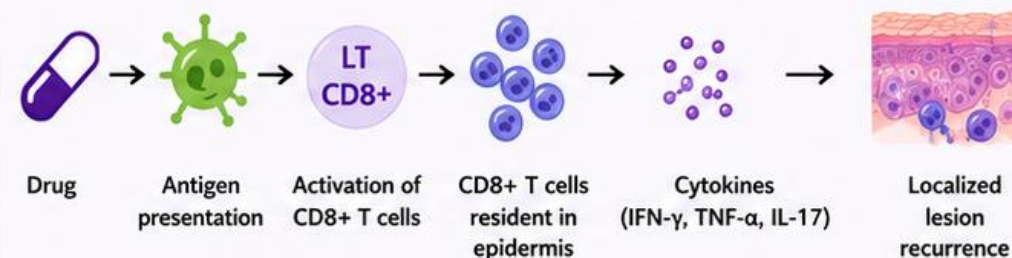
Common drugs: sulfonamides, NSAIDs, paracetamol, tetracyclines, carbamazepine



Initial episode

After reintroduction

MECHANISM (TYPE IVc LOCALIZED)



KEY MESSAGE

The lesion strictly recurs at the same site after re-exposure:
a hallmark of fixed drug eruption.



DRESS syndrome — definition and pathophysiology



SEVERE TOXIDERMAS



Drug Reaction with Eosinophilia and Systemic Symptoms
= severe systemic drug reaction.



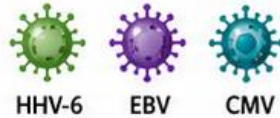
Severe systemic toxidermia, T type IVb lymphocytic mechanism (delayed hypersensitivity).



Long characteristic delay: 2 to 8 weeks
after introduction of the drug.



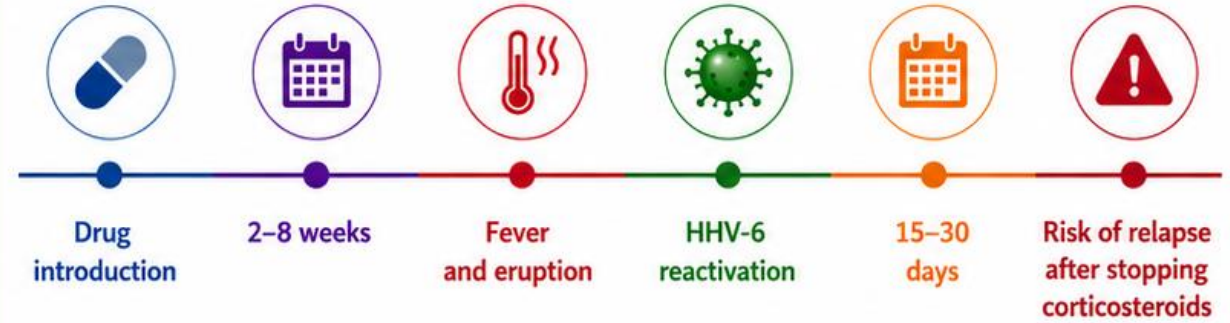
Central role of sequential viral reactivation:
HHV-6, then possibly EBV and CMV.



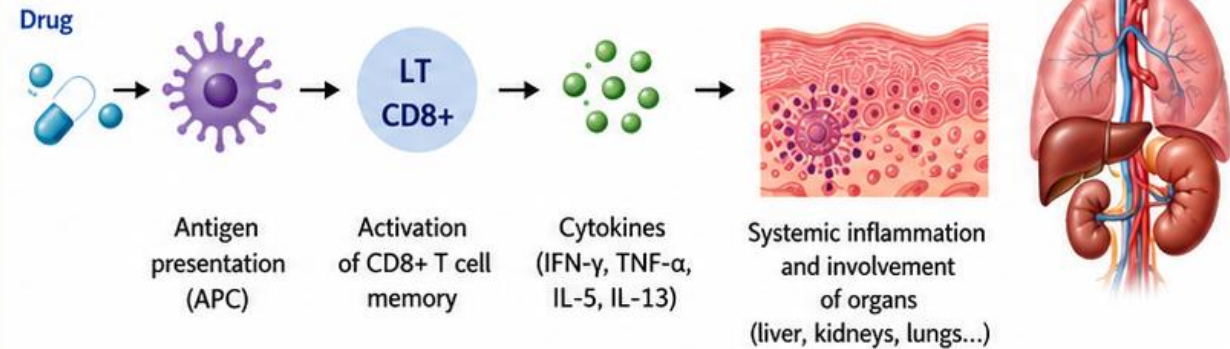
Viral reactivation would amplify the immune response
and prolong its course.



Genetic susceptibility factors (HLA)
and defect in detoxification enzymes
(e.g., epoxide hydrolase).

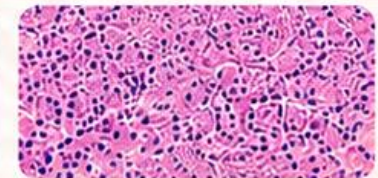


PATHOPHYSIOLOGY (TYPE IVb MECHANISM)



KEY MESSAGE

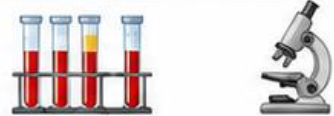
The long delay in onset and sequential viral reactivation distinguish **DRESS** from other drug eruptions.



DRESS — RegiSCAR diagnostic criteria



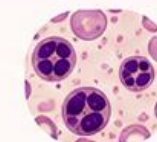
SEVERE TOXIDERMAS

Criterion	Detail		
 Fever		$\geq 38.5\text{ }^{\circ}\text{C}$	
 Lymphadenopathy		At least 2 sites, > 1 cm	
 Skin involvement		Extensive rash (> 50 % body surface area), facial edema	
 Hematologic involvement		Eosinophilia and/or atypical lymphocytes	
 Organ involvement		At least one organ (liver, kidney, lung, heart, etc.)	
 Course		Resolution > 15 days	
 Score		Total score from -4 (excluded) to 9 (definite): < -2 excluded, -2-3 possible, 4-5 probable, > 5 definite	-4 -2 -2-3 4-5 >5     



KEY MESSAGE

The RegiSCAR score classifies DRESS as 'excluded', 'possible', 'probable' or 'definite' according to the total number of criteria met.



DRESS — visceral involvement, prognosis and treatment



Liver: frequent cytolysis, may progress to fulminant hepatitis (1st cause of death)



Kidneys: interstitial nephritis, acute renal failure



Lungs: interstitial pneumonitis



Heart: myocarditis (sometimes late), remote from the initial episode



Mortality: overall estimated at 5–10 %, mainly due to hepatic or cardiac failure



Treatment: immediate withdrawal of the drug, prolonged systemic corticosteroid therapy with slow tapering



Long-term follow-up (several months): risk of relapse and late autoimmune complications (thyroiditis, diabetes)



LIVER

- Cytolysis (↑ ALT/ASAT)
- Bilirubinemia
- Hepatic ultrasound

LUNGS

- Dyspnea
- Chest X-ray / HRCT
- PFTs

KIDNEYS

- Creatininemia
- Urinalysis
- Renal ultrasound

HEART

- ECG
- Troponin
- Echocardiography

GLOBAL MONITORING



CBC with differential



Complete liver panel



Renal function and electrolytes



TSH, glycemia (autoimmunity)



KEY MESSAGE

Too rapid tapering of corticosteroids is the main cause of relapse in DRESS: it should be tapered over **several weeks to months**.



Gradual tapering

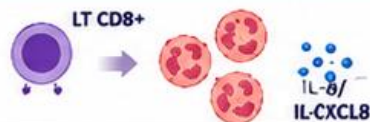


Too rapid tapering

AGEP — Acute generalized exanthematous pustulosis



Mechanism: Type IVd T lymphocytes, massive recruitment of neutrophilic polymorphonuclear cells via IL-8/CXCL8.



Very short and characteristic delay: 24 to 48 hours after taking the drug.



Clinical: numerous sterile, non-follicular pustules on erythematous edematous skin.



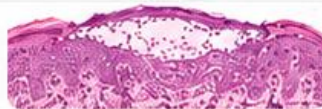
Typical onset: on folds (axillae, groin) then extension.



Fever often elevated and hyperleukocytosis with frequent neutrophilia.



Histology: subcorneal spongiiform pustules, dermal edema.



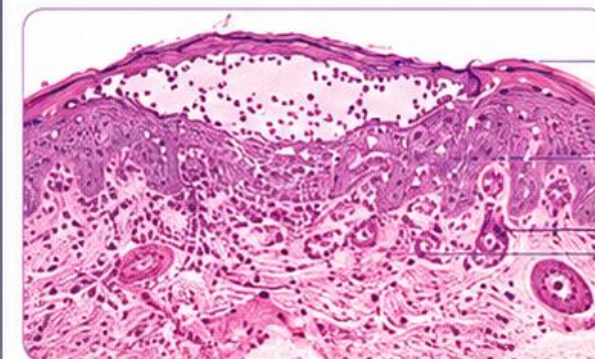
Evolution: rapid resolution after discontinuation of the drug (desquamation in collarlette).



Typical drugs: beta-lactams (aminopenicillins), macrolides, diltiazem, hydroxychloroquine.



HISTOLOGY (subcorneal pustule)



Subcorneal pustule with neutrophils

Epidermal spongiosis

Superficial dermal edema with neutrophilic infiltrate



KEY MESSAGE

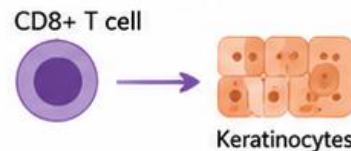
The **very short delay (24–48h)** and the **rapid favorable evolution** distinguish AGEP from other severe drug eruptions.



Stevens-Johnson Syndrome (SJS)



Mechanism : massive keratinocyte apoptosis mediated by CD8+ T lymphocytes and cytotoxic cytokines (type IVc).



Role : of granulysin, perforin/granzyme B and Fas-FasL.



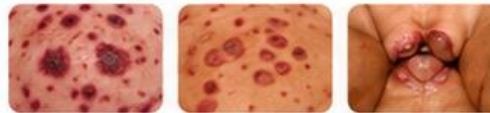
Early signs (prodromes) : fever, malaise, ocular burning, odynophagia — 1 to 3 days before the eruption.



Persistent and early mucosal involvement : oral, ocular, genital (at least 2 sites).



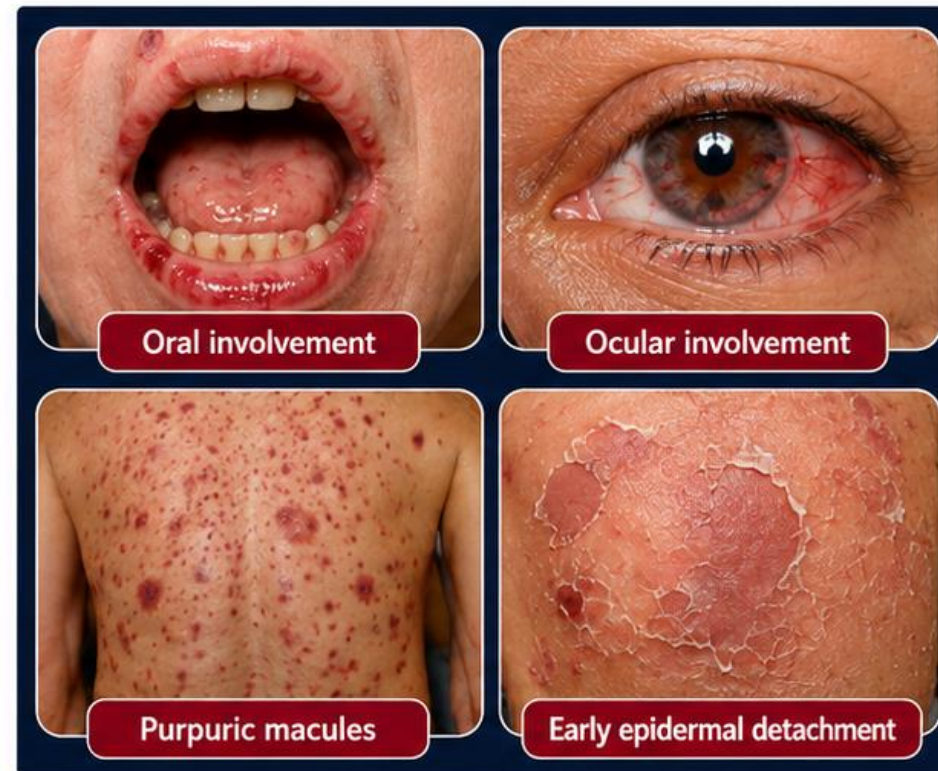
Skin lesions : atypical purpuric macules, "targetoid" lesions, epidermal detachment < 10% of body surface area.



Nikolsky sign : positive in involved areas.



Diagnosis : clinical; histological confirmation if needed (complete epidermal necrosis).



KEY MESSAGE

Any bilateral **mucosal involvement** associated with purpuric macules should raise suspicion of **SJS** and requires **urgent hospitalization**.



SJS — diagnosis, prognosis and treatment



Diagnosis and prognosis



Diagnosis: essentially clinical, confirmed by biopsy



Epidermal detachment < 10% of body surface area (defines SJS)



SCORTEN score calculated within the first 24 hours



Age > 40



Cancer



Tachycardia



Urea > 10 mmol/L



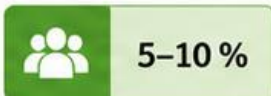
Bicarbonate < 20 mmol/L



Glasgow score < 15



Mortality in SJS alone: approximately 5 to 10%

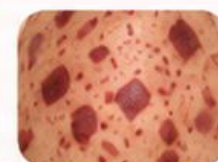


Possible sequelae: ocular synechiae, keratitis, mucosal stenoses



KEY MESSAGE

Any bilateral **mucosal involvement** associated with purpuric macules should raise suspicion of SJS and requires **urgent hospitalization**.



Treatment



Immediate and definitive withdrawal of the culprit drug



Hospitalization in a specialized unit (dermatology/burn unit)



Supportive care: wound care for extensive burns, rehydration, adapted nutrition



Early systematic ophthalmologic follow-up (prevention of sequelae)



IV immunoglobulins or **cyclosporine** depending on the team; corticosteroids are controversial on a case-by-case basis



Toxic Epidermal Necrolysis (Lyell / TEN)

SEVERE DRUG ERUPTIONS



- **Forma la plost grave of the spectro SJS-TEN** : detachment épidermier > 30 % of total surface corpo



- **Steme mechanism pathophysiology came as SJS** (apoptose keratinocyte massivis, type IVc)



- **Clinice** : Grarge-sheet skin detachment, signe de Nikolsky diffusely positive



- **Almost constant severe mucosal involvement** (oral, ocular, genital, sometimes respiratory/digestive)



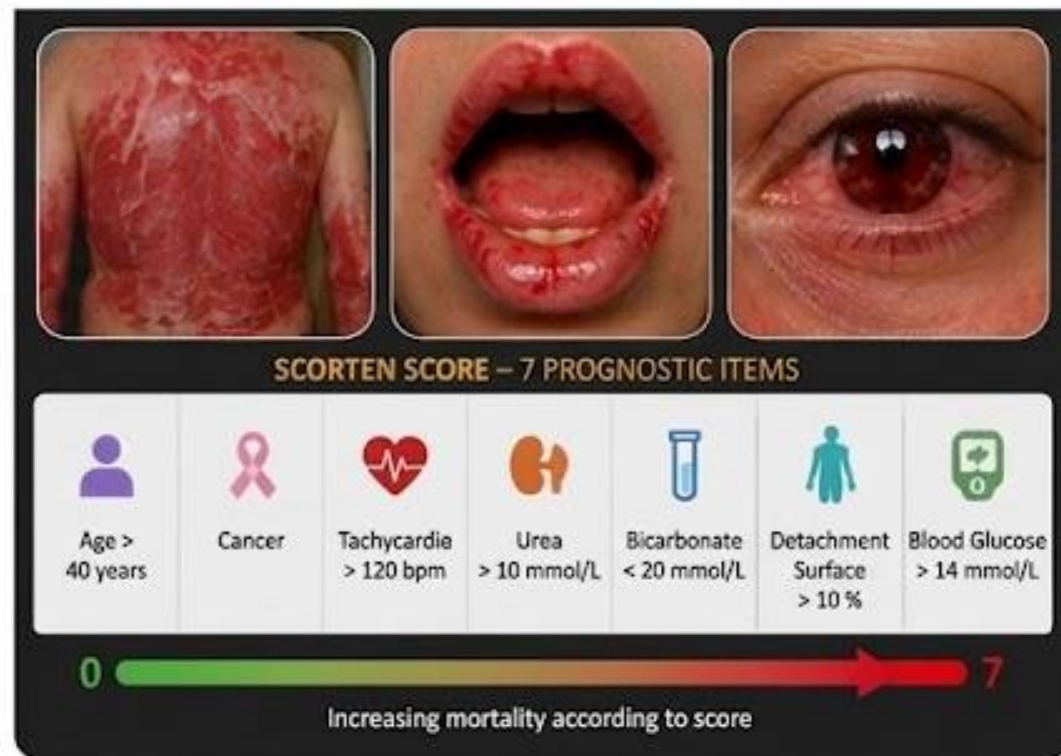
- **SCORTEN Score** : 7 prognostic parameters evaluated at admission, mortality correlated to score



- **Complications** : Sepsis, multiorgan failure, major fluid-electrolyte disturbances



- **Mortality** : 20 to 30% depending on studies, princ cause being sepsis



KEY MESSAGE

TEN is a **medical emergency** requiring immediate transfer to a specialized burn unit or dermatology department



SJS-TEN SPECTRUM – MANAGEMENT IN A SPECIALIZED UNIT

SEVERE TOXIDERMIA



EARLY TRANSFER: to a specialized burn unit or specialty dermatology center when suspected



CONTROLLED ENVIRONMENT: high ambient temperature, strict asepsis, limited handling



28–30 °C



SKIN CARE: non-adherent dressings, gentle cleansing, vigilant monitoring for superinfections



FLUID AND NUTRITION SUPPORT: hydro-electrolyte and nutritional resuscitation adapted to skin loss



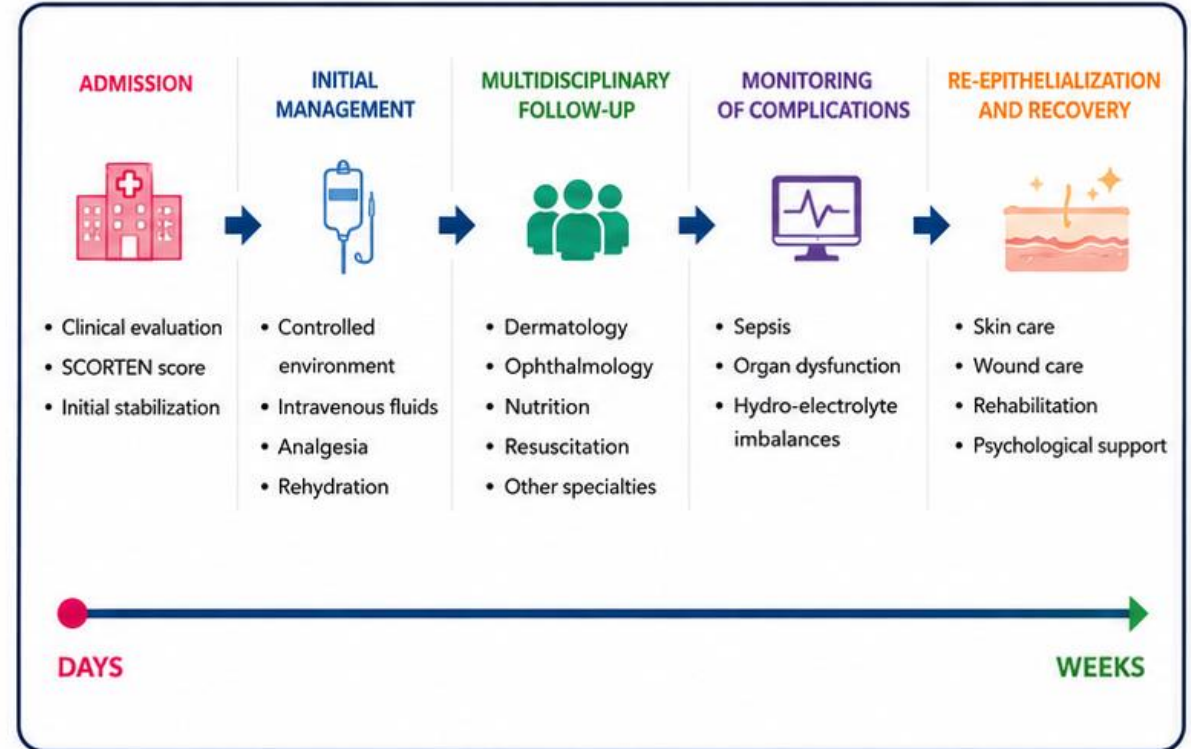
SYMPTOMATIC PAIN MANAGEMENT: severe systemic analgesia (often under-sedation)



AVOID ROUTINE PROPHYLACTIC ANTIBIOTICS: reserved for proven severe sepsis



MULTIDISCIPLINARY FOLLOW-UP: dermatology, ophthalmology, resuscitation, gynecology/urology and genital care as needed



KEY MESSAGE

SJS/TEN is managed like an extensive burn: controlled environment, intensive supportive care, and a multidisciplinary team.



Drug-induced vasculitides and induced lupus

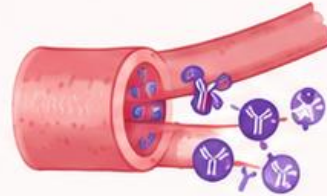
OTHER FORMS



Drug-induced vasculitis



Mechanism: deposition of immune complexes (type III) or ANCA-induced



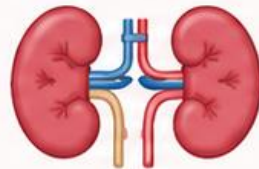
Clinical: palpable vascular purpura of the lower limbs



Common drugs: propylthiouracil, hydralazine, minocycline



Work-up: search for ANCA, renal involvement to be assessed



Drug-induced erythematosus lupus



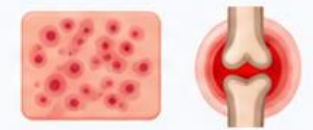
Onset: after prolonged exposure to certain medications



Autoantibodies: frequent anti-histones, anti-native DNA usually absent



Clinical features: cutaneous and articular involvement in the first line, rare renal involvement



Common drugs: hydralazine, procainamide, isoniazid, anti-TNF



Outcome: generally complete after discontinuation of the drug



KEY MESSAGE

These chronic or differential forms require re-evaluation of the entire treatment, including well-tolerated older molecules.



Photosensitivity and lichenoid/psoriasiform eruptions

OTHER FORMS



Drug-induced photosensitivity



Phototoxic (dose-dependent, frequent) or photoallergic (immunologic, rare)



Clinical: sunburn-like erythema exaggerated on photo-exposed areas



Common drugs: cyclines, fluoroquinolones, amiodarone, thiazides



Prevention: strict photoprotection throughout treatment



Lichenoid and psoriasiform eruptions



Lichenoid: violaceous papules, often after several months of treatment (ACE inhibitors, antimalarials, anti-TNF)



Psoriasiform: induced or aggravated by beta-blockers, lithium, anti-TNF (paradoxical)



Diagnosis sometimes difficult to distinguish from idiopathic dermatoses



Improvement slow after discontinuation, over several weeks to months



KEY MESSAGE

These chronic toxicodermias evolve in a torpid manner and are often underdiagnosed due to the obvious lack of a time link.



Pseudolymphomas and SDRIFE (Baboon syndrome)

OTHER FORMS



Drug-induced pseudolymphoma: infiltration of dense cutaneous lymphocytes mimicking a cutaneous lymphoma



Regression after discontinuation of the drug,
without malignant potential



Common drugs: anticonvulsants, ACE inhibitors, antidepressants



SDRIFE (Symmetrical Drug-Related Intertriginous and Flexural Exanthema), called "Baboon syndrome":

- Symmetrical erythema well demarcated in the folds (fossae: inguinal, axillary, etc.)
- Delayed systemic hypersensitivity reaction of type IVa/c in a previously sensitized patient
- Common drug: amoxicillin, in case of reintroduction
- Favorable rapid evolution after discontinuation of the drug



IVa/c



KEY MESSAGE

SDRIFE is recognized by its very characteristic symmetrical distribution in the folds, almost pathognomonic when identified.



Main classes of responsible drugs

 **HIGH-RISK DRUGS**

Class	Typical molecules	Associated toxicodermias
 Antibiotics	Aminopenicillins, sulfonamides, cotrimoxazole	 Exanthema, AGEP, SJS/TEN, DRESS
 Aromatic antiepileptics	Carbamazepine, phenytoin, lamotrigine, phenobarbital	 DRESS, SJS/TEN
 Allopurinol	Allopurinol	 DRESS, SJS/TEN (especially at high initial dose)
 NSAIDs	Oxicams, ibuprofen	 Urticaria, SJS/TEN, photosensitivity
 Antituberculous drugs	Isoniazid, rifampicin, ethambutol	 Exanthema, DRESS, drug-induced lupus
 Antiretrovirals	Abacavir, nevirapine	 Systemic hypersensitivity, SJS/TEN
 Anti-checkpoint immunotherapies	Anti-PD1, anti-PD-L1, anti-CTLA-4	 Lichenoid exanthema, bullous eruptions, DRESS-like
 Biologic therapies	Anti-TNF	 Paradoxical psoriasis, drug-induced lupus, eczema



KEY MESSAGE

A small number of drug classes are responsible for the vast majority of severe toxicodermias: **knowing them by heart is essential.**

Immune checkpoint inhibitor–related toxicodermias

 **HIGH-RISK DRUGS**



Majorly expanded class: anti-PD-1 (nivolumab, pembrolizumab), anti-PD-L1, anti-CTLA-4 (ipilimumab)



Cutaneous toxicities among the most common immune-related adverse effects (irAEs) (**up to 40% of patients**)



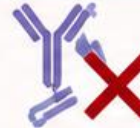
Common clinical patterns: maculopapular rash, pruritus, vitiligo-like (favorable prognostic factor in melanoma)



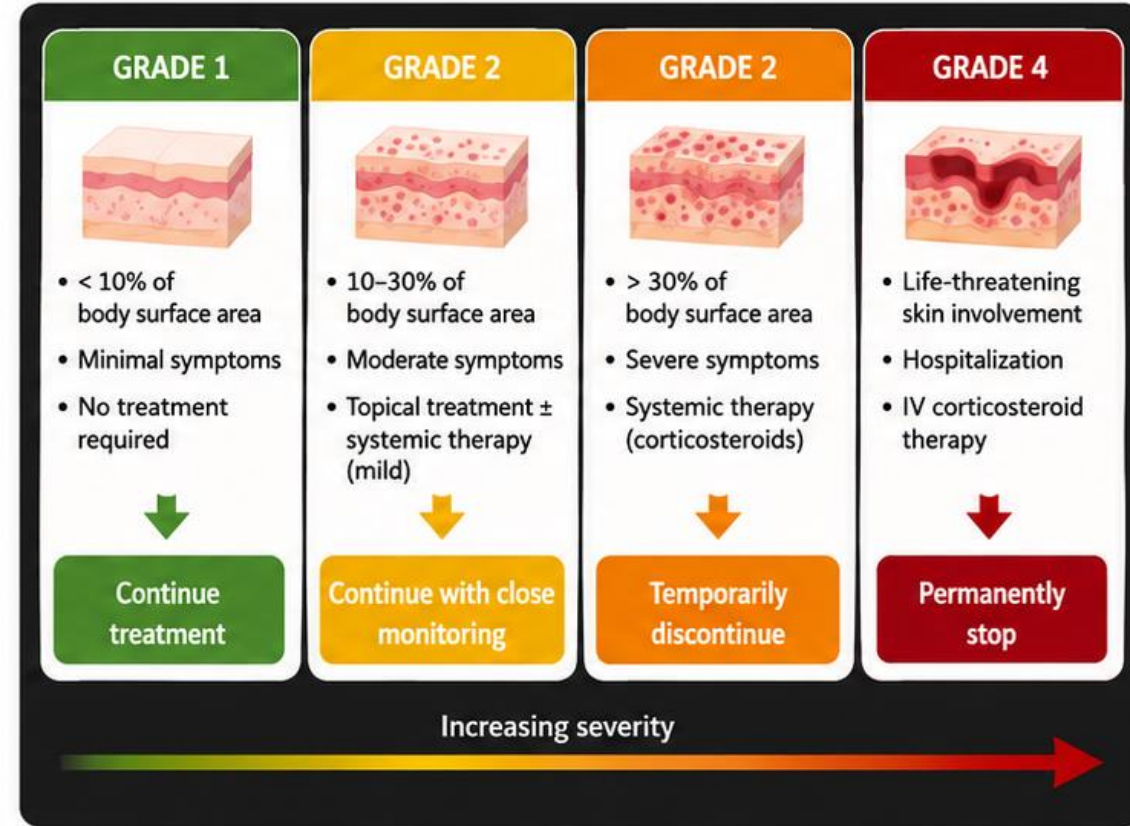
Possible severe forms: bullous autoimmune dermatoses (pemphigoid), DRESS-like, SJS/TEN (rare)



Key feature: the mechanism involves loss of immune self-tolerance, not classical hypersensitivity



Decision to stop vs. continue depends on severity grade (CTCAE classification) and not on immediate systematic discontinuation



KEY MESSAGE

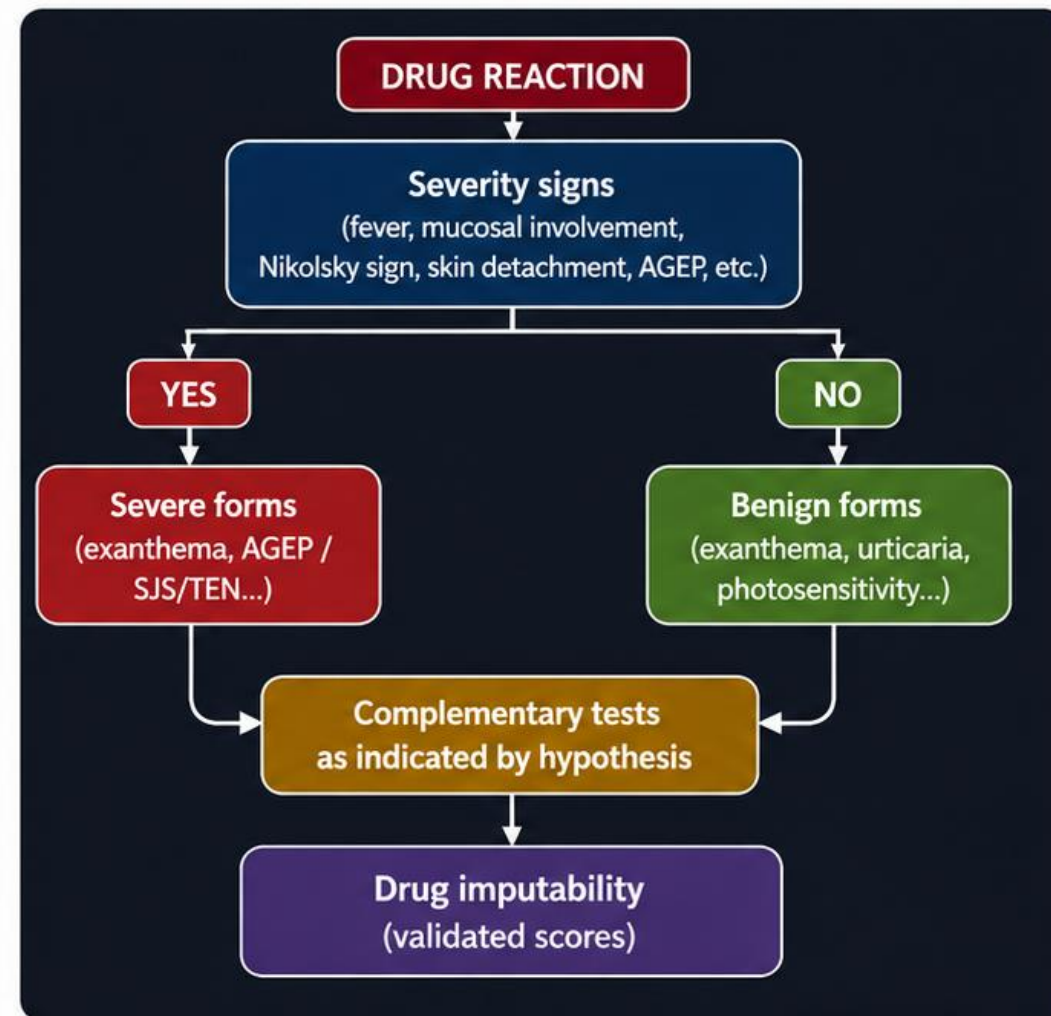
Under anti-checkpoint immunotherapy, the treatment decision is based on a specific severity grading, **in consultation with oncology and dermatology.**



Decision tree for a drug reaction

DIAGNOSTIC APPROACH

-  **Step 1 — Eliminate an immediate vital emergency**
(anaphylaxis, angioedema, laryngeal edema)
-  **Step 2 — Systematically look for severity signs:**
fever, mucosal involvement, skin detachment,
positive Nikolsky sign, facial edema, adenopathies,
altered general condition
-  **Step 3 — Specify the delay between introduction
of each drug and the onset of symptoms**
by reviewing the last 8 weeks
-  **Step 4 — Characterize the morphology of the lesions**
(maculopapular, urticarial, pustular, bullous, purpuric,)
-  **Step 5 — Assess the extent and body surface area
involved**
-  **Step 6 — Order complementary tests**
based on the working hypothesis
-  **Step 7 — Establish drug imputability**
using validated scoring systems



KEY MESSAGE

The systematic search for severity signs must precede any other step in the diagnostic reasoning.

Complementary tests for diagnostic purposes



Test	Main interest
 CBC with differential	Eosinophilia (DRESS), neutrophilia (AGEP), atypical lymphocytes
 Liver function tests	Search for cytolysis/cholestasis (DRESS, severity)
 Renal function tests (urea, creatinine)	Search for renal impairment (DRESS, SCORTEN)
 CRP	Guidance toward systemic infection or inflammation
 Viral serologies (HHV-6, EBV, CMV)	Search for viral reactivation in DRESS
 Skin histology	Diagnostic confirmation, distinction between AGEP/pustular psoriasis, severe SJS/TEN
 Direct immunofluorescence	Exclusion of an autoimmune bullous dermatosis
 Pharmacogenetic tests (HLA)	HLA-B*15:02, HLA-B*58:01, HLA-A*31:01 depending on the suspected drug



KEY MESSAGE

Complementary tests confirm and assess severity; they **never replace** clinical and chronological analysis.



Patch tests, re-exposure tests and pharmacogenetic testing



DIAGNOSTIC APPROACH



- **Drug patch tests:** useful at a distance (minimum 6–8 weeks) for certain forms (exanthema, DRESS, AGEP, fixed drug eruption)



- **Performed on healthy skin** or, for fixed drug eruption, directly on the previously affected area



- **Variable sensitivity** depending on the drug and clinical form, global specificity generally good



- **Re-exposure tests (oral provocation):** gold standard for drug imputability but major risk



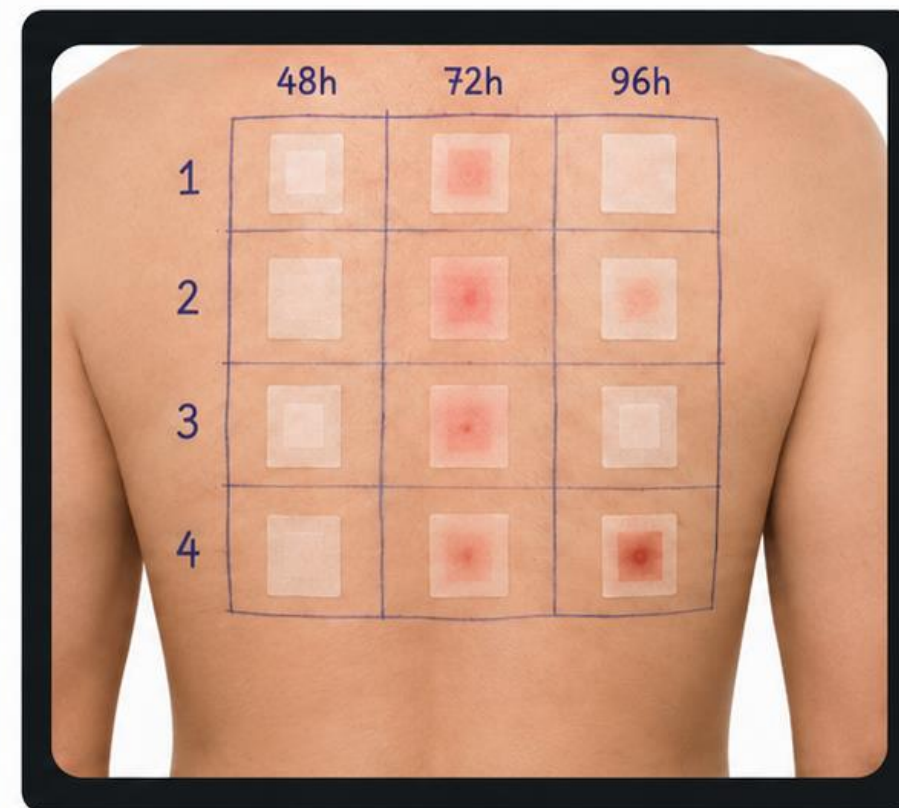
- **Formally contraindicated** after SJS, TEN, DRESS or AGEP due to the risk of potentially life-threatening recurrence



- **Reserved for selected benign forms**, in a specialized setting and under strict monitoring



- **Pharmacogenetic tests (HLA):** preventive screening before introduction, not a routine diagnostic tool



KEY MESSAGE

Never perform a re-exposure test after a severe drug reaction: the diagnostic benefit **never justifies the risk.**

French method and Naranjo algorithm



French method of causality assessment



Combines a **chronological score** and a **semiological score**



Chronological score: delay, evolution after withdrawal, rechallenge effect



Semiological score: evocative semiology, favoring factors, other causes ruled out



Result expressed from **10 (excluded)** to **14 (highly likely)**



Naranjo algorithm

- 1 10 questions with yes/no/unknown answers, each weighted
- 2 Total score classifying the likelihood of an adverse drug reaction
- 3 Internationally recognized tool widely used in pharmacovigilance
- 4 Less specific for severe cutaneous drug reactions than dedicated scores (ALDEN, RegiSCAR)

Total score	Imputability
≤ 0	Doubtful
1 – 4	Possible
5 – 8	Probable
≥ 9	Definite



KEY MESSAGE

These generalist scores structure the reasoning process but must be completed by **specific scores** for severe forms.

Specific scores: ALDEN, RegiSCAR, EuroSCAR



CAUSALITY ASSESSMENT

Score	Use	Principle
 ALDEN	SJS / TEN	 6 weighted criteria (delay, presence of the drug, dechallenge effect, type of reaction, drug notoriety, other causes); score from -12 to +10
 RegiSCAR	DRESS	 7 clinical and biological criteria; score from -4 (excluded) to 9 (definite), certitude threshold >5
 EuroSCAR	AGEP	 Morphological, chronological and histological criteria; score from 0 (absence of AGEP) to 12 (definite), certitude threshold ≥8
 SCORTEN	SJS / TEN (prognostic, not a causality score)	 7 clinical and biological parameters at admission, predictive of mortality



KEY MESSAGE

ALDEN, RegiSCAR and EuroSCAR are dedicated to a specific severe reaction each:
they should not be confused with or replaced by SCORTEN, which assesses prognosis, not causality.

General principles of management



TREATMENT



Most important therapeutic measure: immediate and definitive withdrawal of the suspected drug(s)



In case of doubt about several drugs introduced simultaneously, **stop all non-essential drugs**



Symptomatic treatment adapted to the clinical form: emollients, antihistamines, analgesics



Topical or systemic corticosteroids according to clinical form and severity



Clinical and biological monitoring closely adapted in high-risk forms for secondary worsening



Multidisciplinary management for severe forms (intensive care, ophthalmology, urology/gynecology)



Strict documentation in the medical record of the suspected drug and the context



Therapeutic algorithm graded according to severity:

Mild form
(outpatient)



Moderate form
(short hospitalization)



Severe form
(specialized unit)



OUTPATIENT CARE

- Immediate withdrawal
- Symptomatic treatment
- Antihistamines
- Emollients / topical care
- Clinical monitoring



SHORT HOSPITALIZATION

- Immediate withdrawal
- Systemic corticosteroids if indicated
- Intensive care
- Biological monitoring
- Daily evaluation



SPECIALIZED UNIT

- Immediate withdrawal
- Intensive care
- Multidisciplinary management
- Close monitoring



Documentation and traceability: medical record + reporting if necessary



KEY MESSAGE

No specific treatment replaces the **early withdrawal** of the suspected drug: it is the **key factor** that most influences the **prognosis**.



Management of severe forms

TREATMENT

TREATMENT	MAIN INDICATION	REMARKS
 Systemic corticosteroids	 DRESS (first-line treatment)	 Very progressive tapering over several weeks to months
 IV immunoglobulins	 SJS / TEN (according to team protocols)	 May block Fas–FasL apoptosis; evidence of moderate level
 Cyclosporine	 SJS / TEN	 Inhibits T lymphocytes; recent encouraging data
 Anti-TNF agents (etanercept)	 SJS / TEN (specialized protocols)	 Targets TNF- α involved in keratinocyte apoptosis
 Intensive supportive care	 All severe forms	 Rehydration, nutrition, analgesia, infection prevention



KEY MESSAGE

There is no international consensus on the use of immunomodulatory treatments in SJS/TEN: the decision is made in **specialized centers** according to the team's experience.

Prévention and pharmacovigilance



PRÉVENTION



Systematic and mandatory reporting of every severe drug reaction to the regional pharmacovigilance center



Systematic issue of a drug allergy card indicating the suspected drug and the observed reaction



Clear information for the patient and their family about definitive avoidance and therapeutic alternatives



Preventive HLA screening before initiation in at-risk populations (e.g., carbamazepine, abacavir, allopurinol)



Therapeutic education to raise early awareness of warning signs (fever, mucosal involvement, etc.)



Enhanced vigilance during accidental re-exposure to a drug of the same pharmacological class



DRUG ALLERGY CARD



SUSPECTED DRUG: Allopurinol

REACTION OBSERVED: SJS / TEN

DATE OF REACTION: 15/04/2024

**DEFINITIVE AVOIDANCE OF THIS DRUG
AND DRUGS IN THE SAME CLASS**



**REGIONAL CENTER
FOR PHARMACOVIGILANCE**
Tel.: 05 24 34 56 78



KEY MESSAGE

Prevention is based on three pillars: **reporting**, **traceability** and **patient education**.

Comparative table of the main severe drug reactions



SUMMARY

CRITERIA	 DRESS	 AGEP	 SJS / TEN
 Onset	 2–8 weeks	 24–48 hours	 4–28 days
 Typical skin lesion	Extensive exanthem, facial edema 	Non-follicular pustules 	Purpuric macules, detachment 
 Mucosal involvement	Rare	Rare	Constant and severe
 Fever	Frequent 	Frequent 	Frequent 
 Evocative biology	Eosinophilia, liver cytolysis 	Neutrophilia with PNN 	Variable, correlated with SCORTEN 
 Mortality	5–10 % 	< 5 % 	20–30 % (TEN) 
 Dedicated score	RegiSCAR 	EuroSCAR 	ALDEN (causality) / SCORTEN (prognostic) 



KEY MESSAGE

This summary table should be memorized:
it enables a rapid differential diagnosis at the patient's bedside.

15 key messages to remember



SUMMARY

1

Any cutaneous eruption in a patient receiving treatment is a **toxicodermia** until proven otherwise.



6

AGEP is characterized by **non-follicular pustules** and a rapidly favorable evolution.



11

Rechallenge tests are generally **contraindicated** after a severe toxicodermia.



2

The time from drug initiation to onset is the **key to diagnosis**.



7

SCORTEN should be calculated during the **first 24 hours** of Stevens–Johnson syndrome or toxic epidermal necrolysis.



12

Causality scores (ALDEN, Naranjo) help **structure reasoning** but do not replace clinical judgment.



3

Mucosal involvement or a Nikolsky sign indicates **hospitalization as an emergency**.



8

Immediate withdrawal of the suspected drug is the most important therapeutic measure.



13

Checkpoint inhibitors have a typical and increasing toxidermia profile.



4

Fever, facial edema and lymphadenopathy suggest **DRESS** up to proven otherwise.



9

Severe toxicodermias require management in a **specialized unit** (burns/dermatology).



14

Reporting in pharmacovigilance is a **medical duty**, not an option.



5

DRESS may evolve over several weeks and requires **follow-up** after withdrawal of systemic corticosteroids.



10

Allopurinol, aromatic anticonvulsants and sulfonamides are the **leading causes** of DRESS and SJS/TEN.



15

A **drug allergy card** must be given to the patient after a confirmed toxicodermia.



KEY MESSAGE

This summary table should be memorized: it enables a **rapid differential diagnosis at the patient's bedside**.

Conclusion



Drug reactions encompass a **continuous spectrum**, ranging from benign exanthems to **life-threatening severe reactions**.



Early **recognition of severity signs** is essential to improve patient outcomes and prognosis.



Mastery of **causality assessment and prognostic scores** enables a rigorous and structured evaluation.



Prompt withdrawal of the suspected drug is the cornerstone of management.

