Exanthematous (maculopapular) drug eruption

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Scope

Maculopapular Rash (morbilliform rash)

- Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Acute generalized exanthematous pustulosis (AGEP)

Epidemiology

- Cutaneous drug reactions occur in approximately 2 percent of exposed individuals.

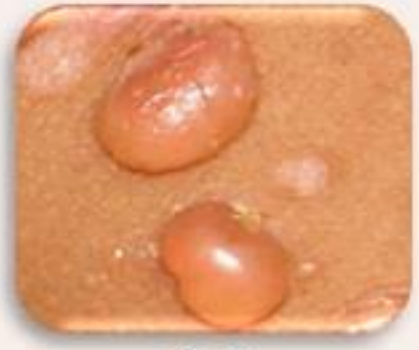
- The **morbilliform (maculopapular)** exanthem accounts for approximately **95 percent** of cutaneous drug reactions.

* Mansouri M, Mesdaghi M, Chavoshzadeh Z, Heidarzadeh M, Abdollah Gorji F. Allergic Drug Reactions: A Cross Sectional Study, Arch Pediatr Infect Dis. 2014 ; 2(3):e14290. doi: 10.5812/pedinfect.14290.

Objectives

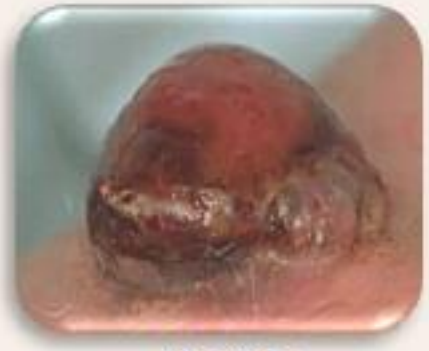
- Definitions
- Clinical presentation
- Most common drugs associated with maculopapular drug eruptions
- Diagnosis & differential diagnoses
- Signs and symptoms of severe reactions
- Management
- Prevention of future reactions

Skin Lesion Reference Guide

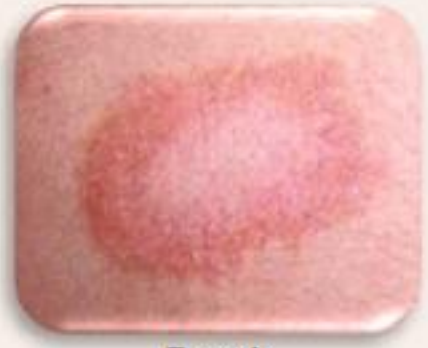


Bulla
Circumscribed collection of free fluid, >1 cm

Macule
Circular flat discoloration, <1 cm brown, blue, red or hypopigmented



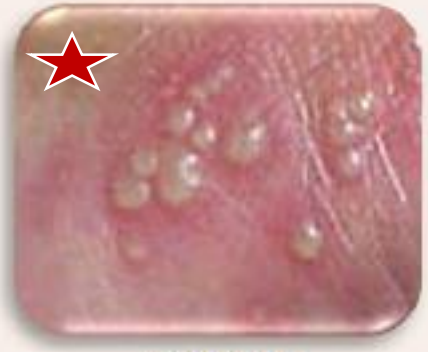
Nodule
Circular, elevated, solid lesion, >1cm



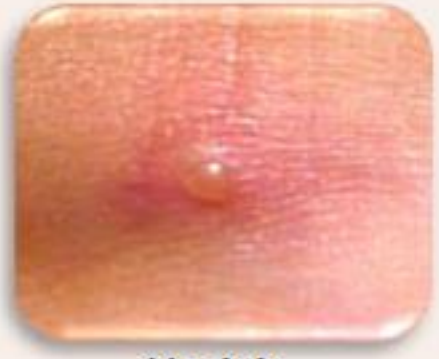
Patch
Circumscribed flat discoloration, >1cm

Papule
Superficial solid elevated, ≤0.5 cm, color varies

Plaque
Superficial elevated solid flat topped lesion, >1 cm



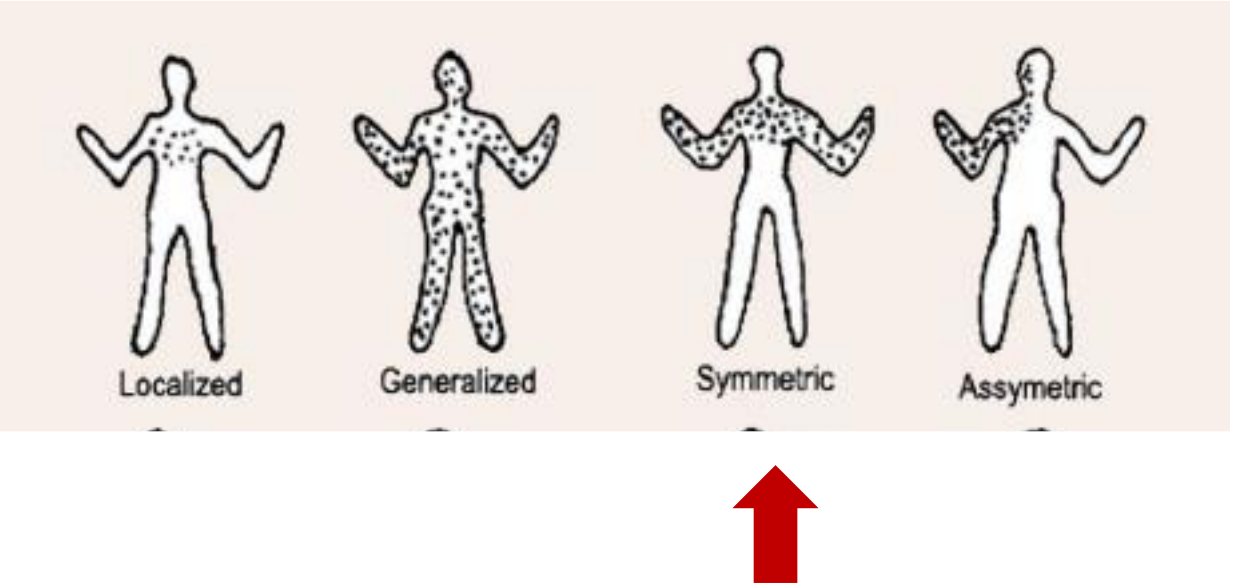
Pustule
Vesicle containing pus (inflammatory cells)



Vesicle
Circular collection of free fluid, ≤1 cm

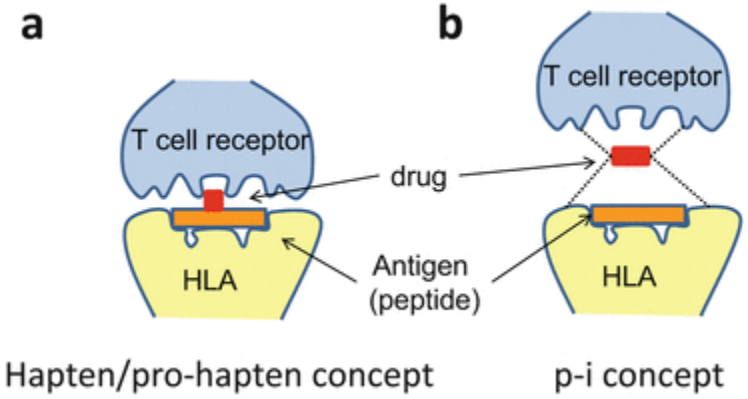
Introduction

- The *most common* type of drug hypersensitivity reaction
- Diffuse and **symmetric eruption** of erythematous macules or small papules
- Occur approximately **one week** or, in previously sensitized individuals, as early as *one or two days* after the initiation of drug.



Pathogenesis

- **Mechanism:**
  - Hapten
  - Direct interaction with specific immune cells (the "p-i concept")



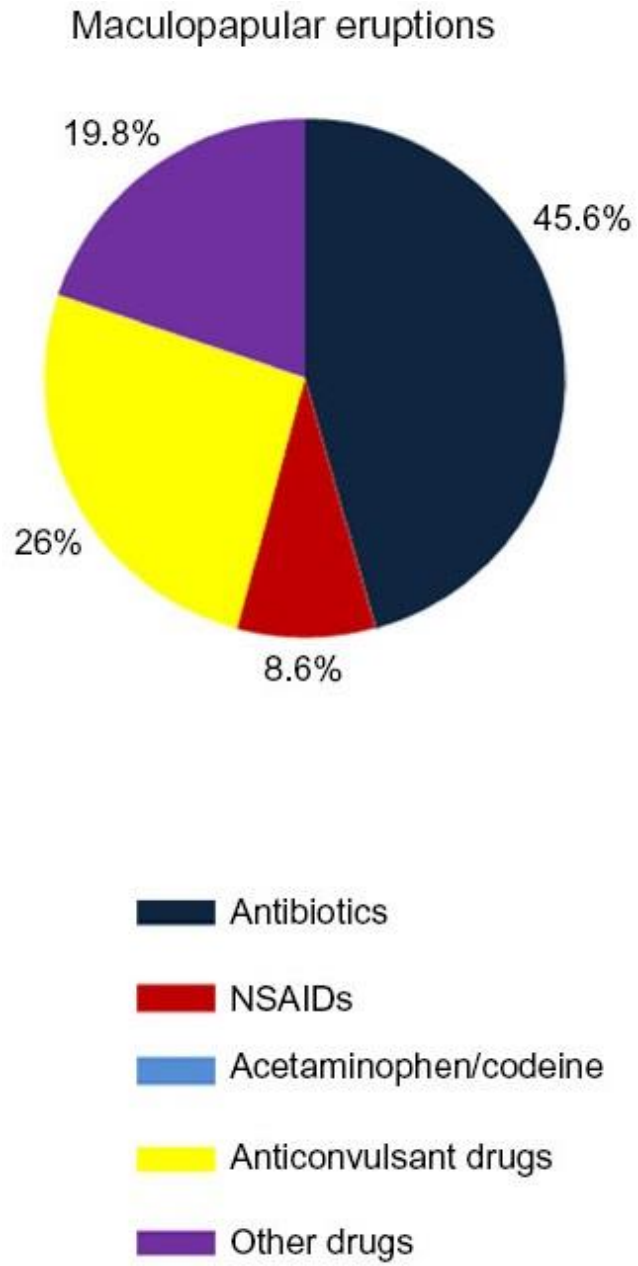
Abe R. (2016) Cutaneous Adverse Drug Reactions: Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis. In: Kabashima K. (eds) Immunology of the Skin. Springer, Tokyo. https://doi.org/10.1007/978-4-431-55855-2_24

Pathogenesis

Immune reaction	Mechanism	Clinical manifestation	Time of occurrence	
Type I (IgE-mediated)	The drug binds to specific IgE on the mast cell surface, triggering the release of histamine and other inflammatory mediators	Urticaria, angioedema, bronchial smooth muscle spasm, pruritus, nausea and diarrhea, anaphylaxis	A few minutes to several hours (but mostly under 1 hour) after drug exposure,	Anaphylaxis, Angioedema, Urticaria
Type II (cytotoxic)	Specific of IgG or IgM which attacks cells that bind to the drug / hapten	Hemolytic anemia, neutropenia, thrombocytopenia	Variable	Cytopenia
Type III (immune complex)	Deposition of drug-antibody complex in the tissue, triggering activation of the complement system and inflammation	Serum sickness, drug fever, rash, arthralgia, lymphadenopathy, glomerulonephritis, vasculitis	1 to 3 weeks after exposure to the drug	Vasculitis
Type IV (*delayed, cell-mediated*)	Presentation of drug molecules via MHC to T lymphocytes, triggering the release of cytokines and inflammatory mediators	Contact sensitivity, skin rashes, organ-tissue damage	2 to >20 days after exposure to the drug	SJS/TEN, DRESS

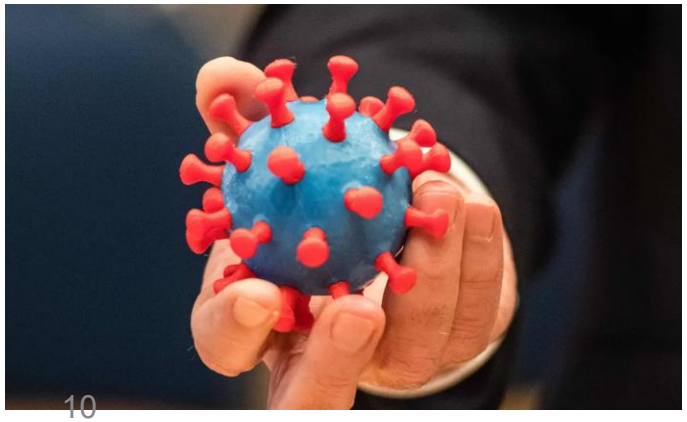
Rates of cutaneous reactions to drugs

Drug	Rate (percent) of allergic cutaneous reactions
Amoxicillin	1.2-5.1
Ampicillin	3.3
Trimethoprim-sulfamethoxazole	2.1-3.4
Semisynthetic penicillins	2.1
Penicillin G	1.9
Cephalosporins	1.5
Erythromycin	2.0
Gentamicin	0.5
Doxycycline	0.5
Fluoroquinolones	0.1-1.6
Furosemide	0.05
Allopurinol	0.8
Metoclopramide	0.3
Heparin sodium	0.1
Barbiturates	0.4
Nitrazepam	0.2
Diazepam	0.04
Lamotrigine	0.6
Carbamazepine	0.3
Maprotiline	0.2
Escitalopram	0.2
Tricyclic/tetracyclic antidepressants	0.07
SSRIs	0.05



Contributing Factors

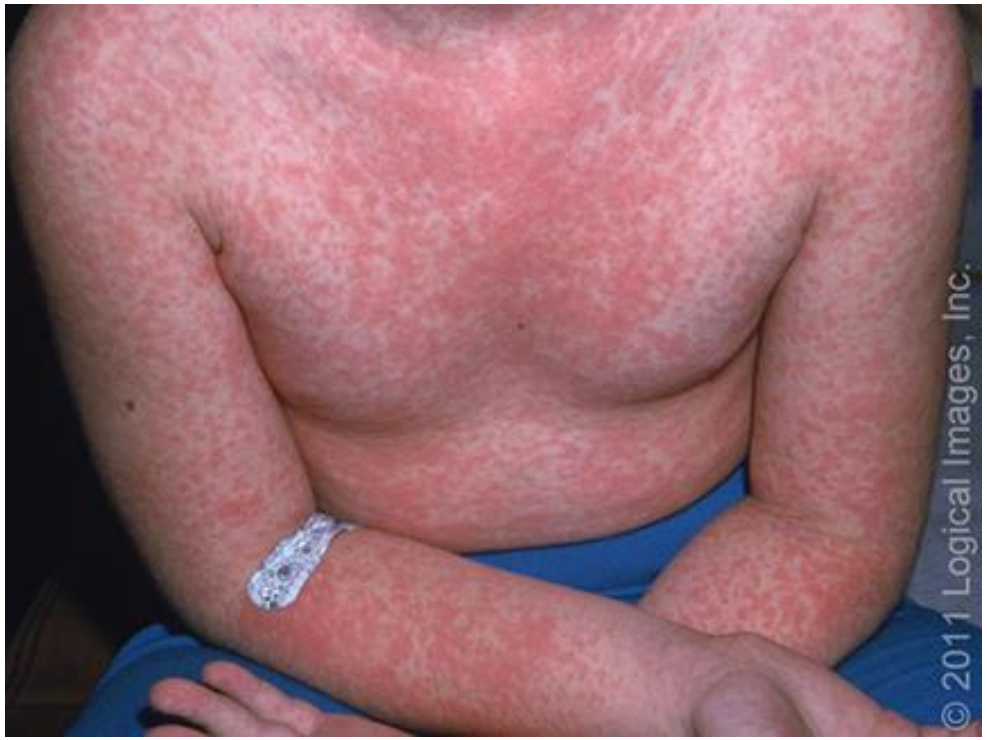
- **Genetic Predisposition**
- **Concomitant disease**
  - Viral infections (particularly Epstein-Barr virus, cytomegalovirus, and human herpesviruses 6 and 7)
  - Patients with inborn, acquired, or iatrogenic immunodeficiency
  - HIV
  - Exanthematous drug eruption (with Antibiotics) in children with viral infection
- **Co-medication**
  - Valproate and lamotrigine



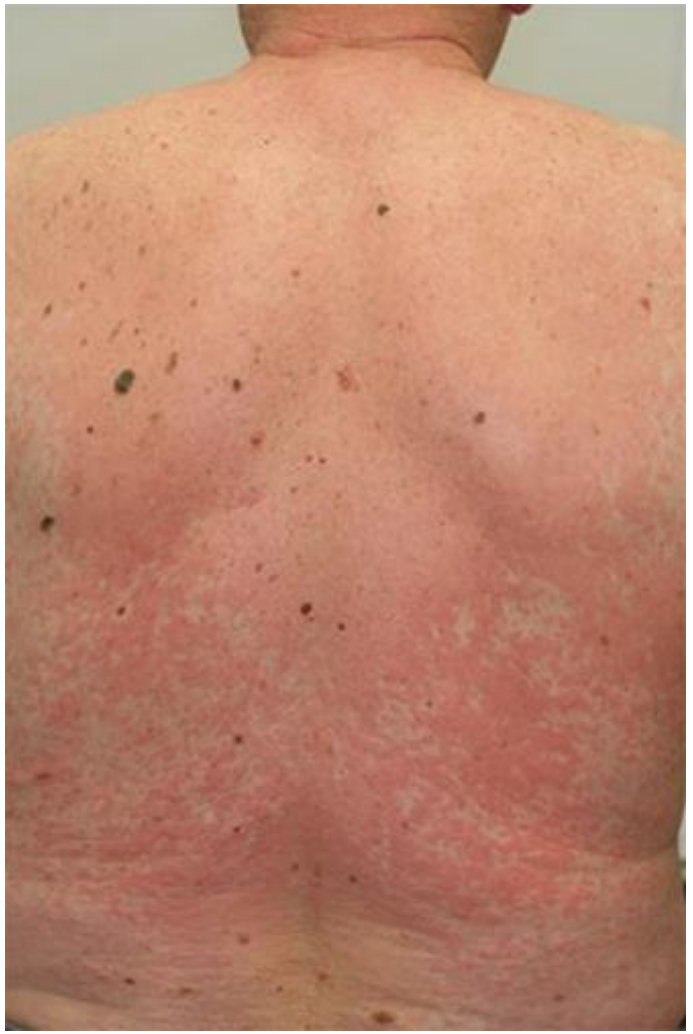
Clinical Presentation

- General features
  - Erythematous macules and papules, and rarely pustules or bullae
  - Predominantly involve the trunk and proximal extremities (acral sites are often spared, whereas in more severe cases, the face, palms, and soles may also be involved)
  - Systemic symptoms
  - Chronology
    - In patients not previously sensitized, the onset of the cutaneous eruption typically occurs within 7 to 10 days (range 5 to 21 days) after starting treatment.
    - patients previously sensitize 6-12 hours after
  - Mucosal involvement (SJS/TEN)

Clinical Presentation



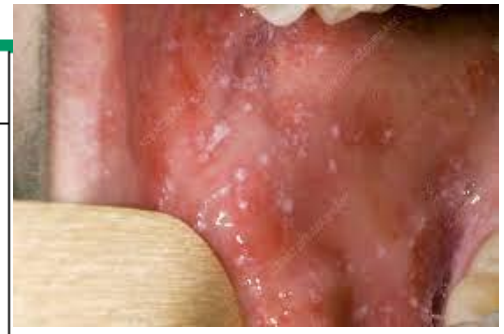
Exanthematous (morbilliform) drug eruption

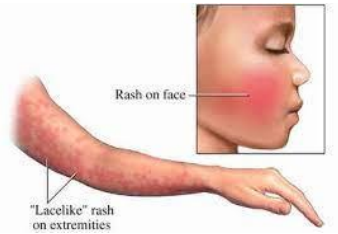


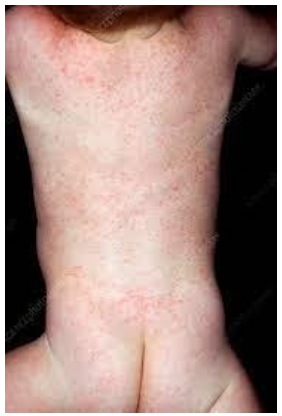
Differential Diagnosis

Differential diagnosis of exanthematous (maculopapular) drug eruptions

Viral exanthems	
Measles (rubeola)	The "brick-red" maculopapular rash often begins on the head and neck area and spreads centrifugally. Patients also complain of fever, cough, coryza, and conjunctivitis. Koplik's spots, tiny punctate elevated white buccal mucosa lesions located adjacent to the lower molars, are pathognomonic of measles and can precede the rash by 24 to 48 hours.
Rubella	The rash resembles measles, but the patient does not appear to be sick; prominent postauricular, posterior cervical, and/or suboccipital adenopathy also assists in the diagnosis
Erythema infectiosum or "fifth disease" (human parvovirus B19)	Children, unlike adults, often develop a characteristic rash with a "slapped cheeks" appearance
Roseola infantum or exanthem subitum (human herpesvirus 6 or 7)	Primarily seen in infants and young children, is characterized by high fever for three to four days, followed by generalized maculopapular rash that spreads from the trunk to the extremities but spares the face
Infectious mononucleosis (Epstein-Barr virus or cytomegalovirus)	Maculopapular rash, usually occurring after administration of ampicillin, in older children, adolescents, or young adults with pharyngitis, fever, lymphadenopathy

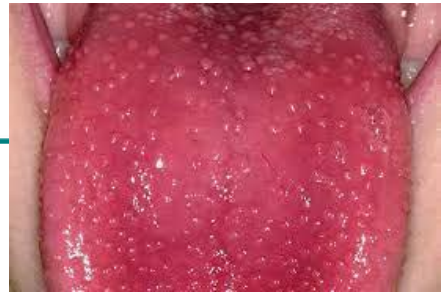


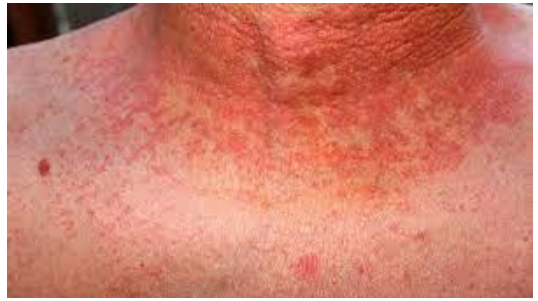




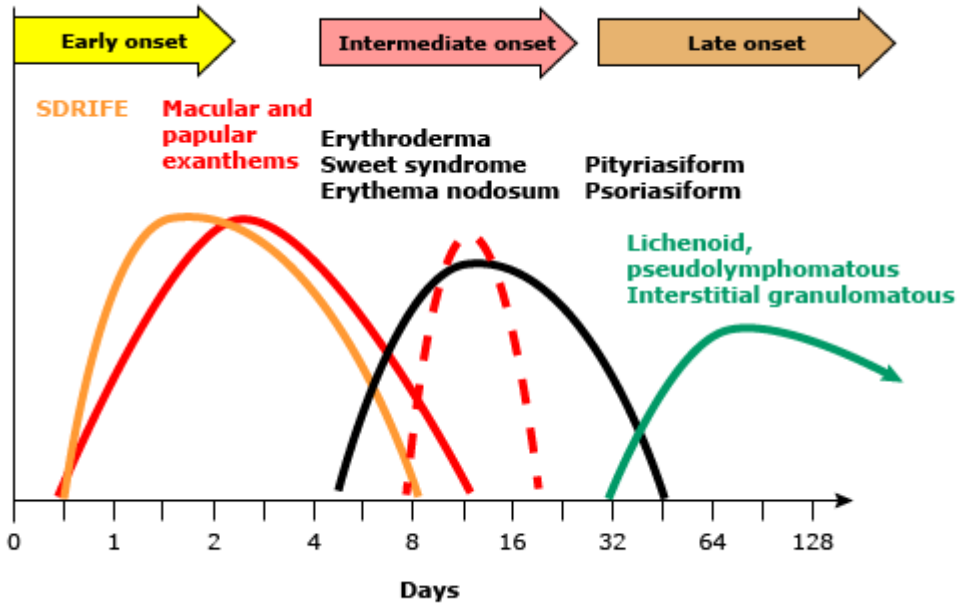
Diagnosis

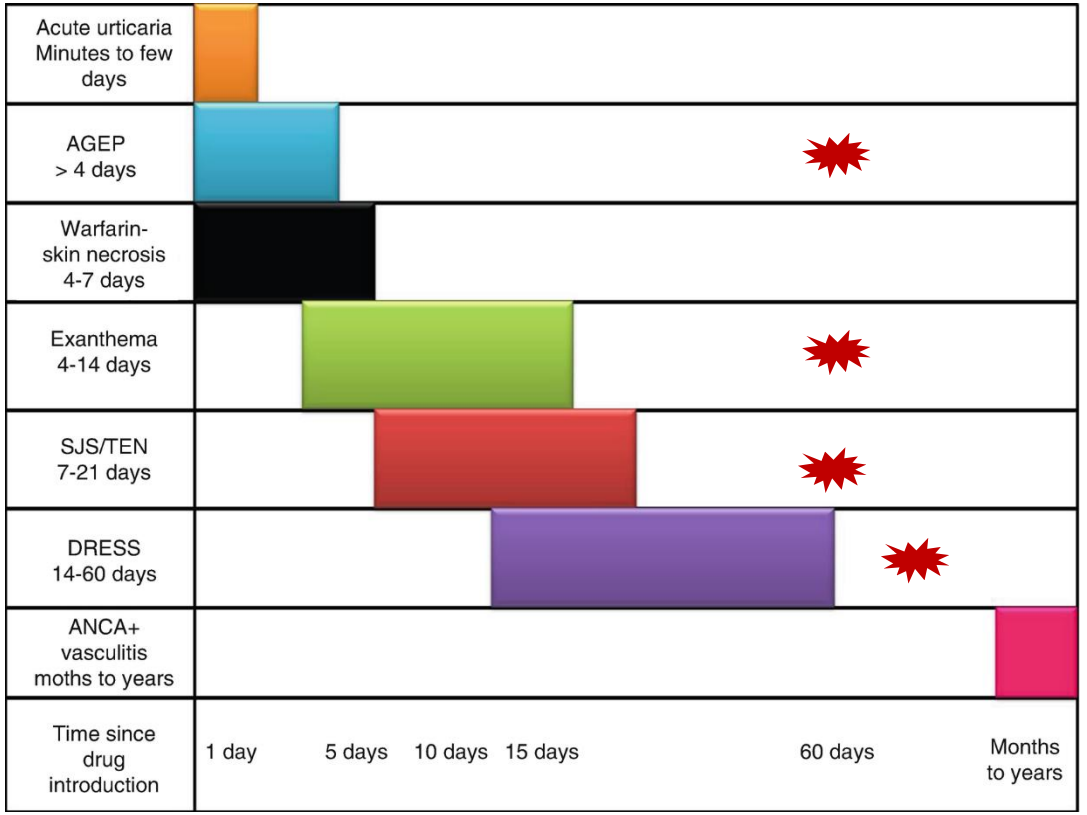
Bacterial exanthems	
Scarlet fever	Coarse, sandpaper-like, erythematous, blanching rash, occurring most commonly in the setting of pharyngitis from group A streptococcus infection
Mycoplasma infection	Mild erythematous maculopapular or vesicular rash, most commonly accompanying respiratory tract infections. Rarely, erythema multiforme or Stevens-Johnson syndrome.
Maculopapular rash associated with autoimmune connective tissue disease	
Juvenile idiopathic arthritis and adult-onset Still disease	Evanescent, salmon pink maculopapular rash occurring with fever. The rash predominantly involves the trunk and extremities, but can also involve the palms, soles, and occasionally the face.
Acute cutaneous lupus erythematosus	Widespread morbilliform eruption often focused over the extensor aspects of the arms and hands. Typically precipitated or exacerbated by exposure to UV light.





Chronology



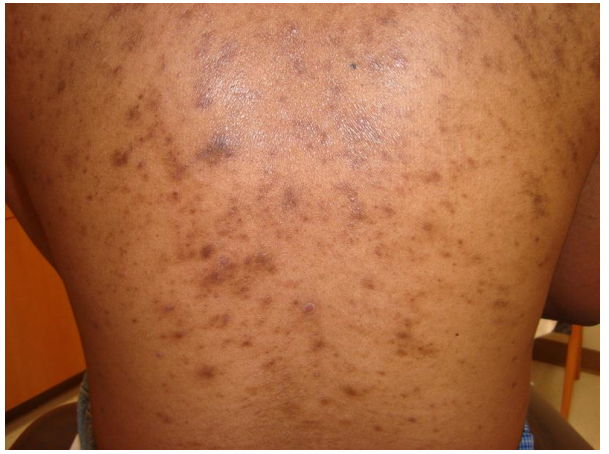


Chronology of drug eruptions

Approximate onset and evolution of uncomplicated drug-induced exanthemas with probable T-cell-mediated pathophysiology in *previously sensitized* individuals. In *newly sensitized* individuals, typically exanthems develop between the 8 and 12 day (red dashed line).

Clinical Course

- Most eruptions are mild-to-moderate
- Evolve rapidly
- **Resolve in 5-14 days**
- Occasionally subside despite continuation
- Post-inflammatory hyperpigmentation can occur in patients with darker skin tones



Diagnosis

- Clinical diagnosis
  - Medication history
  - Resolution of the rash after drug withdrawal

- Laboratory tests
  - Routine laboratory evaluation is **not indicated**
    - CBC Diff
    - Liver and kidney function tests more than twofold increase of liver transaminases and/or abnormal kidney function tests
    - **Patch testing**

Allergy testing

- The clinical diagnosis of drug hypersensitivity based solely on the temporal relationship between drug intake and the development of an exanthem leads to a huge overestimation of the frequency of drug allergy.

- Therefore, allergy testing, if available, is recommended for all patients with suspected, drug-induced exanthem to rule out or confirm drug hypersensitivity, ideally within a time frame of one to six months after complete resolution of the rash.

- If allergy testing is not performed, many patients will be unnecessarily labeled (lifelong) as being drug allergic:

Allergy testing

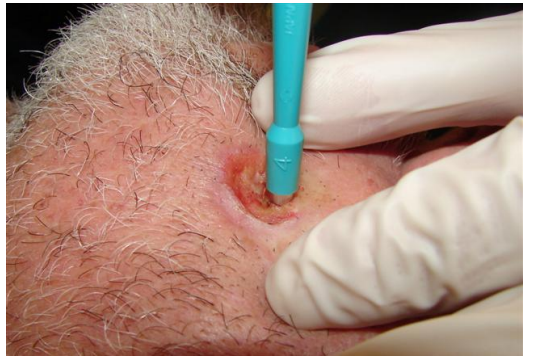
Skin testing – Methods include patch and intradermal testing; test fields should be evaluated for delayed reactions at days 2, 3, and 4.

Provocation (challenge) testing (graded challenge)

Type II-IV

Diagnosis

- Skin biopsy
  - Routine skin biopsy is **not** recommended
  - Potential indications:
    - Suspicion of a non-drug-induced skin disorder
    - Multiple drugs involved without a clear-cut temporal relationship with cutaneous reaction
    - Severe systemic symptoms (eg, fever >38°C [100.4°F] and/or symptoms of internal organ involvement)
    - Evolution to erythroderma, blistering, purpura, or postulation
    - Mucous membrane involvement



Identification of the causative drug

- Current and past medication history (within the last four weeks)
- Simultaneous exposure to multiple drugs (know the relative frequency of cutaneous reactions for specific drugs)
- Previously sensitized patients short latency time (6 to 12 hours and up to a few days)
- Accidental re-exposure
- Resolution of the rash after drug withdrawal

Resolution is usually completed within one to two weeks after the causative drug is discontinued. In some cases with a prolonged course, resolution may take up to three weeks.

When to suspect a severe drug reaction

A severe reaction should be suspected if

Systemic symptoms are present (eg, fever >38°C/100.4°F, lymphadenopathy) and if blisters, erythroderma, erythematous facial swelling, or mucosal involvement develop

Management

- Drug withdrawal
- Symptomatic treatment
  - Topical corticosteroids: high-potency (group 1 to 3) topical corticosteroids one to two times per day for **one week** or until resolution
  - Oral antihistamines (until pruritus subsides)
    - Diphenhydramine – 25 to 50 mg orally every 4-6 hours for adults and children ≥12 years
    - Hydroxyzine – 25 mg orally three to four times per day for adults and children ≥6 years
    - Cetirizine – 10 mg orally once daily for adults and children ≥6 years

Potency group*	Corticosteroid	Vehicle type/form	Available strength(s), percent
Super-high potency (group 1)	Clobetasol propionate	Ointment	0.05
		Cream	0.05
		Lotion	0.05
High potency (group 2)	*Betamethasone dipropionate*	*Ointment*	*0.05*
	Clobetasol propionate	*Cream*	*0.025*
High potency (group 3)	Betamethasone valerate	Ointment	0.1
	Mometasone furoate	Ointment	0.1
Medium potency (group 4)	Fluocinolone acetonide	Ointment	0.025
	Mometasone furoate	Cream	0.1
		Lotion	0.1
		Solution	0.1
	Triamcinolone acetonide	Cream	0.1
		Ointment	0.1
Lower-mid potency (group 5)	Betamethasone valerate	Cream	0.1
	Fluocinolone acetonide	Cream	0.025
Low potency (group 6)	Betamethasone valerate	Lotion	0.1
Least potent (group 7)	Hydrocortisone acetate with pramoxine 1% combination	Ointment	1 or 2.5
		Cream	1 or 2.5
		Lotion	1 or 2.5

Management

- Routine use of systemic corticosteroids is **not recommended** for uncomplicated exanthematous skin eruptions.
- A short course of moderate/high-dose systemic corticosteroids (eg, prednisone 1 to 2 mg/kg per day for 5-7 days) may be beneficial for DRESS, AGEP, or SJS/TEN.

Management

"Treating through"

- **Continuation** of a drug treatment despite a suspected hypersensitivity reaction
- Sometimes adopted when the suspected drug is important and **no alternative** exists
- May be associated with **progressive rash**
- Co-medication with corticosteroids or antihistamines *may be* beneficial

Serious maculopapular rash

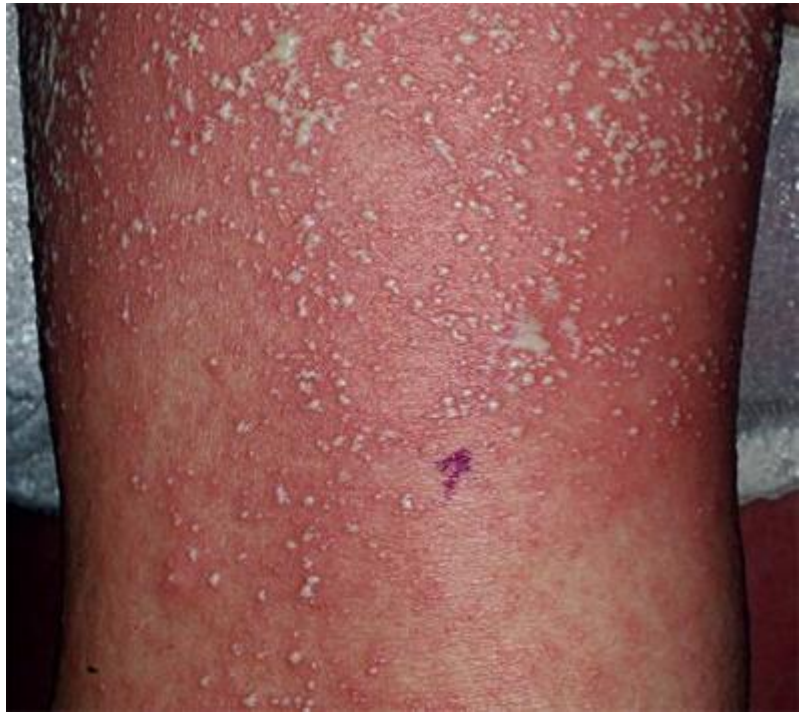
- Acute generalized exanthematous pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)

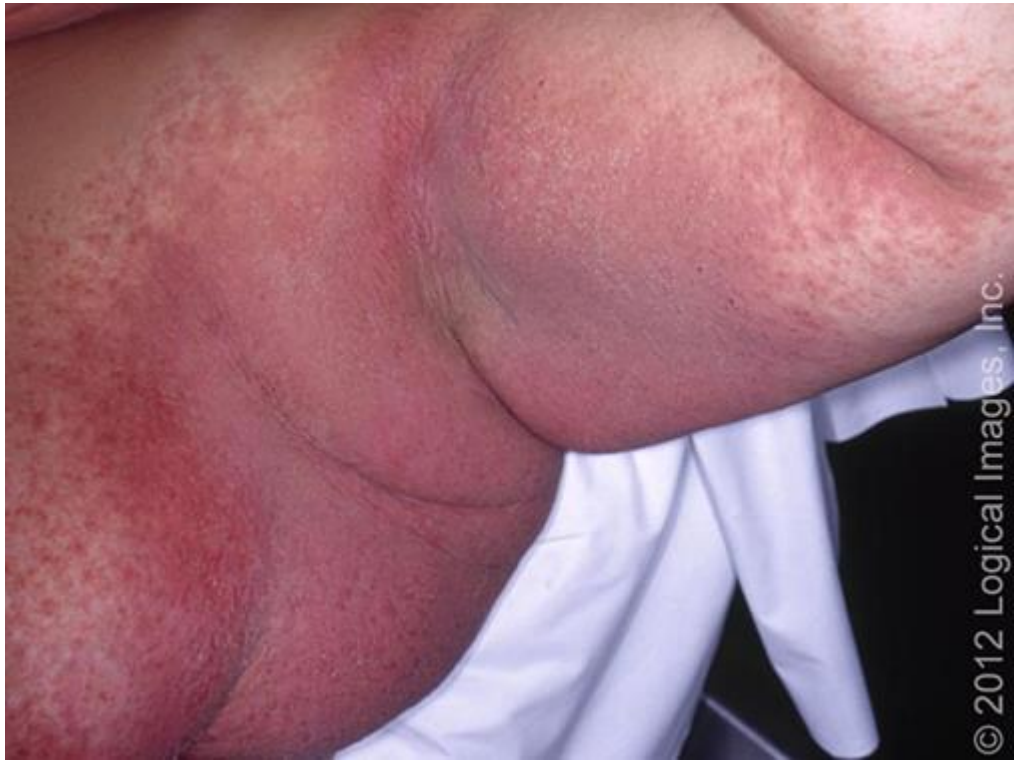
Acute generalized exanthematous pustulosis (AGEP)

Clinical feature

AGEP typically manifests with the rapid development of dozens to hundreds nonfollicular, sterile, pinhead-sized pustules on a background of edematous erythema with flexural accentuation. The eruption usually occurs a few hours to a few days after the administration of the offending drug.

Clinical feature





Clinical Course

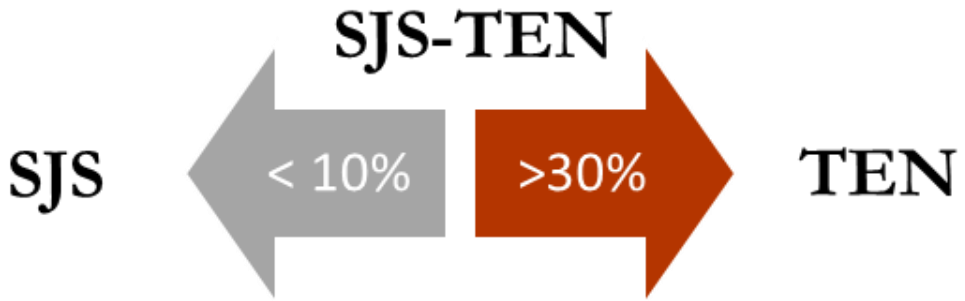
Skin symptoms usually resolve without treatment in one to two weeks after the discontinuation of the offending drug. The pustular eruption is followed by desquamation with characteristic collarettes of scale. Courses longer than two weeks are rare.

Complications (eg, secondary skin infection, hypocalcemia) may occur in older or compromised patients.

Management

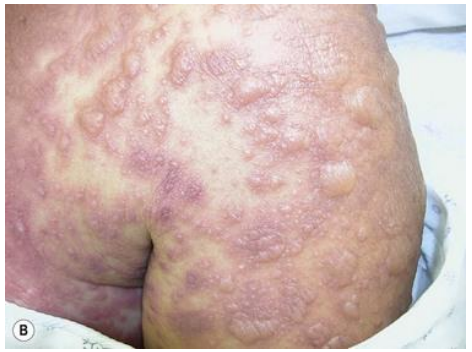
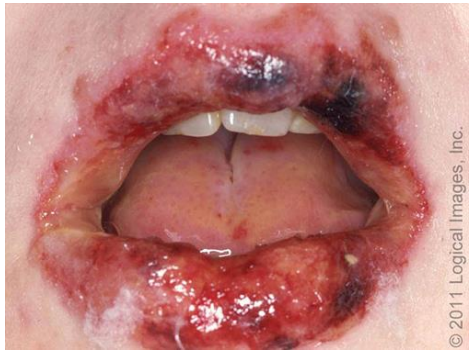
- Prompt withdrawal of the causative agent is the mainstay of treatment of AGEP.
- patients should be counseled to avoid the offending drug and be provided with a written list of the generic and brand names of the offending drug.
- For symptomatic relief of pruritus and skin inflammation, topical corticosteroids are suggested.

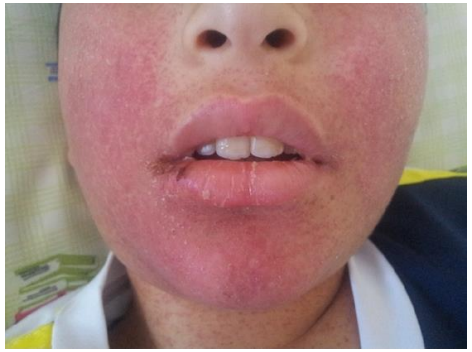
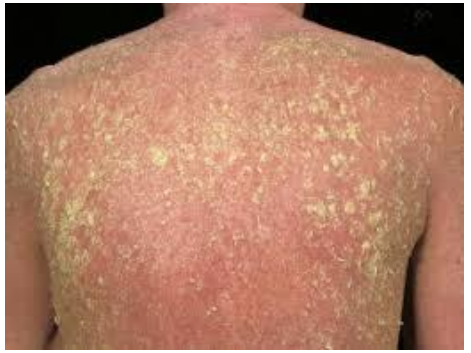
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)



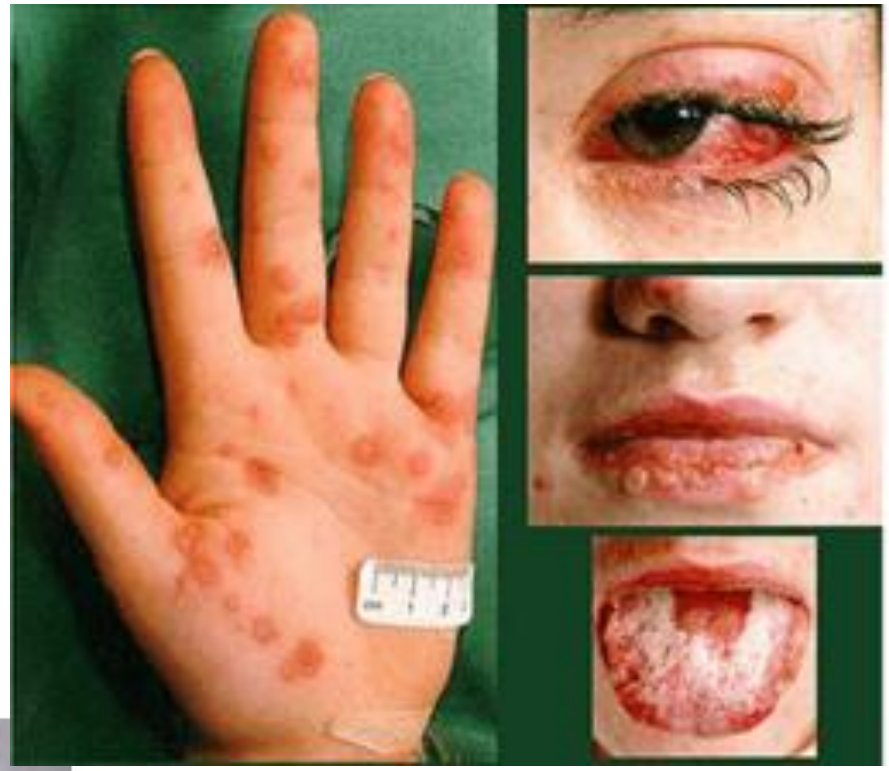
Clinical Presentation

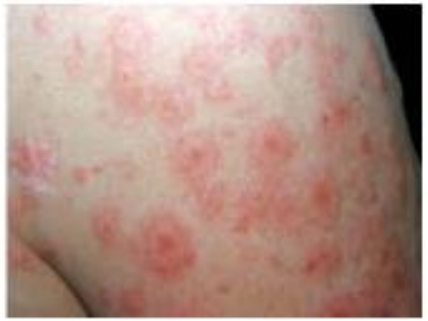
- Early signs of severe reaction
  - Evolution to erythroderma face and thorax before spreading to other areas and are symmetrically distributed
  - Fever >38°C (100.4°F)
  - Facial edema
  - Mucositis (oral, ocular (80%), and urogenital)
  - Skin tenderness
  - Blistering

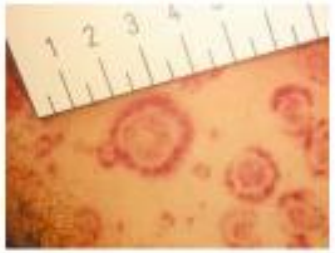



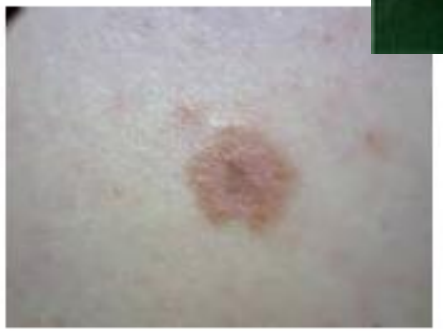



Targetoid lesion (SJS/TEN)









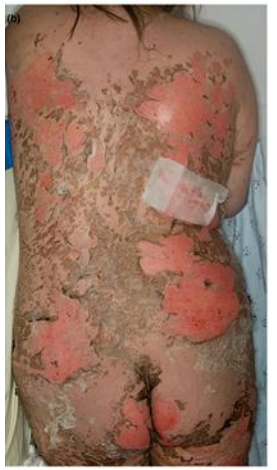
Laboratory abnormalities

- Hematologic abnormalities, particularly anemia and lymphopenia, are common in SJS/TEN. Eosinophilia is unusual; neutropenia is present in approximately one-third of patients and is correlated with a poor prognosis.
- Hypoalbuminemia, electrolyte imbalance, and increased blood urea nitrogen and glucose may be noted in severe cases, due to massive transdermal fluid loss and hypercatabolic state. Serum urea nitrogen >60 mg/dl and glucose >252 mg/dl are considered markers of disease severity

Histopathology

The hallmark of SJS/TEN is the keratinocyte necrosis, ranging from partial to full-thickness necrosis of the epidermis. In early lesions, apoptotic keratinocytes are scattered in the basal layer of the epidermis, but in established lesions, full-thickness epidermal necrosis and subepidermal bullae may be seen.

Clinical course



- The acute phase of SJS/TEN lasts 8 to 12 days and is characterized by persistent fever, severe mucous membrane involvement, and epidermal sloughing that may be generalized and result in large, raw, painful areas of denuded skin.
- Re-epithelialization may begin after several days and typically requires two to four weeks. Skin that remained attached during the acute process may peel gradually, and nails may be shed.

Risk factors

1. High risk medication
2. HIV,CMV and mycoplasma infection

- Genetic
- High doses of medications
- Underlying disease (malignancy (GVHD), SLE)
- Physical and environmental factors (UV, radiation)

Drugs associated with (SJS/TEN)

Strongly associated	Allopurinol, Lamotrigine, Sulfamethoxazole, Carbamazepine, Phenytoin, Nevirapine,Sulfasalazine, Other sulfonamides, Oxicam NSAIDs (piroxicam), Phenobarbital
Associated	Diclofenac, Doxycycline, Amoxicillin/ampicillin, Ciprofloxacin, Levofloxacin, Amifostine, Oxcarbazepine, Rifampin (rifampicin)
Suspected association/lower risk	Pantoprazole, Glucocorticoids, Omeprazole, Tetrazepam§, Dipyrone (metamizole), Terbinafine, Levetiracetam

Genetic

Drug type yielding increased risk of SJS/TEN	HLA type
Sulfonamides	HLA-A29, HLA-B12, HLA-DR7
Oxicam NSAIDs	HLA-A2, HLA-B12
Carbamazepine	HLA-B*15:02
Allopurinol	HLA-B*58:01

Assessment of drug causality

- For patients suspected to have SJS/TEN, the identification of the causative drug is essential because early withdrawal of the offending agent may improve the prognosis.

- In addition, the identification of the culprit drug is of paramount importance to prevent re-exposure in patients recovering from SJS/TEN.

Assessment of drug causality

- The assessment of drug causality is based upon detailed history and clinical judgement.
- Information about the drugs that are most frequently associated with SJS/TEN is helpful.
- An **algorithm of drug causality for epidermal necrolysis** (ALDEN) has been developed as a tool for rapid assessment of drug causality in patients presenting with SJS/TEN, particularly in those exposed to multiple medications.

ALDEN

- Each potentially offending drug is assigned a score from -11 to 10 based upon six parameters

1. Time delay from initial drug intake to onset of reaction
2. Probability of drug presence in the body on the index day
3. A previous history of exposure to the same drug, with or without reaction
4. Presence of the drug beyond the progression phase of the disease
5. Drug notoriety as a cause of SJS/TEN based upon previous studies
6. Presence or absence of other etiologic causes

❖The score is categorized as very probable (≥6), probable (4 to 5), possible (2 to 3), unlikely (0 to 1), and very unlikely (≤0)

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* 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* but liver or kidney function alterations or suspected drug interactions¶ are present	
	Excluded: −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life*, without liver or kidney function alterations or suspected drug interactions¶	
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 similarΔ drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similarΔ 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	−1 to 3
	Associated: 2	Drug with definite but lower risk according to previous case-control studies	
	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 with sufficient number of exposed controlsΔ	
		Intermediate score = total of all previous criteria	
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 to 1: unlikely; 2 to 3: possible; 4 to 5: probable; ≥6: very probable.

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; ATC: anatomical therapeutic chemical.

* Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance.

¶ Suspected interaction was considered when more than five drugs were present in a patient's body at the same time.

Δ Similar drug = same ATC code up to the fourth level (chemical subgroups).

Drug reaction with eosinophilia and systemic symptoms (DRESS)

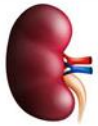
DRESS

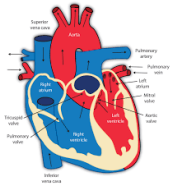
- DRESS is a severe adverse drug reaction characterized by an extensive skin rash in association with visceral organ involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis.

- The clinical presentation is heterogeneous, and the disease course is typically prolonged. Despite the cessation of the offending drug, flares of disease may continue to occur. The latency between drug initiation and onset of disease is prolonged, typically between two to eight weeks.
- Reactivation of latent human herpesvirus infections is a common observed phenomenon.

Organ involvement

- Liver
- Kidney
- Pulmonary involvement
- Cardiac involvment





Epidemiology

- DRESS is estimated to occur in 0.9 to 2 per 100,000 patients per year. In hospitalized patients, DRESS accounts for 10 to 20 percent of all cutaneous adverse drug reactions.

- DRESS may occur in children, although the incidence is likely to be lower than in adults.

- The risk of developing DRESS varies from drug to drug. For high-risk, antiseizure medications, the incidence of DRESS is estimated to be 1 in 1000 to 1 in 10,000 exposures.

Pathogenesis

- Drug-specific immune response
- Reactivation of Herpesviridae — Reactivation of viruses from the Herpesviridae family (eg, HHV-6, HHV-7, Epstein-Barr virus [EBV], cytomegalovirus [CMV]) is a known phenomenon associated with DRESS and occurs in up to 75 percent of patients

Etiology and risk factors

- Drug exposure: 80%, A large proportion of cases (approximately 75 percent) are due to a few high-risk drugs

- Pharmacogenetic susceptibility
  - HLA
  - Genetic polymorphisms

Drugs implicated in DRESS

High-risk drugs	▪ **Allopurinol** ▪ **Aromatic antiepileptic agents:,Carbamazepine, Phenytoin, Lamotrigine, Oxcarbazepine, Phenobarbital** ▪ **Sulfonamides: Sulfasalazine, Dapsone, Trimethoprim-sulfamethoxazole, Sulfadiazine** ▪ **Vancomycin, Minocycline, Nevirapine** ▪ **Antituberculosis agents: Rifampicin, Ethambutol, Isoniazid, Pyrazinamide, Mexiletine**
Lower-risk drugs	▪ Beta-lactams: Amoxicillin, Ampicillin, Piperacillin ▪ Others: • NSAIDs (celecoxib, ibuprofen, diclofenac), Olanzapine, Fluoxetine, Imatinib, Sorafenib, Vemurafenib, Omeprazole, and Raltegravir

HLA alleles associated with susceptibility to DRESS

Drug	HLA/genetic variant	Population
Allopurinol	B*5801	Han Chinese, European, Thai, Korean
Carbamazepine	A*3101	European, Japanese, Han Chinese
Dapsone	B*1301	Chinese
Nevirapine	DRB1*01:01	African, Asian, European
	CW*8, B14	European
	B*35	Asian

Assessment of drug causality

- Prolonged latency (2-8 weeks)
- Exposure to high-risk drugs
- Laboratory investigations: CBC, LFT, Sr Cr> 1.5 baseline, hematuria, proteinuria> 1 g/day
- Amylase, lipase ≥2 times the ULN
- Serology for viral infection:HHV-6, HHV-7, Epstein-Barr virus, cytomegalovirus
- Patch testing

Scoring system for the diagnosis of DRESS

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

Total score:

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

DRESS: drug reaction with eosinophilia and systemic symptoms; BSA: body surface area; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; ANA: antinuclear antibody.

Adapted from:

1. *Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007; 156:609.*
2. *Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169:1071.*

Management of SJS/TEN & DRESS

- **Drug withdrawal** the identification and withdrawal of the causative medication is the mainstay of treatment
- **Supportive treatment:** fluid, electrolyte, and nutritional support. Adjunctive measures include gentle skin care with emollients and warm baths/wet dressings.
- **and monitoring**: Regular clinical, laboratory, and imaging monitoring and timely consultation with specialists (eg, hepatologist, nephrologist, pulmonologist) are warranted.

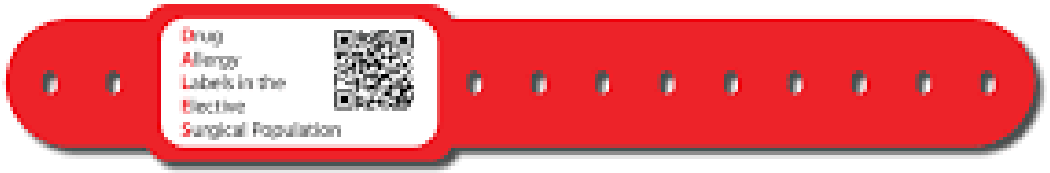
Treatment

- Systemic glucocorticoids
- Second line therapy:
  - Cyclosporine
  - IVIG
  - Other immunosuppressive agents (Tofacitinib)

Prevention

- Patients who recover from DRESS or SJS/TEN should be educated about the need for strict avoidance of the offending drug and cross-reacting drugs. Moreover, as DRESS survivors may have an increased risk of reaction to structurally unrelated drugs in the months following the acute episode, **avoidance of any unnecessary drug** treatments is also recommended.
- Drug allergy labeling needs to be entered in the patient's medical record.

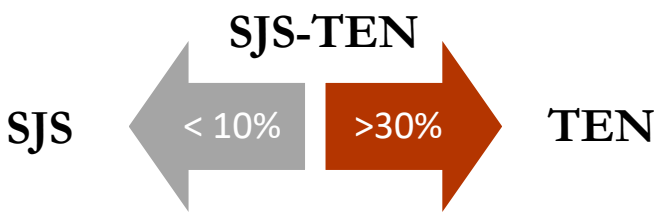
Drug allergy labeling



Prevention

- Avoidance
- Premedication
  - **Premedication with corticosteroids and antihistamines is NOT recommended for the prevention of exanthematous drug eruption in sensitized patients.**
- Desensitization
  - Only established in the management of ***immediate-type* hypersensitivity reactions**
  - *Little evidence* for T cell-mediated delayed-type reactions

Clinical Presentation



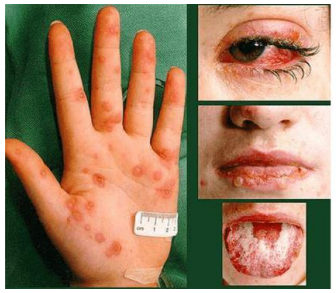
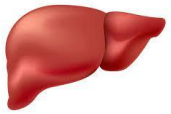
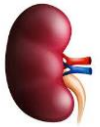


Table 2. Features of Selected Severe Cutaneous Adverse Reactions to Drugs.

Feature	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis (SJS–TEN)	Acute Generalized Exanthematous Pustulosis (AGEP)
Clinical features			
Rash	Widespread rash (involving >50% of body-surface area), often exanthematous, and very inflamed; may have other morphologic features, including erythroderma; facial edema and erythema; exanthematous eruption may become purpuric, especially on lower legs	Severe, acute blistering; initially, rash may be macular erythema or exanthematous eruption and trunk lesions predominate; individual lesions may include "spots" and flat, atypical target lesions but not true target lesions characteristic of erythema multiforme, which is not usually drug-related; Nikolsky's sign (ready removal of the epidermis with slight tangential pressure); diagnosis depends on extent of epidermal necrosis according to body-surface area: 10 to 30% in SJS–TEN versus less than 10% in SJS and more than 30% in TEN	Rapid evolution (over a period of hours) of sterile, nonfollicular pustules on erythematous swollen skin; accentuation of rash in body folds; facial edema
Mucosal involvement	Mucosal involvement infrequent	Mucous membranes nearly always involved with blisters and erosions	Mucosal involvement rare
Onset of rash	Onset of rash often >14 days after first dose of drug, especially in the case of antiepileptic agents; for most other drugs, onset 4 to 21 days after first dose	Onset 4 to 21 days after first dose of drug	Initial onset (<3 days) after first dose of an antibiotic but slower onset with other drugs
Other features	Temperature >38.5°C, malaise, lymphadenopathy, involvement of at least one internal organ: liver (in >80% of cases), kidney, muscle, lung, heart, pancreas	Temperature >38.5°C, malaise, sore throat, dysphagia, dysuria, or photophobia initially	Temperature >38.5°C

Summary

- Antibiotics and anticonvulsants are among the most common drugs associated with maculopapular rash.
- Diagnosis in mainly based on clinical presentation.
- Patients with alarm signs and symptoms must be referred for comprehensive care.
- Treatment include withdrawal, topical corticosteroids, and oral antihistamines.

Drug Saf - Case Rep (2017) 4:1
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CASE REPORT

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with Teicoplanin: A Case Report

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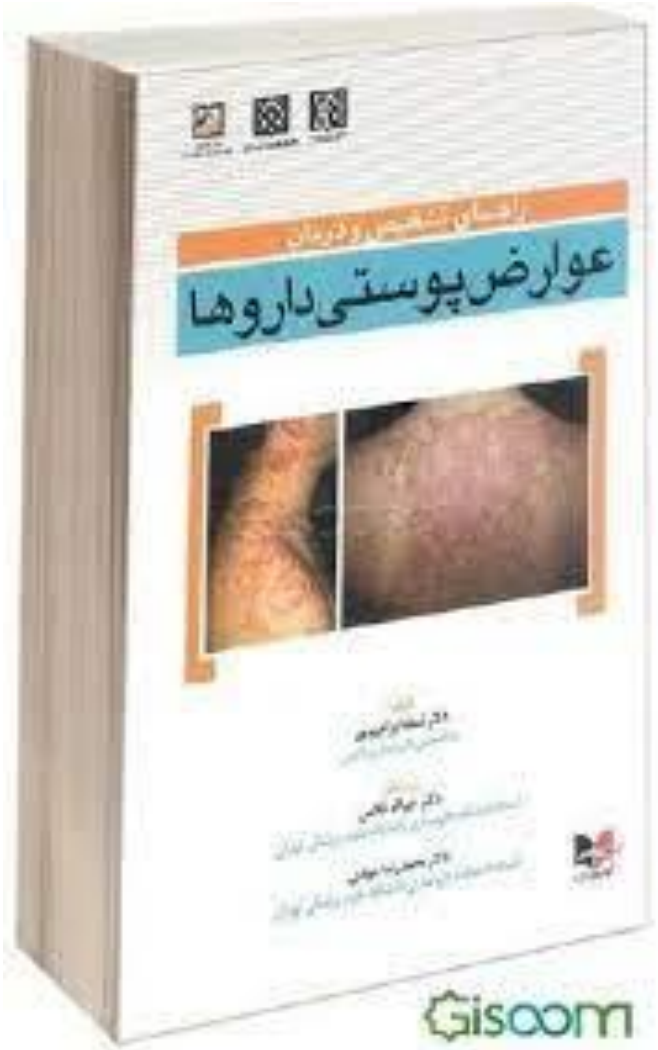
عوارض پوستی داروها
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