

# Drug eruptions

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5% of all dermatoses

15% of drug side effects

- skin changes
- mucosal involvement
- pruritus
- paraesthesia, pain

# Classification of drug reactions

According to the time of onset of symptoms

- early (up to 1 hour)
- late (over 1 hour from the application of the drug)

# **Hypersensitivity drug exanthema**

## **According to the involvement of immune mechanisms**

- allergic:
  - antibody mediated
  - cell mediated
- non-allergic
  - drug interaction with immune receptor of p-i concept cells
  - pseudo allergic - anaphylactoid - no sensitization required



# Allergic reactions according to Coombs and Gell

Type I.	Anaphylactic - IgE antibodies urticaria (nonsteroidal antirheumatic drugs)
Type II.	Cytotoxic - antibody dependent thrombocytopenic purpura
Type III.	Immunocomplex drug vasculitis
Type IV.	T cell mediated IVa allergic contact dermatitis IVb DRESS, maculopapular rash IVc TEN, fixed drug rashes IVd AGEP

# **Hypersensitivity drug rashes**

## **According to the mechanism of cell activation**

- reaction triggered by a hapten-carrier complex
- reaction based on the pharmacological interaction of the drug with cell immune receptors
- pseudoallergic reaction resulting from stimulation or inhibition of inflammatory cell receptors and enzymes

# Hypersensitivity drug rashes

## According to severity

- mild reactions
- severe, life-threatening reactions with possible organ involvement (anaphylactic shock, SCARs)

# Drug rashes from other causes

- Overdose
- Cumulation
- Pharmacological side effects
- Drug interactions
- Microbial imbalance – dysmicrobia

## Clinical signs

- Exfoliative erythroderma
- Haemorrhagic coumarin necrosis
- Alopecia diffusa toxica
- Acneiform eruptions
- Provocation of skin diseases
- Pigmentation (amiodarone)

# History and diagnosis of drug rashes

## *History:*

- **Drugs** – targeted questions on: medications, vitamins, contraception, sedatives, laxatives, hypnotics, analgesics, inhalation, anaesthesia, external medications
- **Complementary and alternative medicine, self-medication**
- **Food influences** – ask about: dyes, fragrances, flavours, preservatives, tonics, artificial sweeteners
- **Previous drug reactions**
- **Exposure** - whether the substance (or a similar substance) has been administered in the past
- **Timing** – onset of rash and administration of the drug (5-10 days from commencing the drug)

*Exclusion of other causes* - other dermatoses, skin manifestations infectious and systemic diseases

# History and diagnosis of drug rashes

*Elimination test* – regression confirms the diagnosis

*Reexposure test* – recurrence confirms the diagnosis

*Laboratory tests:*

- **In vivo:**
  - Intradermal (scarification) in anaphylactic type I reactions
  - Epicutaneous in a type IV hypersensitivity reaction (fixed drug rash)
- **In vitro:**
  - RAST (penicillin)
  - Other: lymphocyte transformation test, etc.

*When more than one drug is given at the same time, the drug likely responsible is:*

- The drug with a higher risk of rash
- The drug administered last











# Drug rashes

## according to clinical findings

- **maculopapular**
- urticaria
- lichenoid ( $\beta$ -blockers, gold)
- acute generalised exanthematous pustulosis (terbinafine)
- papulopustular - acneiform (iodine, bromine, steroids)
- purpura
- fixed erythema - rash (barbiturates, sulfonamides)
- erythema nodosum (hormonal contraceptives, sulfonamides)
- photosensitivity reactions (thiazide diuretics, doxycycline, methotrexate)



















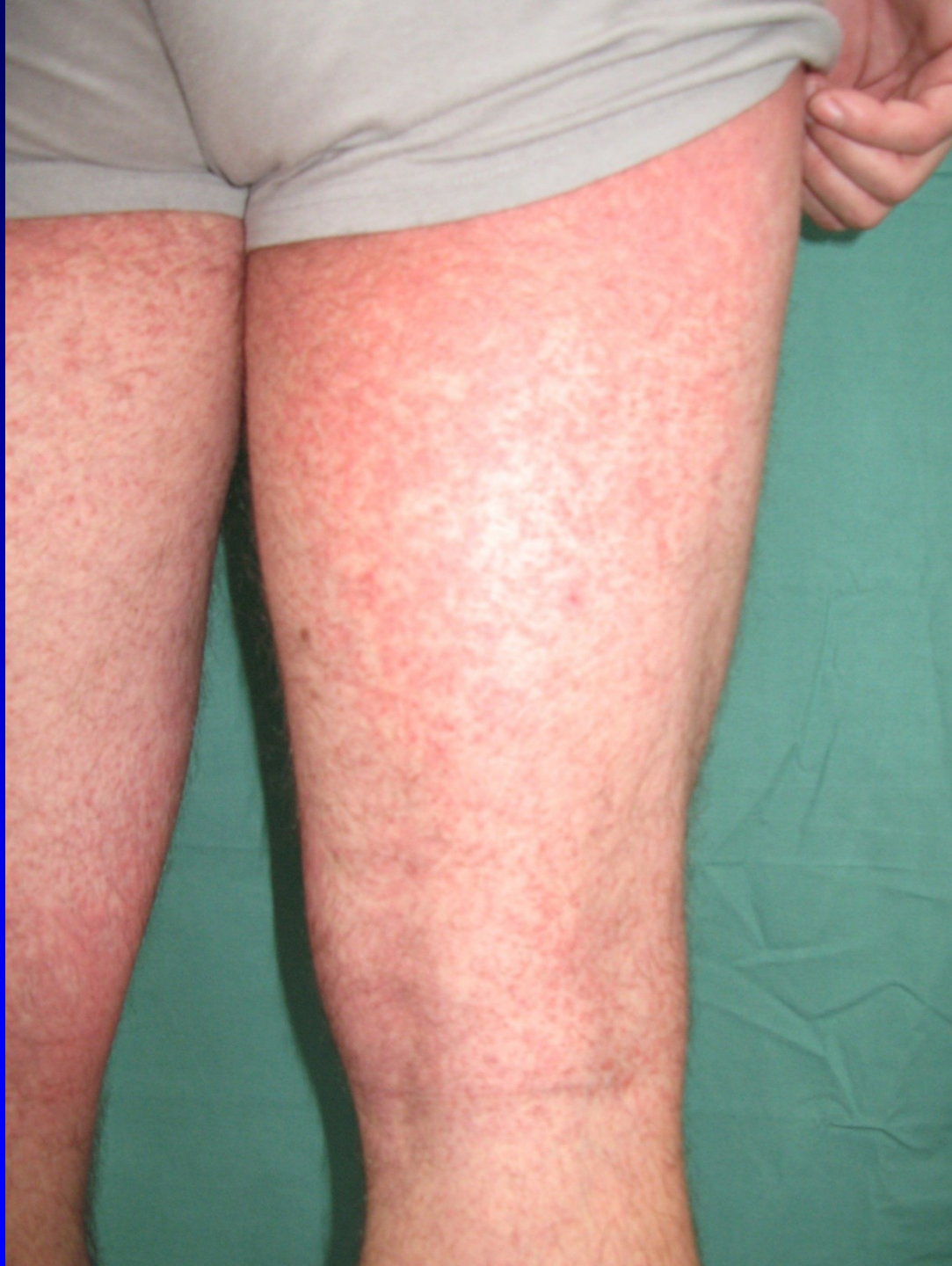












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Maculo-urticarial  
(penicillin)













# Drug rashes

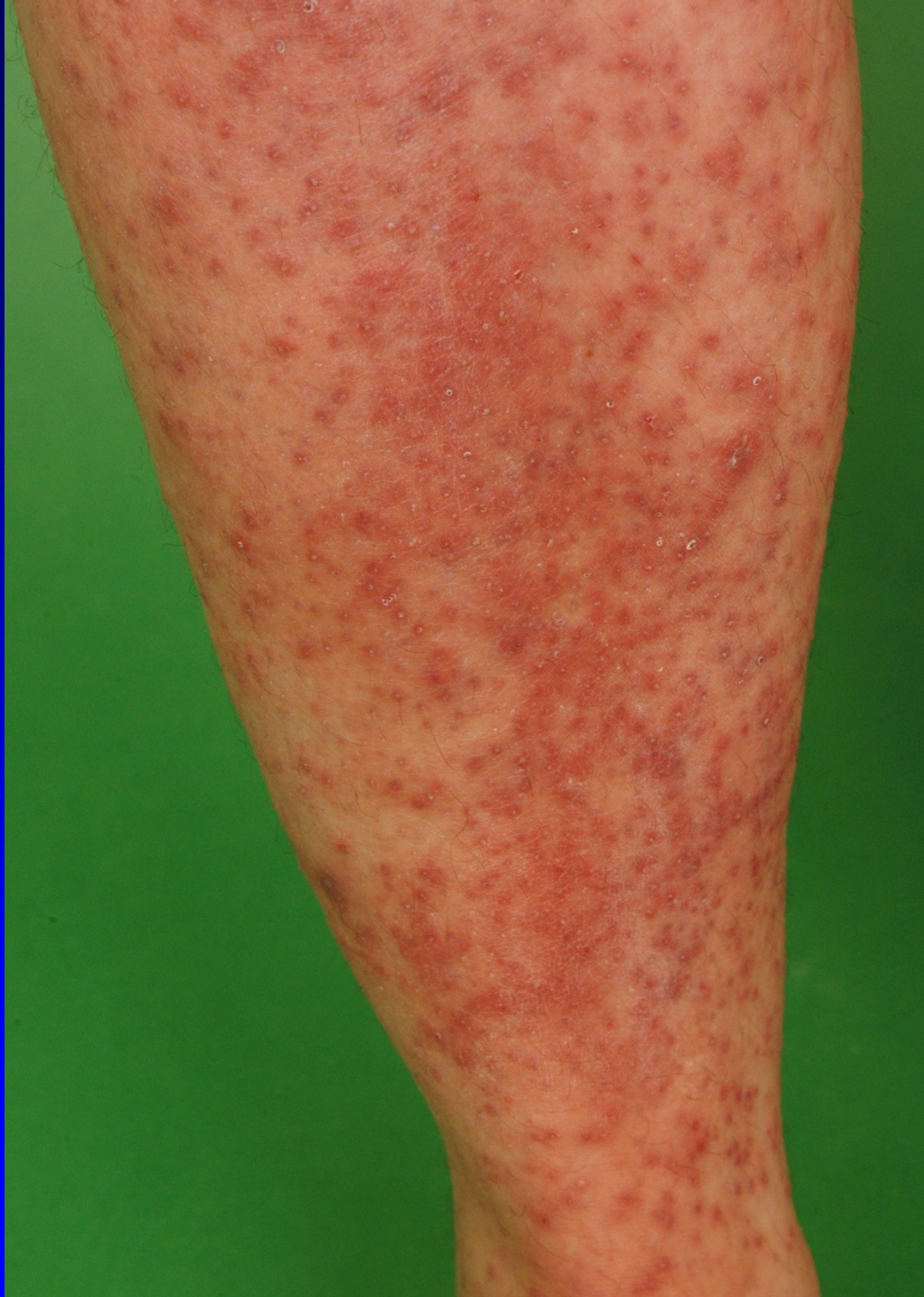
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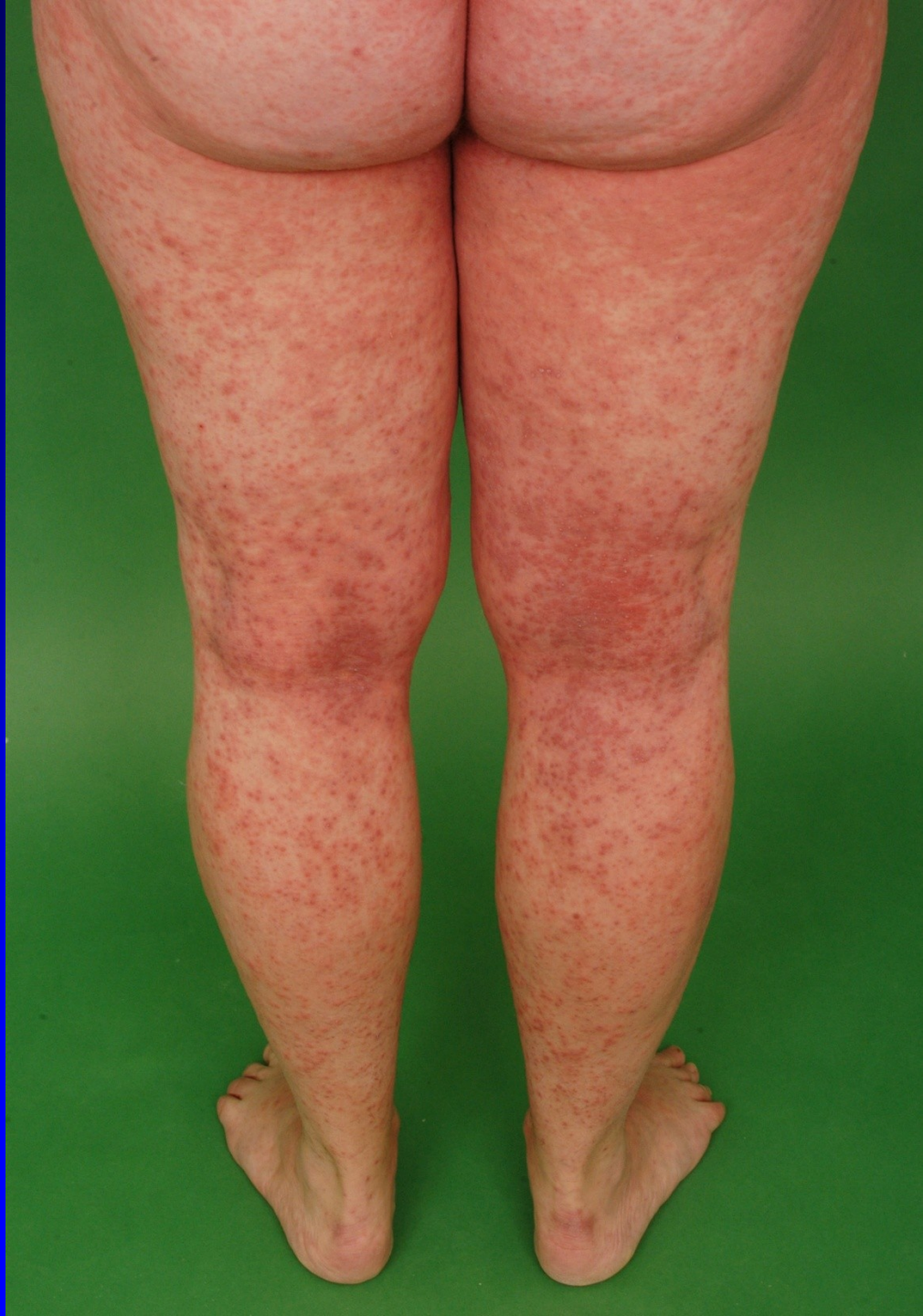












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# Erythema nodosum

Multifactorial etiology:

- infections, drugs, sarcoidosis, others

Allergic reactions - II. type

- IV. type tuberculin

Most common: contraceptives, sulfonamides







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# Erythema multiforme

- multifactorial etiology: infections, drugs, neoplasia, autoimmune disease, idiopathic
- forms: **minor**
  - target lesions
  - up to 2 cm in size
  - symmetrical in acral distribution
  - most commonly HSV
  - mortality 0









- major** - target lesions with blisters
- acral distribution and torso
- blisters < 10 % surface
- most commonly HSV, mycoplasma
- mortality 1 %











# Stevens-Johnson Syndrome (SJS)

- atypical target lesions
- primarily the torso
- blisters < 10 % surface
- mucosal involvement
- possible systemic symptoms
- most commonly drugs
- mortality 6 %











# Toxic epidermal necrolysis (TEN, Lyell's syndrome)

- cell-mediated cytotoxic immune response directed against epidermal antigens with high TNF  $\alpha$  production → keratinocyte necrosis
- drug (metabolite) binding to keratinocytes
- necrosis of the entire epidermis

# Transitional form SJS / TEN

- atypical target lesions
- mucosal involvement
- blisters 10 - 30%
- systemic symptoms
- mortality 25 %



# TEN

- rapidly merging erythema
- linear separation of the epidermis
- positive Nikolsky phenomenon
- mucosal involvement
- severe general condition (fever, impaired consciousness, glomerulonephritis, pneumonia and hepatitis)
- mortality 40% (septicemia, gastrointestinal bleeding, renal failure, electrolyte imbalance)















# TEN

## most commonly triggering drugs

- sulfonamides
- trimethoprim - sulfamethoxazole
- carbamazepine
- phenytoin
- phenobarbital
- non-steroidal anti-inflammatory drugs
- allopurinol
- aminopenicillins



# Differential diagnosis of severe drug eruptions

Disease	Location	Target lesions	Mucous membranes	blisters % surface	mortality %
EM minor	acral	typical		0	0
EM major	acral, torso	typical	+	< 10	1
SJS	torso	atypical	++	< 10	6
SJS/TEN	torso	atypical	++	10-30	25
TEN	torso	atypical	++	> 30	40

EM = Erythema multiforme

SJS = Stevens-Johnson syndrome

TEN = Toxic epidermal necrolysis

# Conclusion

- Drug rashes are usually mild, but in rare instances can be life-threatening (with mucosal involvement and organ failure)
- Drug rashes occur most often within a few days of starting a new drug, but sometimes even after weeks or months of use
- In addition to drugs, other potential triggers - food, vitamins, food supplements, herbal preparations, self-medication and infectious diseases should be considered.