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Cutaneous adverse drug reactions

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Abstract

Adverse drug reactions may be defined as undesirable clinical manifestations resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects, and unanticipated adverse manifestations. Adverse drug effects on the skin are among the most frequent reactions and, according to a study, account for approximately 14% of all adverse drug reactions. However, the incidence of cutaneous adverse effects in general population is unknown. Systemic drug administration results in various cutaneous adverse reactions, and medications used in the treatment of skin diseases themselves have their own adverse effects. Adverse drug reactions include a wide range of effects, from harmless exanthema of short duration, urticaria to systemic cutaneous reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis. Exanthematous eruptions and urticaria are the two most common forms of cutaneous drug reactions. Less common include fixed eruptions, lichenoid, pustular, bullous and vasculitis reactions. The most severe cutaneous and mucosal adverse drug reactions are epidermal necrolysis, which is usually drug-induced, DRESS syndrome, and acute generalized exanthematous pustulosis. Therefore, the diagnostic of adverse drug reactions requires a detailed history of drug intake and development of skin disorders, excellent knowledge of clinical presentations for a wide range of drug-induced skin reactions as well as of the very medications being taken by patients. In addition to details on drug intake, it is necessary to learn about taking herbal and alternative preparations, which may also cause adverse reactions. A drug started within 6 weeks of the development of disorders is considered the most common cause of adverse reaction, as well as drugs taken periodically but regularly. Once a reaction has occurred, it is important to prevent future similar reactions with the same drug or a cross-reacting medication. Early withdrawal of all potentially responsible drugs is essential, particularly in case of severe drug reactions.

Key words

Dermatology; Drug Therapy + adverse effects; Drug Eruptions; Drug Toxicity; Skin Diseases + etiology + therapy

Cutaneous adverse drug reactions are among the most frequent reactions and, according to one study, they account for approximately 14% of all adverse drug reactions. Although information on the incidence of cutaneous adverse effects in general population are unknown, a large prospective study has shown that 2.7% of 48.000 hospitalized patients had cutaneous adverse drug reactions, and Roujeau and Stern have estimated that 1 of 1.000 hospitalized patients had a severe cutaneous adverse drug reaction. In pre-marketing studies, the incidence of adverse reactions is 0.1%-1%, but only in the post-marketing period and after administration of the drug in large patients' series the real incidence can be estimated (1-7). For instance, in a study including 13.697 patients who were examined by a general practitioner, 2.1%, 1.6% and 1.1% had trimetoprim-sulfametoxazol-induced, fluoroquinolone-induced and penicillin-induced cutaneous adverse reactions, respectively (5). This corresponds with the estimation that adverse reactions are caused by antibiotics in 1-5% of patients (1-7). Adverse reactions have also been established to develop more commonly in females and human immunodeficiency virus (HIV) patients, and the incidence has been shown to increase with age and the number of medicines being taken by the patient, but

there is a controversy whether atopic diathesis increases the probability of adverse drug reactions (1-7).

Systemic drug administration results in various cutaneous adverse reactions, and medications used in the treatment of skin diseases themselves have their own adverse effects. Adverse drug reactions include a wide range of rashes, from harmless exanthematous eruptions of short duration and urticaria to systemic cutaneous reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis. Therefore, the diagnosis of an adverse drug reaction requires a detailed history of drug intake associated with skin disorders, an excellent knowledge of clinical presentations for a wide range of drug-induced skin reactions, as well as the history of drug intake by each patient. In addition to details on drug intake, it is necessary to learn about taking herbal and alternative medicine preparations which may also cause adverse reactions. A drug started 6 weeks before the development of reactions is considered the most common cause of adverse reaction, as well as drugs taken periodically but regularly (1-7). This period is significantly longer when drug-induced lupus or pseudolymphoma develops.

Revuz et al. classified cutaneous drug reactions based on their pathogenesis - from drug-induced pharmacologic adverse effects almost inevitably associated with desired effects due to the very mechanism of their action, manifestations of drug overdose to various immune-mediated and idiosyncratic skin reactions with possible underlying immune mechanisms (1). The most severe cutaneous and mucosal adverse drug reactions are epidermal necrolysis, which is almost always drug-induced, DRESS syndrome and acute generalized exanthematous pustulosis.

Table 1 shows the classification of adverse drug reactions: from drug-induced pharmacologic adverse effects almost inevitably associated with desired effects due to the very mechanism of its action, manifestations of drug overdose to various immune-mediated and idiosyncratic skin reactions with possible underlying immune mechanisms. The most severe cutaneous and mucosal adverse drug reactions include epidermal necrolysis, which is almost always drug-induced, DRESS syndrome and acute generalized exanthematous pustulosis.

Table 2 shows expected cutaneous adverse drug reactions.

Table 1. Classification of cutaneous adverse drug reactions*

Cutaneous adverse drug reactions	
Expected	Overdose
	Pharmacologic adverse effects
	Cumulative toxicity
	Delayed toxicity
	Drug interactions
	Metabolic disorders
	Disease exacerbation
Immune-mediated hypersensitivity reactions	IgE-mediated
	Cytotoxic
	Immune complex-mediated
	Cell-mediated
Idiosyncratic (probably by an immune mechanism)	DRESS syndrome
	Toxic epidermal necrolysis/Stevens-Johnson syndrome
	Drug reactions in HIV infection
	Drug-induced lupus

IgE, immunoglobulin class E; DRESS, drug rash with eosinophilia and systemic symptoms; HIV - human immunodeficiency virus

*adjusted from Revuz et al. (1)

Table 2. Expected cutaneous and mucosal adverse drug effects

Adverse effects	The most common cases
Pharmacologic adverse effects	Cyclosporine-induced gingival hyperplasia and hypertrichosis
	Chemotherapy-induced alopecia and mucositis
	Retinoid-induced cutaneous and mucosal xerosis
	Epidermal growth factor receptor (EGFR) inhibitor-induced acneiform eruptions
Cumulative toxicity	Skin hyperpigmentation and discoloration secondary to minocycline and amiodarone
Delayed toxicity	Development of actinic keratoses, palmoplantar keratoses and planocellular carcinoma following arsenic exposure
	Accelerated skin aging, premature skin aging secondary to sunlight and skin cancer in long-term (>12 weeks) voriconazole administration
Metabolic drug effects	Bexarotene: hypertriglyceridemia and xanthomas
	Isoniazid: pellagra-like disorders
Exacerbation of skin diseases	Androgens and corticosteroids: development and acne exacerbation
	Beta-blockers, lithium, interferon-α, tumor necrosis factor
	TNF-α inhibitors: exacerbation of psoriasis

EGFR, epidermal growth factor receptor; TNF-α, tumor necrosis factor α

Immune-mediated and idiosyncratic cutaneous and mucosal reactions

Drug-induced rashes

Drug-induced morbilliform and maculopapular rash accounts for 95% of all drug-induced cutaneous reactions (1-7). Rash develops in the form of small erythematous macules with 2-3 mm in diameter (morbilliform rash) or up to 5 mm in diameter, including formation of papules (maculopapular rash) that may have a sporadic pattern on the trunk and symmetrically expand to upper and lower extremities (Figure 1).

T-cell immune response with drug-specific T-cell proliferation underlies the development of drug-induced rashes (8, 9). Rashes develop within 4-14 days of drug intake and resolve slowly following drug discontinuation, sometimes with subsequent residual hyperpigmentation and desquamation (1-9). Table 3 shows the most common causes of rashes.

Rash is a manifestation of the DRESS syndrome, but may also precede toxic epidermal necrolysis

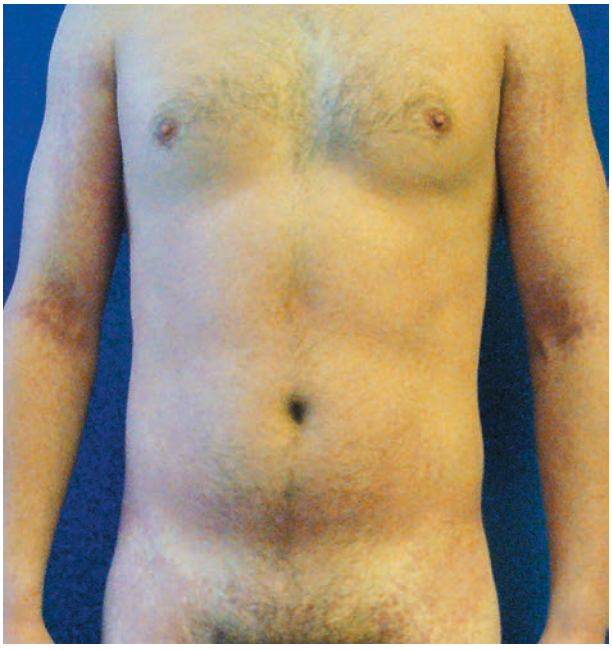

Figure 1. Ampicillin-induced rash

Table 3. The most common inducers of exanthematous drug rash (>3% patients)

Drug
Aminopenicillins
Sulphonamides
Antiepileptic agents
Ceohalosporins

and acute generalized exanthematous pustulosis. Considering that late T-cell-mediated immune response underlies the pathogenesis of these reactions, their clinical presentation depends on the intensity of the immune response and the prevailing effector mechanisms, development of regulatory mechanisms, and mechanisms of resolution of immune reactions (8, 9).

If rash develops, the possible relation to a drug and the chronology of drug intake should be examined using history details. Differential diagnosis includes bacterial and viral infections and some of the systemic diseases of the connective tissue. Of all rashes in children, 10-20% are drug-induced, while in adult patients 50-70% of rashes are drug induced (1,3-6). The risk of developing aminopenicillin (ampicillin, amoxicillin)-induced rash increases in patients with infectious mononucleosis from 3-7% to 60-70%. There is a similar drug-virus interaction also in HIV patients treated with sulphonamides (1-7).

There are several *in vitro* tests used to confirm drug-induced reactions such as: migration-inhibitory factor test, lymphocyte toxicity assay, lymphocyte transformation test and basophils degranulation assay. The sensitivity and specificity of these tests have not been sufficiently evaluated, so they are not completely reliable in clinical settings. In amoxicillin-induced morbilliform rashes, prick and late-reading (20 minutes, 24 hours and 7 days later) tests as well as epicutaneous tests are useful to confirm drug hypersensitivity (1-5, 8, 9). However, these tests lead to very heterogeneous results in other drugs, so their role in the diagnosis of adverse drug reactions has not been confirmed, first and foremost because of their low specificity and sensitivity. If the results turn positive, they may be useful since patients may be advised to avoid the drug causing such reaction. However, if results are negative, the possibility of drug hypersensitivity may not be ruled out (1-5, 8, 9).

If a drug-induced rash is suspected, the first step is to exclude the drug from the treatment. Skin lesions that resolve following the discontinuation of the drug may confirm the idea that rash was drug-induced. The drug introduced in the previous 2-3 weeks (up to 6 weeks) is excluded first and, in patients taking several drugs, any unnecessary medications should be excluded, and the medication considered the least possible cause of the reaction should be reintroduced first. Discontinuation of drugs should always be weighed against the patients' general condition and their need for a specific treatment, and the drugs to be replaced or discontinued should be estimated in cooperation with other specialists participating in the patient's treatment. If a drug is necessary and it may not be replaced, a treatment may be introduced to relieve hypersensitivity reactions without discontinuing the drug, provided the reaction has not spread and there are no signs of developing severe drug reactions. Following the discontinuation of the drug, supportive treatment may be introduced, based on the administration of topical corticosteroids for itching and, if necessary, only briefly, systemic corticosteroids and antihistaminic agents, although there have been no controlled studies to confirm the significance of systemic corticosteroid therapy in the treatment of drug-induced rash (1-5, 8, 9).

Urticaria, angioedema and anaphylaxis

Urticaria/angioedema is drug-induced in approximately (or at least) 10% of patients, with most of them having acute urticaria where the disease has lasted less than 6 weeks (1-5, 10, 11). The development of drug-induced urticaria and angioedema is most commonly a manifestation of mast cell degranulation, although there are non-mast-cell-mediated urticarial reactions. The principal mediators for these reactions

are histamine and prostaglandins released through the mast cell degranulation. The main characteristic of urticaria is development of transient erythematous and edematous papules and plaques which resolve in several hours but develop at other sites, with individual disorders that last not longer than 24 hours. The reaction sometimes presents with deep elastic edemas, angioedemas, isolated and without urticaria or associated with urticaria. Edema and exudation of the laryngeal, respiratory and gastrointestinal tract mucosa result in hoarseness, rhinorrhea, bronchospasm, nausea, vomiting and diarrhea, in some patients causing hypotension, tachycardia, disturbed consciousness and anaphylaxis. Anaphylaxis occurs in 1 of 5.000 cases exposed to penicillin and develops as anaphylactoid reaction with administration of radiocontrast agents (1-5, 10, 11).

Some drugs result in mast cell degranulation without the immune mechanism, whereas other drugs cause mast cell degranulation through specific IgE antibodies created at the very first contact with the drug and through the development of a specific immune reaction to the drug – an early IgE antibody-mediated hypersensitivity reaction (Table 4) (1-5, 10, 11).

Drugs most commonly cause urticaria/angioedema through an early IgE antibody-mediated hypersensitivity reaction (allergic IgE-mediated urticaria) are antibiotics, and in the era of treatment with monoclonal antibodies recognized by the body as foreign proteins, the frequency of acute urticarias will be more and more increasing due to reactions to this drug group. When diagnosing IgE-mediated drug reactions, prick tests showed as useful as well as IgE blood tests. Anyhow, prick tests bear the risk of anaphylactic reactions, so they are only performed by experienced doctors. On the other hand, blood tests for drug IgE antibodies are also useful to confirm the drug reaction if done within the first 6 months following the drug reaction, but so far there is a very small number of drugs for which there are commercially available tests (1-5, 10, 11). The most available tests are the ones used to determine IgE antibodies against penicillin, ampicillin, amoxicillin, cephalosporins, insulin, sulfametoxazole, less frequently against erythromycin and tetracyclines. Although clinicians too often attribute rash to drug reactions and recommend drug avoidance, it has been shown that only 10-20% of patients really had a genuine allergic reaction to penicillin in spite of everyone stating to have been allergic to penicillin. Therefore, in patients in need for penicillin treatment, prick test should be performed. If less than 6 months elapsed since the reaction to penicillin, IgE blood test is also useful (1-5, 10, 11).

Table 4. Agents causing urticaria and angioedema

Type of urticaria	Agents most commonly causing a reaction
Allergic autoimmune urticaria/angioedema/anaphylaxis	Penicillin
	Cephalosporins
	Sulphonamides and other sulpha group
	preparations
	Tetracyclines (minocycline)
Non-immunological direct mast cell degranulation	Opiates (codeine), contrast agents, vancomycine, relaxants, polymyxin B, dextran
Non-immunological-pseudoallergens	Aspirin, other NSAIDs
Non-immunological orofacial angioedema/urticaria	ACE inhibitors
Non-immunological contact urticaria	Sorbic and benzoic acid in the eye drops
Non-immunological systemic capillary leak syndrome	Interleukin-2

NSAIDs, nonsteridal antiinphlammatory drugs; ACE, angiotensin-converting enzyme

Opiates cause degranulation without an immune mechanism, by binding to opiate receptors on mast cells. As a pseudoallergen, aspirin causes exacerbations in 30% of patients with chronic urticaria, and in some patients, pseudoallergen-free low salicylate diet may result in improvement of symptoms or remission (1-5, 10, 11). However, aspirin and other pseudoallergens are quite less commonly the only causes of urticaria. According to an accepted hypothesis, pseudoallergens cause urticaria by affecting the metabolism of arachidonic acid, directing it from prostaglandins to the production of leukotriene, which (as it has beem shown) may cause urticaria following intradermal administration by affecting blood vessels, whereas prostaglandins inhibit mast cell degranulation.

ACE (angiotensin converting enzyme) inhibitors most commonly cause orofacial angioedema with or without urticaria, without involving mast cells, by inhibiting endogenous kininase reducing bradykinin degradation, which has a vasodilatory effect and increases vascular permeability. Bearing in mind the fact that this is the very mechanism by which they lower the blood pressure, this effect of ACE inhibitors may be considered as pharmacological adverse effect. Anyhow, the role of bradykinin in the development of ACE inhibitor-induced angioedema has not been shown yet. This reaction to ACE inhibitors is often overlooked since it may develop for the first time even a year following drug intake (1-5, 10, 11).

When interleukin-2 is administrated, a systemic capillary leak syndrome or Clarkson's syndrome occurs relatively often. The syndrome is caused by a massive leakage into tissues and is often accompanied by angioedema, severe hypertension and anaphylaxis-like vascular collapse that may be life threatening. This reaction is a significant limitation to a wider use of this therapy in cancer treatment (melanoma, renal carcinoma) (1-5, 10, 11).

Drug-induced fixed erythema

Fixed erythema (fixed drug eruption) presents as a solitary erythematous bright or dark erythematous macule, that sometimes evolves into plaque when a pronounced erythema develops, at times having a central bulla with subsequent eroded area (Figure 2). Febricity occurs less frequently. Following drug discontinuation and resolution of the disorder, a long-lived greyish hyperpigmentation remains. If the drug is reintroduced, the disorder develops at the same site. Less commonly, a generalized fixed erythema may asymmetrically develop at several sites on the body (1-7).

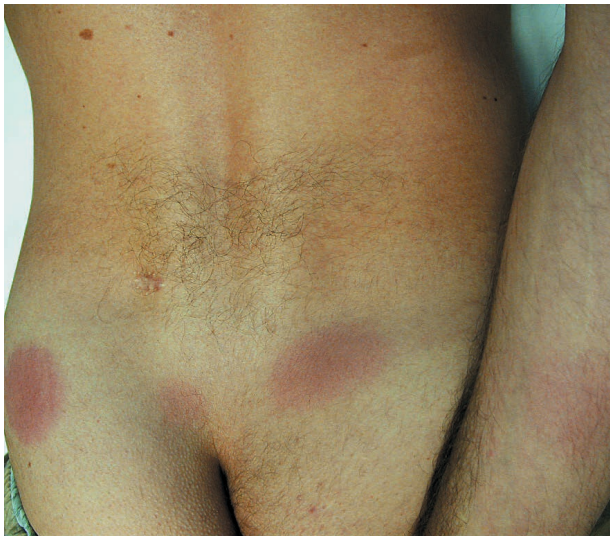

Figure 2. Erythema fixum caused by trimetoprim-sulfametoxazol

Table 5. Agents most commonly causing fixed drug eruption

Drug
Sulphonamides
Ibuprofen
Naproxen
Tetracyclines

Fixed eruption always develops as a drug reaction, occurring 30 minutes to 16 hours after drug intake. Table 5 shows the agents most commonly causing fixed erythema.

Serum sickness-like reaction and drug-induced vasculitis

Some drugs such as cefaclor, cefprozil and bupropion may cause a serum sickness-like reaction, with febricity, lymphadenopathy and eosinophilia, and onset of urticaria and/or rash and arthralgia following 1-3 weeks after the initiation of the treatment. Unlike real serum sickness, there is no renal impairment, immune complex impairment or complement consumption or development of vasculitis (1-7).

Palpable purpura with a histopathological substrate of leukocytoclastic vasculitis may be caused by numerous drugs, most commonly within 7-21 days from the initiation of the treatment. Drug-induced vasculitis develops in 10-15% of cases of cutaneous necrotizing vasculitis (Table 6). As in idiopathic cutaneous necrotizing vasculitis, the eruptions develop on lower extremities, spreading to the trunk and less frequently to upper extremities (Figure 3). Following initial purpura, some disorders develop into bullae, ulcers and nodes, Raynaud's phenomenon or even digital necrosis. At the same time, the same vasculitic process can affect the liver, kidneys, gastrointestinal tract and CNS as well, with fatal consequences. Considering the fact that presence of p-ANCA (perinuclear antineutrophil cytoplasmic antibodies) antibodies was also shown in drug-induced vasculitis, a differential diagnosis of autoimmune systemic vasculitis may be very difficult. Sometimes the presence of eosinophils in a tissue may indicate a possible drug triggering the reaction (1-7, 13).

Drug-induced lichenoid reaction

Drug-induced lichenoid eruption is difficult to be clinically differentiated from idiopathic *lichen planus*, but skin changes are usually more widespread and most commonly there are no mucosal changes in the

Table 6. The most common agents causing cutaneous necrotizing vasculitis

Agent
Propylthiouracil/other antithyroid drugs
TNF blockers
COX-2 inhibitors
G-CSF
Hydralazine
Leukotriene inhibitors
Minocycline
NSAID
Penicillins
Quinolones
Serum reactions and antithymocyte globulin
Streptokinase

TNF, tumor necrosis factor; COX, cyclo-oxygenase; G - CSF, granulocyte colony-stimulating factor; NSAIDs, nonsteridal antiinphlammatory drugs

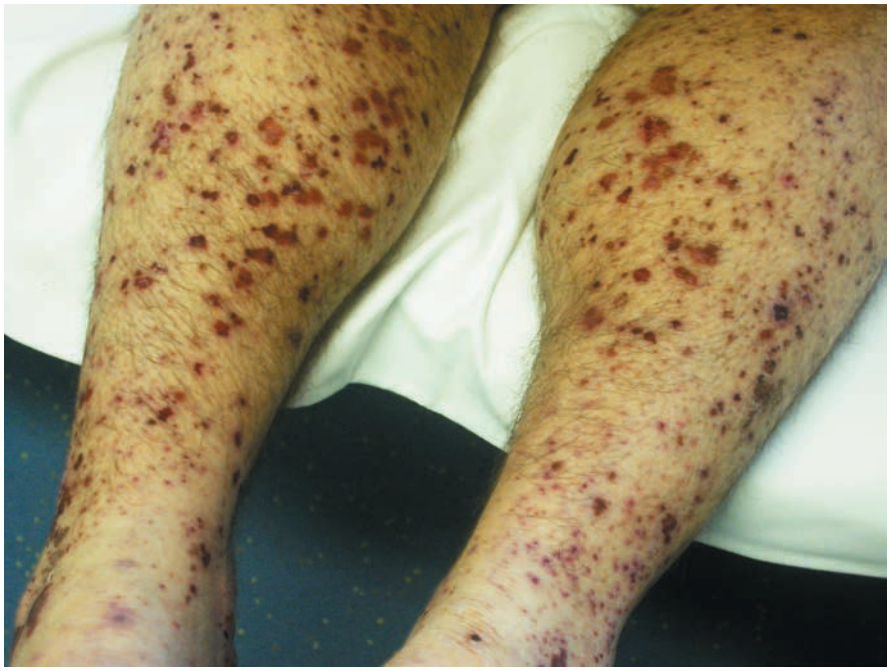

Figure 3. Cutaneous necrotizing vasculitis

oral cavity or nail changes (Figure 4). The pathogenesis of lichenoid reaction is a CD8+ T-cell cytotoxic T-lymphocyte response to drug antigenic determinants which are present on epidermal cells (1-7, 14).

Lichenoid eruptions are characterized by the onset during prolonged administration, i.e. within two months to three years, even within a shorter period of time if the patient has been sensitized previously to

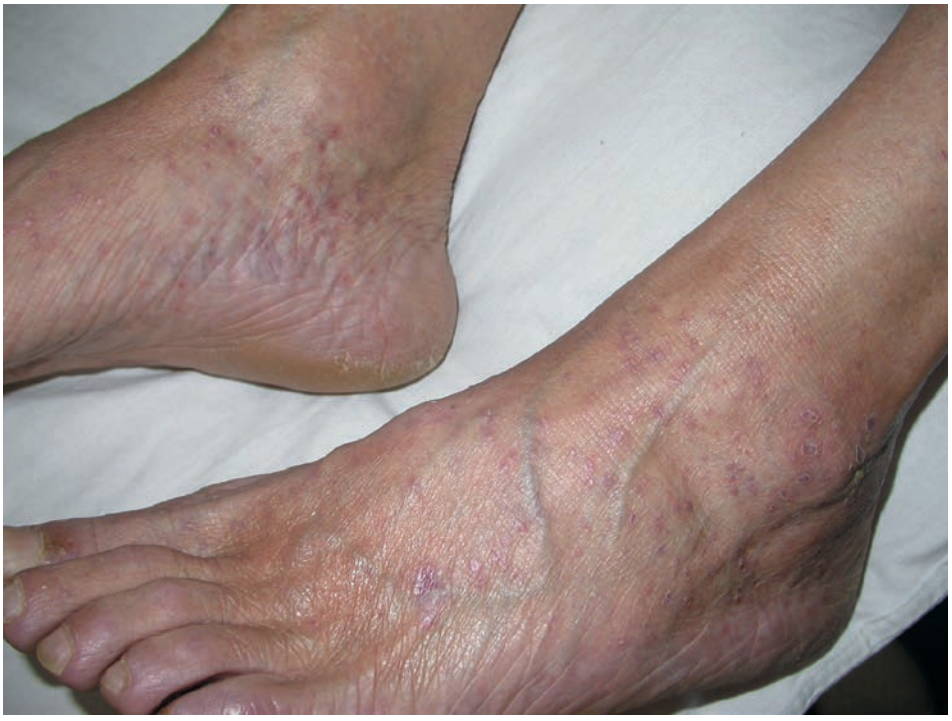

Figure 4. Lichenoid drug eruption caused by hepatitis B vaccination

the drug (Table 7). In addition, a lichenoid eruption, unlike exanthematous eruptions, takes several months following the discontinuation of the incriminate drug to resolve (1-7, 14).

Lichenoid eruption may be more confidentially differentiated from idiopathic *lichen planus* using a histological finding and direct immunofluorescence examination of the skin. Histopathological analysis usually reveals significant presence of eosinophils, while direct immunofluorescence often shows lack of immunoreactant deposits (1-7, 14).

Table 7. Agents most commonly causing lichenoid eruptions

Agent	Time to reaction onset
ACE inhibitors	3 - 6 months
Beta blockers	1 year
Penicilliamine	2 months - 3 years
Antimalarial agents	

ACE, angiotensin-converting enzyme

Phototoxic and photoallergic reactions

Drug-induced photosensitivity includes reactions where the drug - light (sunlight, artificial light) interaction results in non-immune mediated phototoxicity mechanisms and an immune-mediated photoallergic reaction (1-7).

In phototoxic reactions, which may be expected in some drugs, the drug enters into interaction with light in the skin causing damage evidenced by the development of uniform erythema in areas exposed to sunlight, resolving gradually but leaving hyperpigmentation. In pseudoporphyria, it developed less commonly, most frequently as a reaction to naproxen, vesicles and erosions occur, but if the process involves nails as well, it results in nail plate elevation from the nail bed, i.e. photo-onycholysis. Phototoxic reactions, with or without photo-onycholysis, are caused by tetracyclines (doxycycline, demeclocycline), NSAIDs (nonsteroidal antiinphlammatory drugs) and fluoroquinolones, high-dose methotrexate, less frequently by psoralens (PUVA psoralen and ultraviolet A treatment), phenothiazines and amiodarone (1-7).

Photoallergic reactions include development of new antigenic determinants during the drug-light interaction, together with the immune reaction to the so-called "photoallergen". Once the reaction occurs, it does not require further exposure to sunlight to be maintained. In their clinical manifestations, photoallergic reactions resemble eczema or a lichenoid eruption, but the changes are distributed to sunlight-exposed areas, at least in the initial period. These changes are always associated with pronounced itching and later lichenification. Following the discontinuation of the drug, they resolve very slowly and sometimes remain for several months, even years thereafter. Such patients are in the range of so-called "chronic actinic dermatitis". Drugs most commonly causing such reactions usually contain sulpha group of drugs: thiazide diuretics, sulphonamides, phenothiazines and sulphonylurea. Photoallergic reactions are less commonly caused by quinine, quinidine, tricyclic antidepressants, antimalarial agents and NSAIDs 1-7).

Systemic and severe adverse drug reactions

DRESS syndrome (Drug Rash/Reaction with Eosinophilia and Systemic Symptoms)

When describing a drug reaction associated with systemic symptoms, the term DRESS has replaced the term hypersensitivity syndrome. Although the original acronym contained the term *drug rash*, it has been replaced with *drug reaction* due to isolated cases of drug reactions with eosinophilia and systemic symptoms but without rash (1-7, 15).

DRESS presents with febricity and generalized rash, morbilliform or maculopapular rash, with

Table 8. Diagnostic criteria for DRESS syndrome

Criterion
Rash
Haematologic criteria
Eosinophilia ≥1500/mm3
Atypical lymphocytosis
Systemic symptoms
Lymphadenopathy ≥2cm in diameter, or
Hepatitis (transaminase elevation ≥2 fold), or
Interstitial nephritis, or
Interstitial pneumonitis, or
Myocarditis

*Three criteria are sufficient for the diagnosis

possible later evolution into erythrodermia with pronounced facial edema, vesicles and tense bullae due to tissue edema, follicular and non-follicular sterile pustules.

The following systemic symptoms develop: lymphadenopathy, fulminant hepatitis that may be fatal, pneumonitis, interstitial nephritis, myocarditis and thyroiditis. Eosinophilia (often over 1500/mm^3) and atypical lymphocytosis may be found in peripheral blood. Table 8 shows the suggested diagnostic criteria for DRESS syndrome, although they have not been accepted by all authors (1-7, 15, 16).

DRESS syndrome develops 2-6 weeks following the initiation of the drug, following the discontinuation of the drug and administration of a systemic corticosteroid and supportive treatment. Rash, hepatitis and eosinophilia slowly resolve over weeks, with possible relapses even when the drug is not reintroduced. Although systemic corticosteroids are used in the treatment, there have been no well-controlled studies to confirm their significance in the treatment of DRESS syndrome. Their prolonged use may result in the reactivation of HHV-6 (human herpes virus-6) which is an additional factor in the development of DRESS syndrome along with the hypersensitivity drug reaction (1-7, 15, 16).

Drugs most commonly causing DRESS are phenytoin, carbamazepine, phenobarbiton, sulphonamides, allopurinol, gold salts, dapsone and minocycline.

Stevens-Jonhnson syndrome and toxic epidermal necrolysis

Toxic epidermal necrolysis is one of the most severe drug reactions with a fatal outcome in up to 30% of patients. The estimated incidences are 0.4-1.2/10^6 and 1.2-6/10^6 for toxic epidermal necrolysis and Stevens-Johnson syndrome, respectively. The incidence is higher in the elderly and patients with HIV infection, and the men-women ratio is 0.5:0.7 (1-7, 17, 18).

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are most commonly caused by drugs and are in the range of the same disease (Table 9). At one end of the range, there is Stevens-Johnson syndrome manifested with severe erosive stomatitis, involvement of eye mucosa and generalized rash in the form of dark erythematous macules, whereas at the other end there is toxic epidermal necrolysis, with intensive involvement of the whole skin and with epidermal lifting, giving the impression of peeled skin (Figures 5 and 6) (1-7, 19, 20). Epidermal necrolysis and erythematous

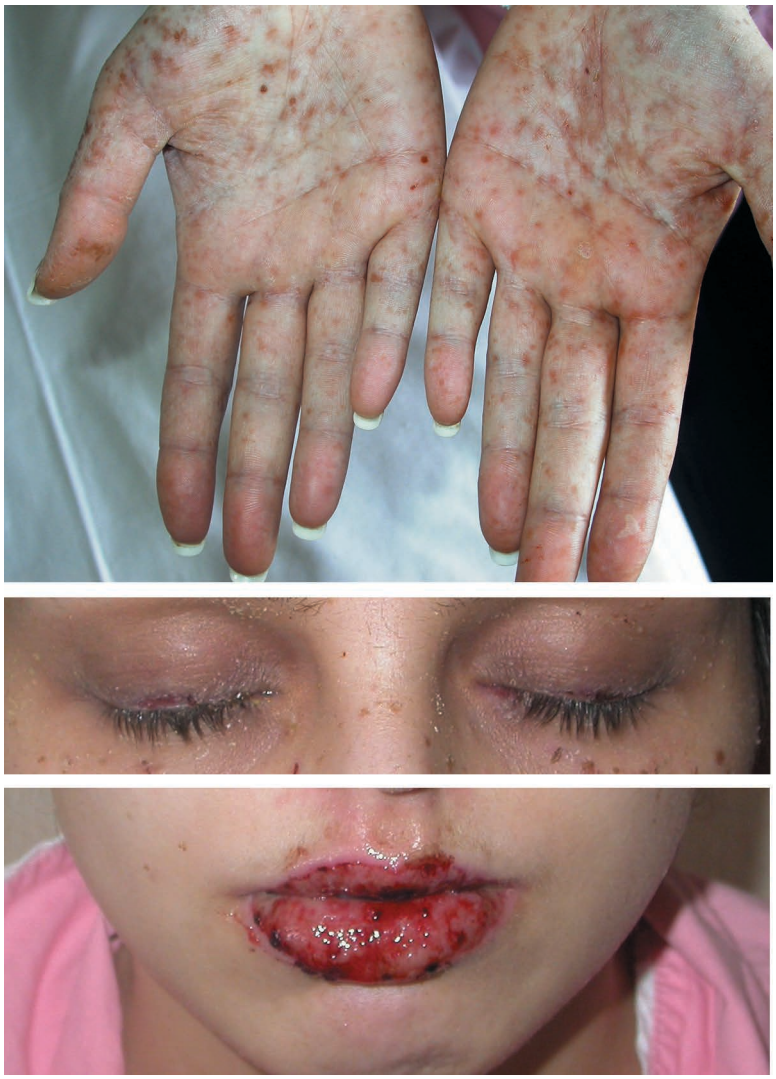

Figure 5. Stevens-Johnson syndrome (lamotrigine-induced)

macules may develop even in more intensive forms of SJS and TEN, respectively, indicating the grade of intensity of such changes as the difference between these two entities. Necrolysis involving more than 30% of the skin surface is considered a limit for the diagnosis of toxic epidermal necrolysis, and necrolysis 10 - 30% of the skin surface is considered a SJS/TEN overlap syndrome. The treatment is based on the discontinuation of the drug and a supportive symptomatic therapy. This process may be stopped by an early administration of intravenous immunoglobulins and infliximab. Administration of systemic corticosteroids over several days or weeks is contraindicated in TEN, since they slow down the healing and increase the risk of sepsis. Patients with necrolysis involving large body surfaces should be managed in sterile burn unit rooms since appropriate care and supportive therapy are necessary (1-7, 19, 20).

Differential diagnosis of SJS includes first and foremost erythema multiforme, which used to be, in its major form, considered a synonym for Stevens-Johnson syndrome, although these two entities may be both clinically and histologically differentiated, having etiologic differences as well. EM is most commonly caused by a virus, whereas SJS is most commonly caused by a drug and in less than 5% of cases by an infection. Its most common cause is *Mycoplasma pneumoniae* (1-7, 17-20).

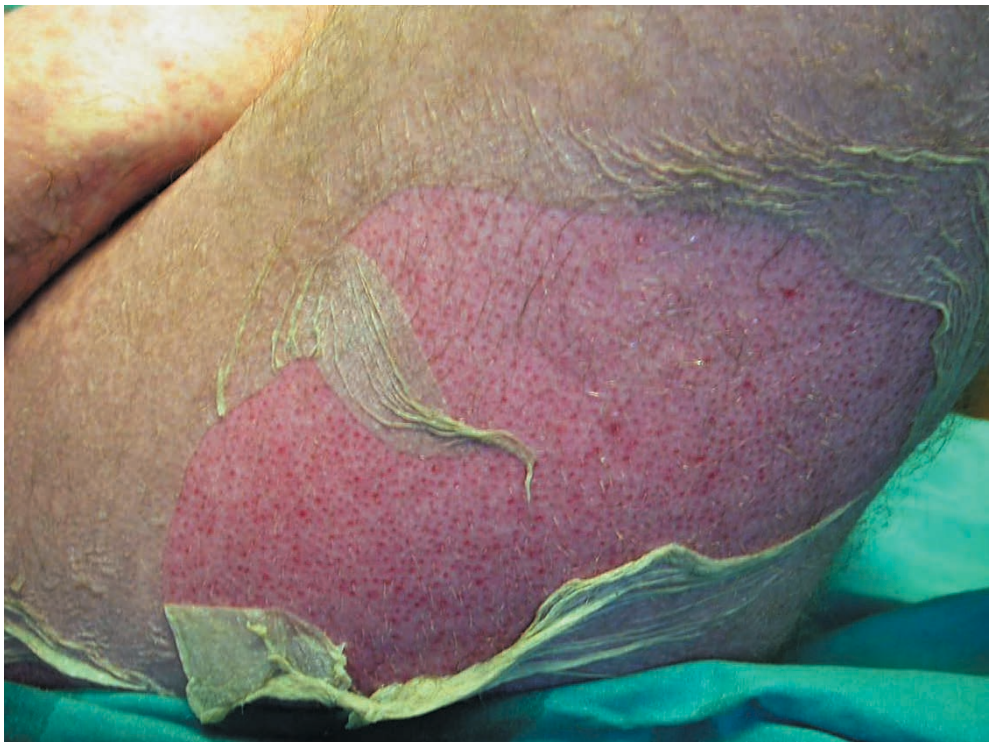

Figure 6. Toxic epidermal necrolysis

Acute generalized exanthematous pustulosis is a neutrophilic drug eruption associated with fever of up to 40°C and generalized body rash first in the form of exanthematous rash starting on the face and then expanding cephalocaudally, with targetoid lesions resembling erythema multiforme, followed by tiny non-follicular sterile pustules most commonly present on the trunk and flexural areas, but developing as generalized on the whole body surface including the face (Figure 7). When these changes resolve, a superficial desquamation may be visible at sites of pustules that have been located subcorneally. The rash is associated with elevated sedimentation, leukocytosis and neutrophilia, rarely with eosinophilia. Transient renal dysfunction and decreased blood calcium levels are common, while toxic hepatitis is rare. Specific T-cell immune drug response is probably underlying this reaction, with effector mechanisms that release cytokines responsible for the activation and mobilization of neutrophils such as interleukin IL-8

Table 9. Agents most commonly causing SJS/TEN

Agent
Trimethoprim sulfamethoxazole
Sulfadiazine
Anticonvulsant agents: carbamazepine, phenobarbiton, phenytoin
Oxicam - NSAIDs
Allopurinol

NSAIDs, nonsteridal antiinphlammatory drugs

Table 10. Adverse drug reactions manifested as idiopathic dermatoses (1-7, 22-25)

Clinical presentation	Drugs most commonly causing a reaction
Systemic contact dermatitis (reaction-inducing drugs/cutaneous allergen)	Aminophylline, hydroxyzine, cetirizine/ ethylenediamine dihydrochloride
	Disulphiram/tiuram
	Oral antibiotics/quinolones
	Streptomycin, kanamycin/neomycin
Erythroderma	Allopurinol, beta-lactam antibiotics, carbamazepine, oxcarbamazepine,gold salts, phenobarbiton, phenytoin, sulphonamides, sulphasalazine, zalcitabine
Acneiform eruptions/folliculitis	Corticosteroids, androgens, hydantoins, lithium, oral contraceptives, halogenides, rarely azathioprine, chinidine, ACTH, EGFR-inhibitor-induced acneiform eruptions
Warfarin and heparin-induced skin necrosis	Warfarin
	Heparin and low molecular weight heparin
Pemphigus	Drugs containing the thiol group: penicillamine, ACE inhibitors (capropril), gold salts, pyritinol
	Drugs not containing the thiol group: antibiotics (especially β-lactam antibiotics), pyrazolone derivatives, nifedipine, propranolol, piroxicam,phenobarbiton
Bullous pemphigoid	Furosemide, penicillin and its derivatives, sulphasalazine
Linear IgA dermatosis	Vancomycin, β-lactam antibiotics, capropril, NSAID, phenytoin, rifampicin, sulphonamides, lithium, furosemide, amiodaron,G-CSF
Pityriasis rosea	Gold salts, ACE inhibitors, metronidazole, isotretinoin, blockers (labetalol), barbiturates, arsene, sulphasalazine, bismuth, clonidine,imatinib, mercury preparations, metoxypromazine, penicillamine, ketotifen, tripelennamine
Psoriasiform eruptions	Lithium, beta blockers, antimalarial agents, interferon-α
Cutaneous pseudolymphoma	Phenobarbiton, carbamazepine, chlorpromazine, promethazine imatinib,angiotensin II receptor blockers
Systemic lupus erythematosus	Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, propylthiouracil, chinidine, practolol, penicillamine, PUVA, anti-TNF-α agents, minocycline
Subacute lupus erythematosus	Hydrochlorothiazide, calcium channel blockers, terbinafine, NSAID, griseofulvine, docetaxel, PUVA, interferon, antiTNF-α agents
Sweet's syndrome	G-CSF, GM-CSF, all-trans retinoic acid
Neutrophilic eccrine hidradenitis	Cytarabine, mitoxantrone, bleomycin, anthracyclines, cyclophosfamide

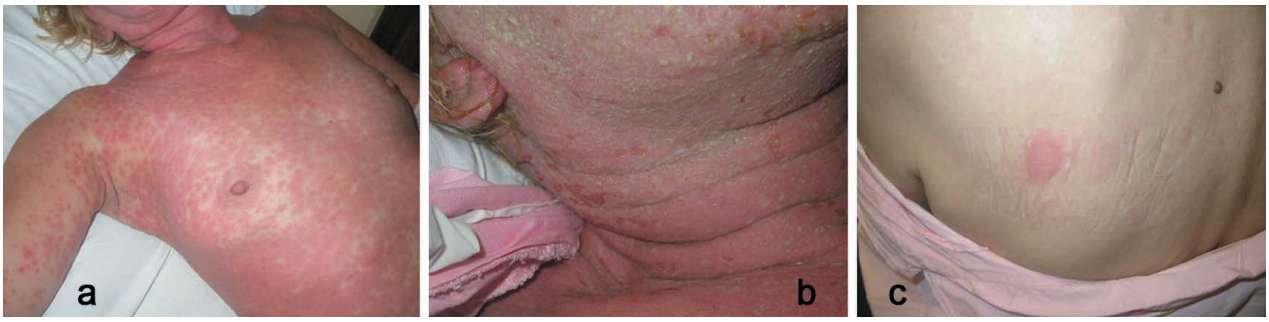

Figure 7. Diltiazem-induced acute generalized exanthematous pustulosis and positive epicutaneous patch test with diltiazem

and G-CSF (granulocyte colony stimulating factor) (1-7, 21).

More than 90% of cases of acute generalized exanthematous pustulosis (AGEP) are drug-induced and very rarely are manifestations of enteroviral infections.

Drugs most commonly causing AGEP are β-lactam antibiotics, diltiazem and other calcium channel blockers, and antimalarial agents (1-7, 21).

Differential diagnosis includes pustular psoriasis and DRESS syndrome, which may develop pustules within their clinical presentations, but may be associated with atypical lymphocytosis and eosinophilia (1-7, 21).

Adverse drug reactions manifested as idiopathic dermatoses

Table 10. shows the range of rare adverse drug reactions. Many of these entities do not differ in their clinical manifestations from immune mediated idiopathic dermatoses, but in each patient changes on the skin should be examined as adverse drug reactions (1-7, 22-25).

Abbreviations

DRESS - Drug rash with eosinophilia and systemic symptoms
HIV - Human immunodeficiency virus
IgE - Immunoglobulin class E
EGFR - Epidermal growth factor receptor
TNF-α - Tumor necrosis factor α
NSAIDs – Nonsteroidal antiinphlammatory drugs
ACE - Angiotensin-converting enzyme
p-ANCA - Perinuclear antineutrophil cytoplasmic antibodies
COX - cyclo-oxygenase
G - CSF Granulocyte colony-stimulating factor
PUVA - Psoralen and ultraviolet A
HHV-6 - Human herpes virus-6
SJS - Stevens-Johnson syndrome
TEN - Toxic epidermal necrolysis
EM - Erythema muliforme
AGEP - Acute generalized exanthematous pustulosis
GM - CSF Granulocyte–macrophage colony-stimulating factor

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Dematološka neželjena dejstva lekova

Sažetak

Definicija: Neželjena dejstva lekova mogu se definisati kao nepoželjna klinička manifestacija, to jest posledica primene određenog leka što uključuje reakcije usled predoziranja lekom, predvidljive neželjene efekte i neočekivane neželjene manifestacije. Neželjena dejstva lekova na koži jedna su od najčešćih reakcija i, prema jednoj studiji, obuhvataju oko 14% svih neželjenih reakcija na lekove.

Kliničke manifestacije: Neželjene reakcije na lekove obuhvataju širok spektar manifestacija, od bezazlenih egzantema kratkog trajanja, preko urtikarije do sistemskih reakcija koje se manifestuju i na koži, poput sindroma egzantema izazvanog lekom s eozinofilijom i sistemskim simptomima - DRESS sindrom (eng. *drug induced rash with eosinophilia and systemic symptoms*) ili toksične epidermalne nekrolize. Dve najčešće forme neželjenih reakcija na koži koje izazivaju lekovi su egzantemi i urtikarija. Ređe forme neželjenih reakcija na koži koje izazivaju lekovi su fiksne erupcije, lihenoidne, pustulozne, bulozne i vaskulitis reakcije. Najteže neželjene reakcije lekova na koži i sluzokožama jesu toksična epidermalna nekroliza koja je gotovo uvek izazvana lekom, DRESS sindrom i akutna generalizovana egzantematozna pustuloza.

Dijagnoza: Postavljanje dijagnoze neželjene reakcije na lek stoga zahteva detaljne anamnestičke podatke o hronologiji uzimanja lekova i pojave promena na koži, dobro poznavanje kliničke slike velikog spektra

različitih reakcija koje lekovi izazivaju na koži, ali i dobro poznavanje samih lekova koje pacijent uzima. S obzirom da biljni preparat i preparat alternativne medicine mogu takođe izazvati neželjene reakcije na koži, neophodno je saznati i podatke o njihovom uzimanju. Smatra se da je lek koji je počeo da se uzima u periodu od šest nedelja od nastanka promena najčešći uzročnik neželjene reakcije, kao i lekovi koji se povremeno ali redovno uzimaju.

Lečenje: Kad nastane reakcija, važno je kod pacijenta sprečiti buduće slične reakcije na isti lek ili ukrštenu reakciju lekova. Rano povlačenje svih potencijalno odgovornih lekova od suštinske je važnosti, posebno u slučaju ozbiljnih reakcija na lekove.

Ključne reči

Dermatologija; Farmakoterapija + neželjena dejstva; Kožne erupcije; Toksičnost lekova; Kožne bolesti + etiologija + terapija