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POSITION PAPER

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EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity

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Abstract

Drug hypersensitivity reactions (DHRs) are common, and the skin is by far the most frequently involved organ with a broad spectrum of reaction types. The diagnosis of cutaneous DHRs (CDHR) may be difficult because of multiple differential diagnoses. A correct classification is important for the correct diagnosis and management. With these guidelines, we aim to give precise definitions and provide the background needed for doctors to correctly classify CDHR.

1 | INTRODUCTION

Drug hypersensitivity reactions (DHRs) affect more than 7% of the population and are a concern for doctors and patients alike.[1,2] The skin is by far the most frequently involved organ,[1,3] with a broad spectrum of reaction types with different morphology, chronology and mechanisms.[4] Different entities have not only unique clinical features, but also have own implications for causative drugs, diagnostic methods and management. We have described these entities where differences in clinical presentations and prognosis are clear, for example FDE (fixed drug eruption), DRESS (drug reaction with eosinophilia and systemic symptoms), SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis) and anaphylaxis. For benign exanthems, a subclassification has been attempted (eg morbilliform, lichenoid or maculopapular), but these terms are descriptive only because there is no evidence of pathologic or prognostic implications to distinguish the benign phenotypes. Therefore, we have collectively labelled all benign exanthems as maculopapular exanthems (MPEs). Misclassification may

Abbreviations: AGEP, acute generalized exanthematous pustulosis; CDHR, cutaneous drug hypersensitivity reaction; DHR, drug hypersensitivity reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; FDE, fixed drug eruption; GBFDE, generalized bullous fixed drug eruption; MPE, maculopapular exanthem; NSAIDs, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; SCAR, severe cutaneous adverse reactions; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TNF, tumour necrosis factor.

easily lead to the wrong conclusion regarding diagnosis and management. This guideline focuses on the clinical manifestations of DHR which aid correct diagnostic classification. As recommended by the international consensus on drug allergy, we use the term DHR for objectively reproducible symptoms or signs initiated by exposure to a defined drug at a dose tolerated by a normal person that clinically resembles allergy, and we are focusing on cutaneous DHR (CDHR).[1] Other terms used for CDHR nomenclature are explained in Table S1.

The guideline aims to assist all clinicians managing DHR by providing the approach needed for doctors to correctly classify CDHR. Importantly, we have included precise definitions of CDHR, which we hope can become a standard tool for reference. Included in this guideline are criteria for when to think of DHR; an overview and a classification of CDHR; a detailed clinical description of morphological aspects in the skin; differences between urticaria and exanthems; differential diagnoses; how to distinguish between different forms of CDHR; danger signs; and important considerations for diagnosis and management.

Another part of the guideline is aimed at patients to give a standardized and better description of their skin manifestations as well as for important information to be given to the patient by the physician. Finally, recommendations for audit points are included.

2 | MATERIAL AND METHODS

This guideline was commissioned by the European Academy of Allergy and Clinical Immunology (EAACI) and undertaken by the Task Force on the Classification of Cutaneous Drug Hypersensitivity Reactions. It is based on evidence as well as on expert opinion. The preparation included a literature search in MEDLINE focusing on the search words listed in Table S1. We restricted the content of this article to CDHR after systemic exposure. During the development of these guidelines, the consultation process included meetings in Munich in November 2016, in Zurich in April 2017 and in Helsinki in June 2017. Comments and suggestions were carefully considered and consented by the whole group.

3 | DESCRIPTION OF CUTANEOUS DHRS

3.1 | How to classify cutaneous DHRs

Correct classification of CDHR into well-defined entities strongly depends on a thorough clinical examination and correct description of morphological features of the skin. As skin lesions constitute the essential foundation for later diagnosis, they are explained and summarized in Figure S1 and Table S2. Furthermore, dermatological terms used for the morphological description are given in Table S3.

Drug hypersensitivity reactions have also been classified according to chronology. Immediate (acute) DHRs are correspondent to urticaria, angioedema and/or anaphylaxis occurring nearly always within the first hour, and nonimmediate (late) exanthems occur later than 6 hours, mostly 24 hours, after drug intake. Whilst morphological classification from characterization of primary lesions and clinical features remains most important, sometimes chronology gives further clues to the diagnosis, or aids exclusion of CDHR, or differentiation between CDHR. For example, chronology is very helpful to distinguish between urticaria and early MPEs (Table 1). It is important to recognize that, post hoc, history of reported chronology is potentially unreliable, because it depends on the information provided by the patient. Morphology is more reliable, if it is assessed by experienced physicians in the acute phase, but needs to be described and classified correctly. Disease extent can be described as generalized (widespread; no major regions of skin are exempt), disseminated (several skin regions are involved) or localized (limited to a certain area of the body).

3.2 | Clinical phenotypes of generalized or disseminated DHR

3.2.1 | Urticaria, angioedema and anaphylaxis

Urticaria is characterized by the sudden appearance of wheals (circumscribed areas of raised erythema and oedema of the superficial dermis) in variable number and size accompanied or not by angioedema (Figures 1 and 2).[5] Wheals can be localized anywhere on the body. Urticaria has a fleeting nature, with the skin returning to its normal appearance, usually within 24 hour,[5] but the continual appearance and disappearance of new lesions is characteristic.[6]

When oedema in the skin is larger and involves the deeper dermis ± subcutis, the condition is called angioedema. Angioedema often affects the face (cheeks, eyelids, lips or ears) and genitalia, but also buccal mucosa, tongue, larynx and pharynx. It is often accompanied by pain and heat rather than itching. Its resolution is slower than that of wheals and may last for several days.[7] Urticaria and angioedema are associated in about half of cases.

Urticaria and angioedema can be accompanied by systemic involvement (normally cardiovascular or respiratory involvement), which has been defined as anaphylaxis[8] and can lead to respiratory collapse, shock and death.[9] Anaphylaxis mostly comes with skin lesions such as urticaria or a generalized flush, but rarely may occur without either. Drug-related urticaria, angioedema or anaphylaxis usually begins within 1 hour of drug administration. However, angioedema alone (without urticaria) induced as a side effect of angiotensin-converting enzyme inhibitors may begin after months or years of treatment, although this is not a true "hypersensitivity" reaction.

3.2.2 | Disseminated and generalized exanthems

An exanthem is not a disease, but a description of a clinical picture. There is no consensus definition of an exanthem. Medical dictionaries define it either as any rash, as a widespread rash, or as a rapidly erupting rash that may have diagnostic features of an infectious disease. In Greek, exanthema (ἐξάνθημα *exánthēma)* stands for "blossoming" or "breaking out" highlighting the sudden appearance and colour change in the eruption. We define an exanthem as an acutely

TABLE 1 Typical time intervals between initial drug use and first onset of symptoms

Hypersensitivity reaction	Time interval from intake to reaction	Most common elicitors	Proportion of cases drug induced
Urticaria/angioedema[a], anaphylaxis	Typically within 1 h[a]	Penicillin Cephalosporin NSAID	Often spontaneous or nondrug induced
SJS/TEN	4–28 d after start of use[b]	Allopurinol, Certain antiepileptics Antibacterial sulphonamides Nevirapine Oxicam-NSAIDs	Mostly drug induced
AGEP	1–12 d after start of use[c]	Beta-lactam antibiotics Macrolides Diltiazem Terbinafine (Hydroxy-) Chloroquine	Vast majority drug induced
Vasculitis	7-21 d after start of use	Beta-lactam antibiotics NSAIDs Antibacterial sulphonamides	Seldom drug induced
DRESS	2–8 wk after start of use	Certain antiepileptics Allopurinol Dapsone Antibacterial sulphonamides	Vast majority drug induced
SDRIFE[d]	Up to 7 d	Beta-lactam antibiotics	Vast majority drug induced
MPE	4–14 d after start of use[e]	Antibiotics Antiepileptics Allopurinol NSAIDs	Often infectious exanthems, exanthematic diseases
FDE	30 min-8 h after readministration	Antibacterial sulphonamides NSAIDs Barbiturates Tetracyclines Carbamazepine Metamizole	Vast majority drug induced
Systemic photoallergic reactions	Days-years	NSAIDs Promethazine Chlorpromazine	Mostly drug induced

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; MPE, maculopapular exanthem; NSAID, nonsteroidal anti-inflammatory drugs; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]ACE (angiotensin-converting enzyme) inhibitors specifically induce angioedema, not associated with urticaria, that may begin even after months or years of treatment.

[b]Sometimes longer with allopurinol.

[c]Mostly 1–2 d with antibiotics, often 7–12 d with other medications.

[d]Systemic reactivation of ACD.

[e]Time interval in repeated reactions typically shorter compared with the first reaction. In maculopapular drug eruptions, reaction typically seen after 1–4 d, typical time interval for repeated reactions has not been investigated in AGEP, SJS, TEN, and DRESS.

Source: Adapted from Brockow et al.[48]

erupting, widespread distribution of multiple small, round to oval erythematous macules and/or papules with different degrees of confluence. The individual lesions persist for several days (in contrast to urticaria wheals which resolve more rapidly). Before the diagnosis of a MPE is made, other entities where exanthems are associated with blisters, pustules or special distribution have to be ruled out (Table 2, Figures 1 and 2).

Bullous exanthems

Small isolated vesicles and pustules may develop in any MPE. The more severe bullous entities are called SJS and TEN. SJS and TEN are considered as severity variants of the same disease entity, recently referred to as epidermal or epithelial necrolysis (EN),[10] and have to be differentiated from erythema multiforme majus (EM with mucosal involvement; EMM). EMM presents with typical target lesions with or without raised atypical target lesions, any minimal epidermal detachment is confined to the very small localized centres of the targets, and the lesions do not show confluence. EMM is often restricted to the limbs, but can sometimes be disseminated. In contrast, the lesions in SJS/TEN are macules and flat atypical targets that do show confluence and on which blisters occur leading to various amounts of skin detachment. Haemorrhagic erosions of mucous

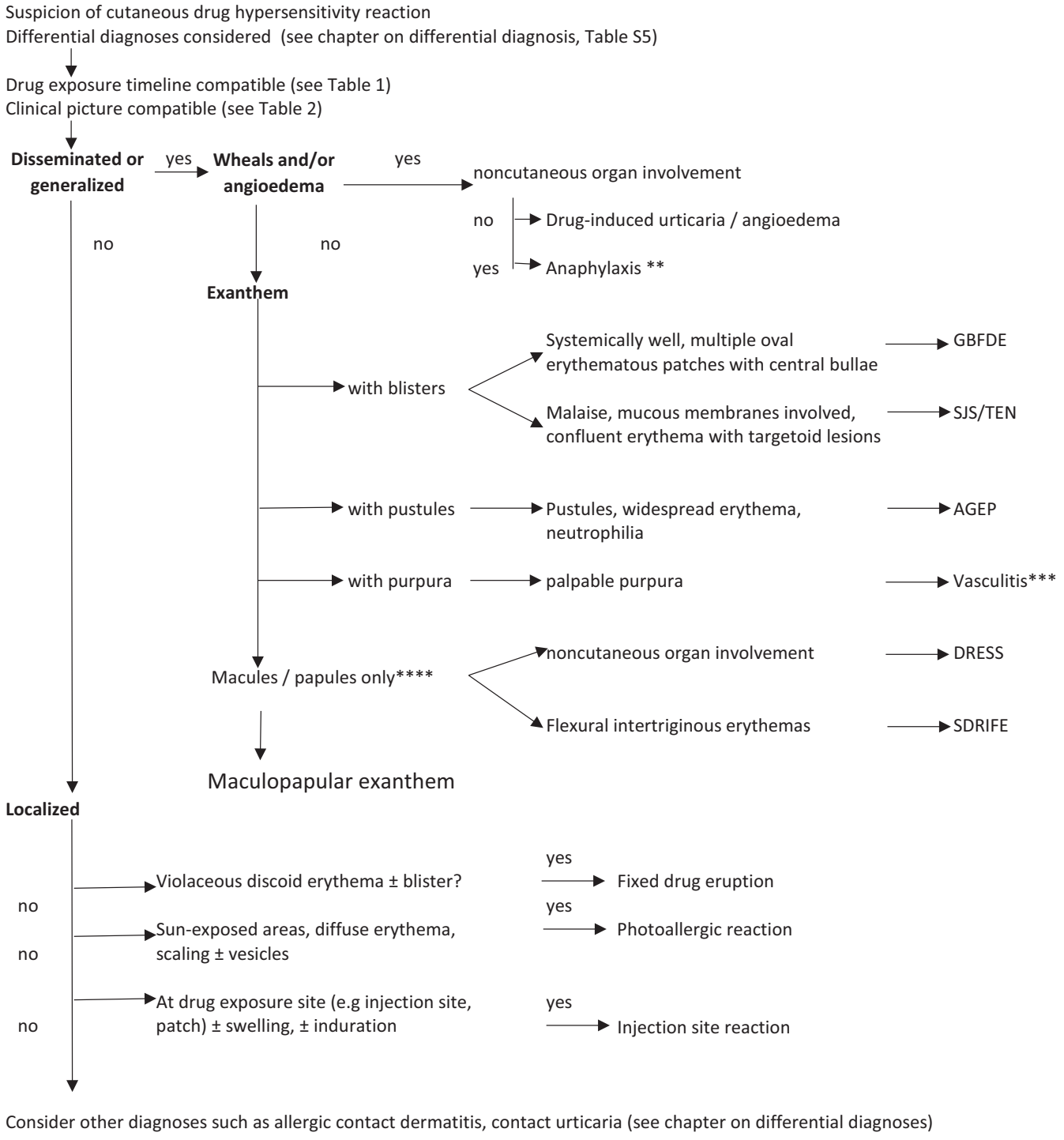


FIGURE 1 Algorithm for cutaneous drug hypersensitivity reaction. *This is a suggestive algorithm focusing on the most important entities of systemic effects of drugs and not exhaustive in diagnostic procedures recommended. **For criteria for anaphylaxis see Muraro A, et al. Allergy 2014; 69: 1026–1045. ***Pure drug induced vasculitis is rare and may complicate other hypersensitivity reactions. ****Single/minimal vesicles, pustules, purpura or eczema may in selected cases occur in maculopapular exanthem or drug reaction with eosinophilia and systemic symptoms (DRESS) and may not justify classification in above entities

membranes and fever are present in both conditions and therefore are no criterion for differentiation.[11] EMM is mainly, if not exclusively caused by infections (especially respiratory viral or mycoplasma pneumoniae infections), and is often associated with a flu-like illness. SJS/TEN cases are, in the majority circumstances, caused by drugs. SJS/TEN typically starts with small blisters arising on purple macules and atypical flat target lesions, which are widespread and usually predominant on the trunk. The skin may be initially painful. Bullous lesions develop fast, often within 12 hours, both on the skin and on mucous membranes (oral, nasal, conjunctival, genital, anal).

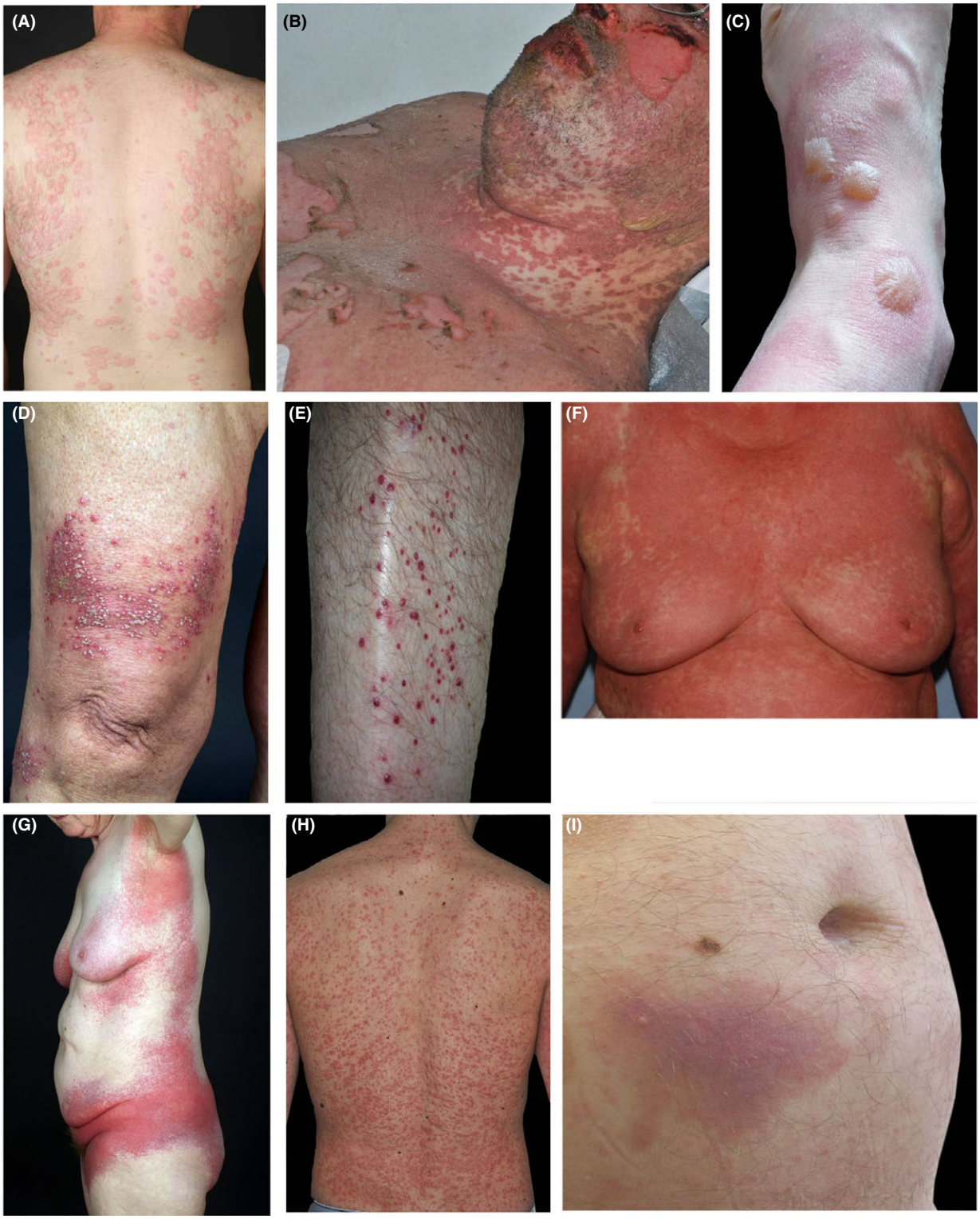


FIGURE 2 Clinical pictures of cutaneous drug hypersensitivity reactions. A: Urticaria with wheals persisting only for <24 h at the same spot, B: Stevens-Johnson syndrome with mucosal erosions and crusts as well as atypical target lesions and macules with confluent bullae and erosions, C: Generalized bullous fixed drug eruption with central bullae on sharply demarcated violaceous erythema, D: Acute generalized exanthematous pustulosis with superficial pustules on erythemas, E: Vasculitis with palpable purpura, F. drug reaction with eosinophilia and systemic symptoms with widespread erythematous infiltrated lesions, G: Symmetrical drug-related intertriginous and flexural exanthem with intertriginous distribution, H: Maculopapular exanthem with widespread erupting macules and papules and I: Injection-site reaction with an indurated violaceous plaque after subcutaneous injection of a drug

TABLE 2 Typical clinical manifestations of cutaneous drug hypersensitivity reactions

	Primary lesion and typical features	Distribution	Other important symptoms/findings/complications	Diagnostic tests
Urticaria	Wheals (hives)	Single or widespread wheals	Eventually concomitant angioedema, beware of anaphylaxis	Clinical, duration of a wheal
Angioedema	Deep swelling	Usually face (eyelids, lips), less often extremities and genitals Often asymmetric	Eventually concomitant urticaria, beware of anaphylaxis, Involvement of larynx, epiglottis -> upper airway obstruction (stridor)	Clinical
SJS/TEN[a]	Dusky red macules and flat atypical target lesions with blisters on top	Isolated lesions/confluence of lesions	Prodromal fever, upper respiratory tract symptoms Mucosal involvement Usually systemic symptoms	Clinical, Histology (subepidermal blisters, full thickness necrosis, immunofluorescence negative)
GBFDE	Erythematous well-demarcated patches/plaques with blisters	Widespread lesions with large areas of uninvolved skin	Mucous membranes may be involved No systemic symptoms	Clinical (often no mucosal involvement, patients are well)
AGEP	Pustules on oedematous erythema	Begins typically on face or intertriginous area, dissemination within hours	Fever Leucocytosis, neutrophilia, transient renal failure can occur	Clinical, bacterial swab (sterile pustules)
Vasculitis	Purpuric papules	Lower extremities primarily	Systemic organ involvement may be present, haemorrhagic and/or necrotic lesions	Clinical (purpura), Histology (leucocytoclasia)
DRESS	Variable: macules, papules, small superficial pustules, or vesicles, eczema-like, target-like lesions, purpura	Face, upper trunk, extremities, widespread	Fever Eosinophilia Lymphadenopathy Hepatitis, myocarditis, interstitial pneumonitis and nephritis, thyroiditis, arthritis	Clinical, differential blood count and organ function abnormalities, lymphadenitis
SDRIFE	Sharply delineated erythema	Flexural and intertriginous areas	Usually no systemic involvement	Clinical (involvement of body folds)
MPE	Macules, papules	Trunk > extremities	May be accompanied by low-grade fever, pruritus and eosinophilia	Clinical, blood tests (lack of systemic involvement)
FDE	Erythematous macule(s), plaque(s)	Solitary lesion(s)	By readministration recurrence at the same sites	Clinical (typical elicitor)
Systemic photoallergic reactions	Dermatitis	Sun-exposed areas, may spread	Does not arise immediately on sun exposure (delay)	Clinical (sun-exposed sites), Photopatch test
Injection site reaction	Erythematous plaque	Drug injection site	No systemic symptoms In extreme cases can spread into MPE	Clinical (history of injection)

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; GBFDE, Generalized bullous fixed drug eruption; MPE, maculopapular exanthem; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
See text for diagnostic details.
[a]Detachment SJS < 10%, SJS/TEN overlap 10%-30%, TEN > 30%.

Patients are severely ill and often develop fever. The area of confluent bullae leading to detachment of the skin is <10% (as calculated in burns) of the total body surface in SJS, 10%-30% in SJS/TEN overlap and >30% in TEN. Nikolsky's sign is positive (lateral extension of a blister with light pressure from a finger). Mortality is high (9% in SJS, 29% in SJS/TEN overlap, 48% in TEN) and mainly depends on age of the patient and extent of skin detachment.[12] Furthermore, the time to withdrawal of the culprit drug is important prognostically.[13] The typical time latency between first dose of drug and onset of SJS/TEN is 4 days to 4 weeks, but can be up to 8 weeks for drugs with a long half-life. The drugs most commonly implicated in SJS/TEN are allopurinol, antibacterial sulphonamides including sulfasalazine, certain antiepileptics (carbamazepine, lamotrigine, phenobarbital, phenytoin), nevirapine and oxicam-nonsteroidal anti-inflammatory drugs (NSAIDs).[14]

Sometimes multilocular FDEs do occur. If they are bullous and widespread over the body, they are called generalized bullous fixed drug eruption (GBFDE). In contrast to patients with SJS/TEN,

patients with GBFDE have no systemic symptoms, the lesions are well demarcated, and the mucous membranes are rarely or only minimally involved. In contrast to SJS/TEN, the culprit drug has usually been taken and tolerated before (sensitization period) and milder earlier episodes are often reported. However, recurrent events may increase in severity leading to a substantial death rate in elderly patients (up to 22%).[15]

Acute generalized exanthematous pustulosis

Sudden onset of disseminated nonfollicular, small sterile pustules on the background of a widespread confluent exanthem is the hallmarks of acute generalized exanthematous pustulosis (AGEP). Intertriginous areas and the trunk are often involved. Pustules may become confluent and form large very superficial detachment sometimes misdiagnosed as progression to SJS/TEN. Patients do have fever, and leukocytosis with neutrophilia and sometimes mild eosinophilia in the peripheral blood. Internal organ involvement is usually absent but has been observed in elderly patients. Resolution of the eruption is associated with typical postpustular desquamation and sometimes extensive scaling. Mortality has been calculated to be 4% and mainly affects elderly patients. Medications with a high risk for AGEP are aminopenicillins, cephalosporins, macrolides and other antibiotics, but also terbinafine, (hydroxyl-)chloroquine and diltiazem. The reaction usually develops after 1-2 days of systemic intake for antibiotics, but needs longer for other drugs (up to 11 days), for example diltiazem.[16]

Vasculitis

Vasculitis is frequently suspected and seldom confirmed to be caused by drug ingestion.[17,18] The most common type, drug-induced leukocytoclastic vasculitis, presents with palpable purpura, petechiae, bullae which can lead to necrosis and is indistinguishable from vasculitis due to other causes. When accompanied by fever, arthralgia, haematuria or proteinuria as well as lymphadenopathy, a serum sickness reaction can be suspected. Serum-sickness-like reactions have been particularly described in children after intake of cefaclor.[19]

Drug reaction with eosinophilia and systemic symptoms

Drug reaction with eosinophilia and systemic symptoms is a severe condition that often starts with MPE also involving internal organs. Erythematous central facial swelling is typical. Fever, malaise and lymphadenopathy are mostly present. In the peripheral blood, eosinophilia, leukocytosis and atypical lymphocytes are often found. Agranulocytosis and anaemia may occur. Concerning further involvement of internal organs, hepatitis with elevation of liver enzymes (twice the normal value on at least two different days) is most commonly found. Other visceral organ involvement, such as nephritis, pneumonitis, colitis and pancreatitis or arthritis, is less often seen. The exanthem typically starts relatively late after the first dose of medication (2-12 weeks). As in SJS/TEN and most cases of AGEP, DRESS usually arises during the first continuous use of the culprit drug.

Mortality has been variably reported, usually related to liver failure, but in a large series of strictly validated cases of DRESS was 2%.[20] However, prolonged courses and flare-ups, even after discontinuation of the culprit drug, are common. This has been linked to reactivation of herpes viruses (human herpes virus 6/7, Epstein-Barr virus [EBV], cytomegalovirus), which are commonly detected in DRESS. Drugs with a high risk for DRESS include antiepileptic drugs (eg carbamazepine, lamotrigine, phenobarbital and phenytoin), minocycline, allopurinol and dapsone. In a recent study, allopurinol and carbamazepine accounted for 38% of DRESS cases.[20]

Symmetrical drug-related intertriginous and flexural exanthem

A special pattern of a MPE with a characteristic distribution pattern involving flexural and intertriginous areas is called symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). Typically, a sharply delineated erythema of the perigenital and perianal area as well as the axillae and other intertriginous folds is seen. Males are more often affected than females. Few pustules may be observed and there may be an overlap with AGEP. The patients are generally well without systemic symptoms and signs. Postexanthematous desquamation is often seen. The main elicitors of SDRIFE are aminopenicillins.[6]

Maculopapular exanthem

The most frequent DHRs are MPE.[21,22] MPEs usually appear between four and 14 days after a new drug has been started. However, in a sensitized individual, initial symptoms already may appear within few hours and develop into a typical exanthem after 1 or 2 days. MPE can also arise a few days after the drug intake has been stopped. Erythematous macules and infiltrated papules are the primary lesions. The trunk and the proximal extremities are most often involved in a symmetric distribution. However, widespread exanthems may generalize, become confluent and develop into erythroderma. Whereas in early phases typically no scaling occurs, desquamation is common in the later clearing phase. Mucous membranes are normally not involved. Pruritus is typical. Fever and systemic involvement may occasionally occur but are very mild. It is important to understand that exanthems with macules and papules can be the early presenting findings of severe CDHR (eg DRESS, SJS/TEN), which usually become evident within 48 hours (see danger signs).

Distinguishing MPE from other disseminated and generalized exanthems

It is important to note that MPE is essentially diagnosed by exclusion. Although the patient with MPE may develop fever, mild systemic symptoms, or rarely minimal vesicles or pustules, they do not show the typical features of one of the specific severe entities (as described above). Therefore, the course of the MPE has to be regularly monitored in the initial phase to exclude early signs of DRESS, SJS/TEN or AGEP. A diagnosis of MPE is retained because of the benign course and clinical picture.

There are cases, which show features of two different of the described entities, for example DRESS and SJS/TEN, AGEP and SJS/TEN or AGEP and SDRIFE, or any of these and MPE. We do not encourage the routine use of the term "overlap" and it is recommended to use one diagnosis based on the most important clinical features, although this may be difficult in some patients.

3.3 | Localized reactions

3.3.1 | Fixed drug eruption

Fixed drug eruption manifests with a characteristic erythematous to violaceous, sometimes oedematous plaque, which may become bullous centrally. This lesion always arises at the same site <2 days after re-exposure to the culprit drug. The lesion characteristically resolves with residual hyperpigmentation. Multisite bullous FDEs may occur (see GBFDE above).

3.3.2 | Systemic photoallergic reactions

Photoallergic and phototoxic reactions to systemically applied drugs develop after ingestion of the sensitizer medication where light initiates an immune or a phototoxic response. In the case of photoallergic reactions, these are manifested by interaction between the immune system and a photohapten. Phototoxic reactions are mediated by drug-induced epidermal photo-oxidative stress, and not classical hypersensitivity. Systemic photoallergy induces dermatitis (eczema) predominantly affecting the sun-exposed areas (may also spread to covered body sites), whereas phototoxic reactions cause sunburn-like changes (sharply demarcated erythema, with or without vesicles and blisters, and subsequent hyperpigmentation). The onset of photoallergy after drug exposure varies from a few days to 3 years of daily drug intake.[23-26] Such variability may be due to the fact that the development of photoallergy is also dependent upon the highly unpredictable exposure of individuals to provoking light. Differentiating photoallergic and phototoxic reactions can difficult and will often require specialist assessment. In the case of photoallergic reactions, borders of involved areas are typically less well demarcated, with erythema, oedema and papules often spreading to covered skin areas. The eruption often demonstrates an aggravating "crescendo" pattern lasting for a few days after discontinuation of exposures, whereas phototoxic reactions usually subside immediately after withdrawal of either provoking factor (drug, light).[24] Photopatch testing with suspected drugs is essential for diagnosis.[27]

3.3.3 | Injection-site reactions

Injection-site CDHRs are typically nonimmediate indurated pruritic erythematous patches or plaques, sometimes oedematous swellings, developing few hours to days after intramuscular or subcutaneous injection of drugs.[28] In extreme cases, MPE may develop, if the application of the drug is continued. More serious reactions may reveal vesicles or bullae, necrosis or ulceration.

3.4 | Specific clinical reaction patterns to chemotherapeutic and biopharmaceuticals

Chemotherapy and biopharmaceuticals are associated with urticaria and anaphylaxis (often elicited by platinum salts,[29] taxanes[30] and biological drugs such as cetuximab, infliximab or rituximab). In addition, chemotherapeutic and biopharmaceuticals may lead to a variety of CDHRs with a distinct chronology and specific clinical features characteristic to the individual drug. Whereas severe cutaneous adverse reactions, such as SJS/TEN or DRESS are rare, cutaneous toxicities, such as alopecia and stomatitis, are frequent to many chemotherapeuticals. Additionally, it is important to recognize that immunologically mediated but nonallergic cutaneous drug reactions are associated with many modern chemotherapy treatments. Whilst a full review of these reactions is beyond the scope of this manuscript, selected important issues are discussed: (a) Antiangiogenic agents, such as sorafenib, can cause hand-foot syndrome, eczema-like lesions and palmoplantar erythrodysesthesia.[31] (b) Hand-foot syndrome is a specific CDHR that begins 2 days to 3 weeks after a chemotherapy course with redness and a tingling or burning sensation on palms and soles, develops into a symmetric, sharply demarcated erythema of the palms and soles and can involve painful blisters, fissures and oedema. Lesions may spread to the rest of the body, especially intertriginous zones (eg axilla, groin). (c) Flagellate dermatoses are pruritic erythematous linear streaks with or without induction by scratching, which heal with hyperpigmentation on the trunk or extremities[32] and may occur 12 hours to 6 months after chemotherapy initiation (eg bleomycin). (d) Injection-site reactions are commonly caused by injectable biopharmaceuticals, whereas exanthems are less common. (e) Checkpoint inhibitors typically induce pruritus and vitiligo. However, genuine CDHRs are also frequent, varying from mild (MPE) to severe (eg bullous drug eruptions). (f) Phototoxicity is also a common problem, especially for erlotinib and vemurafenib. The latter also often causes folliculitis, cysts, pruritus and exanthems.[33,34] 7) Epidermal growth factor receptor (EGFR) inhibitors (cetuximab, panitumumab, gefitinib, erlotinib) may cause a papulopustular eruption (acneiform rash), which develops after 1-2 weeks or later. Papules and pustules can be itchy or painful.[35] EGFR reactions characteristically include the central face, upper chest, and back[36] and the severity correlates with disease response to therapy. Chronic eczema-like dermatoses may also develop, mainly located on the face and limbs and sometimes predominate in light-exposed areas. Xerosis can be isolated or associated with erythema and pruritus.[35] Cutaneous appendages may be involved with nail or hair abnormalities and painful paronychia.

4 | DIAGNOSTIC PROBLEMS, PITFALLS AND CLUES

4.1 | Identification of the clinical picture

An important and sometimes very difficult differentiation is between urticaria and an exanthem. Both manifestations can be differentiated by their different primary skin lesions (Table S2). The single wheal in urticaria is always temporary and will disappear within 24 (–36) hours, whereas every single lesion in an exanthem will persist for several days, because it is composed by a cellular infiltrate in the skin. Prior therapy with corticosteroids or antihistamines may reduce the oedematous component leaving only the macular aspect

of an urticaria. It is recommended to circle around one or several lesions of a patient with a pen and check the persistence of these outlines for differentiation after 1 and 2 days. Chronological information, monitoring the course of the disease and duration of wheals (±histology rarely), may be needed to make the distinction.

Exanthems may be morphologically subdivided according to their dominant primary skin lesions, shape or resemblance of other diseases into maculopapular, lichenoid (resembling lichen planus), urticarial (resembling urticaria, but longer lasting lesions), morbilliform (measles-like), vesicular (with vesicles), pustular (with pustules), acneiform (resembling acne vulgaris) exanthem (Table S4). We are summarizing all these forms under the diagnosis MPE to avoid confusion in nomenclature and because the predominant picture may change with time as well as not be consistent in all skin areas.

4.2 | Danger signs

Importantly, MPE and SJS/TEN or DRESS are different entities and it is believed that a severe CDHR cannot develop out of a persistent MPE. However, CDHR in early phases (within the first 2 days) may resemble MPE and identifying features (danger signs) for the severe CDHR may have to be looked for repeatedly. Specific early danger signs pointing to SJS/TEN are tiny vesicles or crusts, grey-violaceous or dusky colour of lesions, painful or burning skin and/or mucosa in addition to fever and malaise. When haemorrhagic erosions of mucous membranes and skin detachment are present, the reaction is obviously more severe, and differential diagnosis of SJS/TEN and other bullous conditions has to be considered. In cases of DRESS, the cutaneous lesions may appear like MPE for several days, but progression to more than 50% of the body surface area should prompt to further diagnostic means such as repeated check of laboratory values (differential blood count, liver and kidney parameters, etc.). Furthermore, facial oedema and oedematous and infiltrated skin inflammation may point to a more severe reaction. Facial oedema can arise in DRESS as well as AGEP and blood counts may differentiate by revealing eosinophilia or neutrophilia respectively. Of the severe CDHR, AGEP is less likely to be misdiagnosed as MPE in the early stages, because it typically presents with larger areas of erythema, often predominantly in body folds and flexures of extremities. Dozens of nonfollicular pustules usually occur within 1-2 days after occurrence of erythema. Acute fever of 38.5°C and higher is typically seen in AGEP, DRESS and SJS/TEN, but may rarely also accompany MPE.

In AGEP and SJS/TEN transient elevation of liver enzymes and kidney parameters can be observed, but neither are diagnostic. However, biochemical abnormalities are hallmarks of DRESS, where the sequence of events is rather variable. The majority of reactions start with a skin eruption, followed by eosinophilia after several days (occasionally more than 1 week later), and by liver involvement another week later. Therefore, repeated laboratory tests are needed to confirm or exclude DRESS, especially when an extensive skin eruption with constitutional symptoms is present.[37,38]

4.3 | Differential diagnosis

There are multiple differential diagnoses for CDHR. The most important differential diagnosis of a drug-induced exanthem is an exanthem caused by an infection.[39,40]

On a population level, the most common cause of an exanthem is a viral infection, particularly in children.[41] Traditionally, six classic infectious exanthems have been described, that is measles (measles virus infection), scarlet fever (group A streptococcus infection), rubella (rubella virus infection), erythema infectiosum (syn. slapped cheek/fifth disease; parvovirus B19 infection), and exanthema subitum (syn. Roseola infantum; HHV-6 infection). Duke disease, syn. fourth disease, is no longer considered a specific entity. These exanthems are characterized by pathognomonic features (Table S5). "Atypical" exanthems[42] caused by a variety of viruses or bacteria, such as Streptococcus are even more common and difficult to differentiate from drug exanthems, especially as drugs are often prescribed during a viral and/or bacterial infection. It has been shown that the vast majority of exanthems occurring during an antibiotic treatment are due to a viral infection.[39,40] Distinction between those and drug-induced exanthems during the acute phase is difficult. The chronology of the exanthem development, in comparison with the drug exposure timeline, may give important clues (Table 1). Sometimes histology is helpful, although it is seldom solely diagnostic. Serology or polymerase chain reaction (PCR) can be helpful during the diagnostic process, although a concomitant acute infection does not totally exclude drug hypersensitivity (ie EBV and amoxicillin hypersensitivity).[39,43] In cases, where a CDHR cannot be ruled out based on clinical grounds, drug avoidance is mandatory after resolution of the disease until drug allergy testing can be arranged if indicated.[1]

Also other dermatological diseases may mimic CDHR and have to be recognized. The most important differential diagnosis for drug-induced urticaria is spontaneous acute urticaria. Urticaria, angioedema and anaphylaxis often have triggered other than drugs and may occur spontaneously (idiopathic). Chronology is important to suspect drugs as a trigger (Table 1). Acute urticaria can be the first sign of evolving anaphylaxis. However, if urticaria is ongoing for some time without other organ involvement in the first few hours, development of anaphylaxis is highly unlikely.

Differential diagnoses for exanthems include psoriasis, lichen planus, eczema and pityriasis rosea. Characteristic lesions of psoriasis typically present with silvery, white scales on sharply demarcated erythematous plaques, coin-sized or guttate lesions in typical distribution of the lesions involving the scalp, extensor elbows and extensor knees. A pustular variant of psoriasis has to be distinguished from AGEP. Several drugs may elicit or exacerbate psoriasis (such as beta-blockers or even tumour necrosis factor [TNF] alpha-blockers) in a nonimmunological manner.[44-46] In a person with genetic background for psoriasis, a drug-induced exanthem may induce psoriasis. Lichen planus is characterized by flat-topped violaceous papules favouring the wrist, forearms and often the buccal mucosa with different clinical variants. The differentiation between a lichenoid appearing drug-induced MPE and lichen planus may be challenging.

TABLE 3 Drug hypersensitivity questionnaire (shortened from 47)

DRUG HYPERSENSITVITY

Protocol No: .....

Date of protocol: .....

INVESTIGATOR:

Name:.....Center:.....

Address:.....Tel/Fax/E-mail: .....

PATIENT:

Name:.....Date of birth:..... Age:.....years Weight:.....kg

Height:.....cm

Profession:.....Origin:.....Sex: ☐ M ☐ F

Riskgroups: ☐ Medical staff ☐ Pharmaceutical Industries ☐ Farmers ☐ others/specify.....

CURRENT COMPLAINTS:.....

.....

.....

.....

DRUG REACTION: **DATE OF REACTION**:.....

(Multiple boxes can be ticked; underline the choice if necessary; chronology can be characterized with numbers)

■ CUTANEOUS SYMPTOMS:

☐ Maculopapular exanthema
☐ Macular exanthema
☐ Urticarious exanthema
☐ AGEP (Acute generalized exanthemous pustulosis)
☐ Eczematoid exanthema
☐ Erythema exudativum multiforme
☐ Bullous exanthema
☐ Stevens Johnson Syndrome / TEN (M. Lyell)
☐ Fixed drug exanthema
☐ Purpura -> Thrombocyte count :.....
☐ palpable ☐ haemorrhagic-necrotizing
☐ Visceral organ involvement:.....
☐ Contact dermatitis ☐ Topic cause ☐ Haematogenous cause ☐ .....
☐ Urticaria vasculitis
☐ **ONLY** Pruritus
☐ Urticaria
☐ Angioedema/Location/s: .....
☐ Conjunctivitis
☐ Other/Specification:.....

☐ Morphology/Location/s:.....

.....

■ DIFFERENTIAL DIAGNOSIS:

☐.....

☐.....

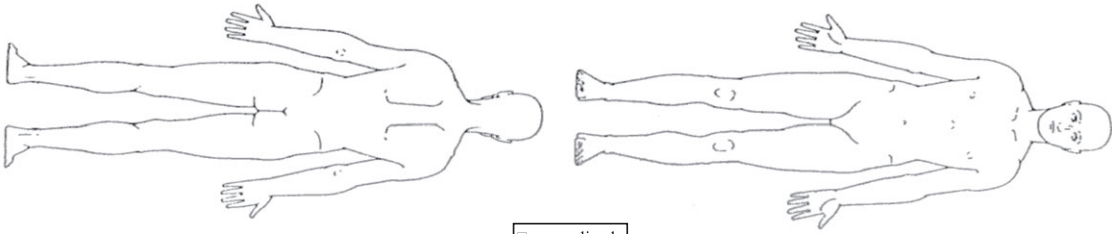
☐.....

■ CONTRIBUTING FACTORS:

☐ Viral infections: ☐ Flu like infection ☐ Other:.....
☐ Fever
☐ Suspicion of photosensitivity ? ☐ No ☐ Yes ☐ Unknown
☐ Stress
☐ Exercise
☐ Other/Specification: .....
.....

■ EVOLUTION:

■ EFFLORESCENCES: Distribution / Dynamics (⇑ ⇓)



☐ generalized

■ GASTROINTESTINAL AND RESPIRATORY SYMPTOMS:

☐ Nausea/Emesis
☐ Diarrhea
☐ Gastro intestinal cramps

☐ Cough
☐ Dysphonia
☐ Dyspnea PEFR or FEV1:.....
☐ Wheezing/Bronchospasm

☐ Rhinitis
☐ Rhinorrhea
☐ Sneezing
☐ Nasal obstruction
☐ Other/Specification:.....

■ PSYCHIC SYMPTOMS:

☐ Fear/Panic reaction ☐ Vertigo
☐ Fainting
☐ Paraesthesia/Hyperventilation

■ ASSOCIATED SYMPTOMS:

☐ Involvement of: ☐ Liver ☐ Kidney ☐ Other/Specification: .....
☐ Fever .....°C
☐ Malaise
☐ Pain/Burning ☐ Location/s:.....
☐ Edema ☐ Location/s:.....
☐ Arthralgia/Myalgia ☐ Location/s:.....
☐ Lymphadenopathy
☐ Other/Specification:.....

■ CARDIOVASCULAR SYMPTOMS:

☐ Tachykardia Pulse rate: ...../min
☐ Hypotension Blood pressure: .....mmHg
☐ Collapse
☐ Arrhythmia
☐ Other/Specification: .....

■ INVOLVEMENT OF OTHER ORGANS :

(eg. peripheral neuropathy, lung involvement, cytopenia, etc.)

☐.....

(Continues)

TABLE 3 Continued

□ Sweating □.....
□ Other/Specification:..... □.....

■ **CLINICAL OUTCOME:** .....
.....
.....

■ List all drugs including Over The Counter-substances, natural remedies and additiva containing food taken at the time of the reaction:
.....
.....
.....
.....

■ **SUSPICIOUS DRUGS:**

Drug's generic name ± additives / Indication:	Daily dose / Route of application / Duration of therapy:	Interval between dose and reaction	Previous therapy with this drug:
1.	.....mg/d; .....; .....d		□ No □ Unknown □ Yes ->Symptoms:.....
2.	.....mg/d; .....; .....d		□ No □ Unknown □ Yes ->Symptoms:.....
3.	.....mg/d; .....; .....d		□ No □ Unknown □ Yes ->Symptoms:.....
4.	.....mg/d; .....; .....d		□ No □ Unknown □ Yes ->Symptoms:.....
5.	.....mg/d; .....; .....d		□ No □ Unknown □ Yes ->Symptoms:.....
6.	.....mg/d; .....; .....d		□ No □ Unknown □ Yes ->Symptoms:.....

.....

□ CURRENT DRUGS: ..... □ Antihistamines .....
□ β-Blockers .....

■ MANAGEMENT FOLLOWING ACUTE DRUG REACTION: □ No therapy
□ Stop of suspicious drugs No.# .....
□ Antihistamines □ local □ systemic
□ Corticosteroids □ local □ systemic
□ Bronchodilatators □ local □ systemic
□ Shock treatment □ Epinephrine □ Plasma expanders □ Other: .....
□ Change to substitute/s:
□ Type/Name: .....
□ Tolerance: .....
□ Other/Specification:.....
□ Dosis reduction (Drug.....).....
□ Other/specify.....
.....

PERSONAL HISTORY:

1) HAVE SIMILIAR SYMPTOMS BEEN OBSERVED WITHOUT THE INTAKE OF THE SUSPICIOUS DRUGS ? □ Yes □ No □ Unknown

2) MEDICAL HISTORY:

□ Asthma	□ Autoimmune (Sjögren, Lupus, etc)	□ Urticaria pigmentosa / syst. mastocytosis
□ Nasal polyposis	□ Lymphoprolific (ALL, CLL, Hodgkin, etc.)	□ Chronic urticaria
□ Cystic fibrosis	□ Intervertebral disk surgery	□ HIV positivity
□ Diabetes	□ Liver:.....	□ Kidney: .....

□ Other/Specification: .....

3) ALLERGIC DISEASES: .....
(eg. pollinosis, atopic dermatitis, food allergy, hymenoptera venom allergy, latex allergy, etc.)

4) DRUG REACTIONS DURING FORMER SURGERY: .....□ Dentist □ Local anaesthesia □ General anaesthesia (No:.....)

5) REACTIONS DURING FORMER VACCINATIONS: .....□ Polio □ Tetanus □ Rubella □ Measles □ Hepatitis B
□ Diphteria □ Other:..... □ Unknown

FAMILY HISTORY: Allergies / Drug allergies:
.....

REMARKS:
.....
.....
.....

In eczema, the clinical presentation of lesions is more diffuse and shows primary scaling reflecting epidermal inflammation (as compared to disseminated smaller lesions without scaling in the first days of MPE). Erythroderma (Table S3) may also be induced by drugs, but more commonly erythroderma is induced by atopic dermatitis, psoriasis, pityriasis rubra pilaris and cutaneous lymphoma. Pityriasis rosea is a, sometimes pruritic, self-limited eruption mainly in adolescents and young adults. In this disease, a primary well-demarcated plaque on the trunk is followed by eruption of numerous smaller plaques with central fine scales often in a "Christmas tree" pattern. Other dermatological diseases that may mimic drug exanthems include systemic lupus erythematosus and dermatomyositis, and in cases with blisters, autoimmune blistering skin diseases, such as bullous pemphigoid or IgA-linear dermatosis. Kawasaki disease, unilateral laterothoracic exanthem and Schönlein-Henoch purpura are primarily differential diagnoses to CDHR in children.

5 | CONCLUSIONS AND FUTURE NEEDS

The diagnosis of CDHR may be difficult because of multiple differential diagnoses, particularly acute spontaneous urticaria and infectious exanthems, but also other dermatological diseases. To suspect a CDHR:

1. A new drug (or repeated intake of a drug) has to be introduced to the patient with a specific time interval between intake and development of first symptoms (Table 1) and
2. Typical clinical manifestations should be present (Table 2). These features differ substantially between the various clinical conditions. To make the correct diagnosis based on morphology, it is crucial to identify primary and secondary lesions (Table S2) and to use allergological (Table S1) and dermatological terms appropriately (Table S3).

Most cases are elicited by classical culprit drugs (Table 1). However, this CDHR must be considered due to nonclassical drugs if points 1 and 2 are met. The history and the clinical picture have important implications for management in the acute stage of the disease and for planning of diagnostic tests to be done later. If possible, patients should be assessed by experts during the acute phase of a reaction, enabling exclusion of several differential diagnoses both from the clinical picture and by histopathology, classification of clinical manifestations, recording of drugs used and follow-up of the course of the reaction. A standardized questionnaire to collect relevant information is available[47] (Table 3), and its use is recommended for recording the relevant information to plan the management of the patient. Translations of this questionnaire into different languages are available under (http://www.eaaci.org/organisation/eaaci-interest-groups/ig-on-drug-allergy/resources.html). Often, information regarding the clinical reaction is only available from the patient or caregiver, in some cases with medical records (eg discharge letter, medical chart, anaesthesia protocols). In these cases, photography of the clinical reaction by the patient (often with smartphones) to identify the lesion pattern and body distribution is very helpful and should be asked for. Appendix S1 describes a questionnaire for the patient to identify the principal information about the reaction. However, it is important to recognize that the information given by the patient is prone to error with significant limitations because of the lack of medical training. To monitor internal standards of these recommendations, audit points are given (Table S6).

CONFLICT OF INTEREST

The corresponding author and coordinator declare no conflict of interest. There has not been any conflict of interest by any of the coauthors. All named authors were involved consensus group meetings, retrieval of information of drug allergy documentation in different countries and in the discussion and approval of the final manuscript.

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REFERENCES

1. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. *Allergy*. 2014;69:420-437.
2. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol*. 2005;5:309-316.
3. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001;137:765-770.
4. Brockow K. *Drug Allergy: Definitions and Phenotypes*. St. Louis, MO: Elsevier; 2018.
5. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau A, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2009;64:1417-1426.
6. Ardern-Jones MR, Friedmann PS. Skin manifestations of drug allergy. *Br J Clin Pharmacol*. 2011;71:672-683.
7. Greaves M, Lawlor F. Angioedema: manifestations and management. *J Am Acad Dermatol*. 1991;25(1 Pt 2):155-161; discussion 161-155.
8. Simons FE. 9. Anaphylaxis. *J Allergy Clin Immunol*. 2008;2(Suppl):S402-S407.
9. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology*. 2005;209:123-129.
10. Roujeau JC, Mockenhaupt M, Guillaume JC, Revuz J. New evidence supporting cyclosporine efficacy in epidermal necrolysis. *J Invest Dermatol*. 2017;137:2047-2049.
11. Paulmann M, Mockenhaupt M. Fever in Stevens-Johnson syndrome and toxic epidermal necrolysis in pediatric cases: laboratory work-up and antibiotic therapy. *Pediatr Infect Dis J*. 2017;36:513-515.
12. Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis: clinical patterns, diagnostic considerations, etiology, and therapeutic management. *Semin Cutan Med Surg*. 2014;33:10-16.

13. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol*. 2000;136:323-327.
14. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol*. 2008;128:35-44.
15. Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A, et al. Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol*. 2013;168:726-732.
16. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck JN, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case–control study (EuroSCAR). *Br J Dermatol*. 2007;157:989-996.
17. Merkel PA. Drugs associated with vasculitis. *Curr Opin Rheumatol*. 1998;10:45-50.
18. Antiga E, Verdelli A, Bonciani D, Bonciolini V, Quintarelli L, Volpi W, et al. Drug-induced cutaneous vasculitides. *G Ital Dermatol Venereol*. 2015;150:203-210.
19. Gomes ER, Brockow K, Kuyucu S, Saretta F, Mori F, Blanca-Lopez N, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy*. 2016;71:149-161.
20. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, 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;169:1071-1080.
21. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol*. 2003;149:1018-1022.
22. Bircher AJ. Uncomplicated drug-induced disseminated exanthemas. *Chem Immunol Allergy*. 2012;97:79-97.
23. Horio T. Photosensitivity reaction to dibucaine. Case report and experimental induction. *Arch Dermatol*. 1979;115:986-987.
24. Spiewak R. Systemic photoallergy to terbinafine. *Allergy*. 2010;65:1071-1072.
25. Foti C, Cassano N, Vena GA, Angelini G. Photodermatitis caused by oral ketoprofen: two case reports. *Contact Dermatitis*. 2011;64:181-183.
26. Sanchez-Borges M, Gonzalez-Aveledo LA. Photoallergic reactions to angiotensin converting enzyme inhibitors. *J Eur Acad Dermatol Venereol*. 2011;25:621-622.
27. Bruynzeel DP, Ferguson J, Andersen K, Goncalo M, English J, Goossens A, et al. Photopatch testing: a consensus methodology for Europe. *J Eur Acad Dermatol Venereol*. 2004;18:679-682.
28. Zeltser R, Valle L, Tanck C, Holyst MM, Ritchlin C, Gaspari AA. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor: Fc fusion protein. *Arch Dermatol*. 2001;137:893-899.
29. Leguy-Seguin V, Jolimoy G, Coudert B, Pernot C, Dalac S, Vabres P, et al. Diagnostic and predictive value of skin testing in platinum salt hypersensitivity. *J Allergy Clin Immunol*. 2007;119:726-730.
30. Feldweg AM, Lee CW, Matulonis UA, Castells M. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol*. 2005;96:824-829.
31. Lipworth AD, Robert C, Zhu AX. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology*. 2009;77:257-271.
32. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer: part I. Conventional chemotherapeutic drugs. *J Am Acad Dermatol*. 2014;71:203.e201-203.e212.
33. Sinha R, Edmonds K, Newton-Bishop JA, Gore ME, Larkin J, Fearfield L. Cutaneous adverse events associated with vemurafenib in patients with metastatic melanoma: practical advice on diagnosis, prevention and management of the main treatment-related skin toxicities. *Br J Dermatol*. 2012;167:987-994.
34. Luu M, Lai SE, Patel J, Guitart J, Lacouture ME. Photosensitive rash due to the epidermal growth factor receptor inhibitor erlotinib. *Photodermatol Photoimmunol Photomed*. 2007;23:42-45.
35. Reguiai Z, Bachet JB, Bachmeyer C, Peuvrel L, Beylot-Barry M, Bezier M, et al. Management of cutaneous adverse events induced by anti-EGFR (epidermal growth factor receptor): a French interdisciplinary therapeutic algorithm. *Support Care Cancer*. 2012;20:1395-1404.
36. Braden RL, Anadkat MJ. EGFR inhibitor-induced skin reactions: differentiating acneiform rash from superimposed bacterial infections. *Support Care Cancer*. 2016;24:3943-3950.
37. Paulmann M, Mockenhaupt M. Severe drug-induced skin reactions: clinical features, diagnosis, etiology, and therapy. *J Dtsch Dermatol Ges*. 2015;13:625-645.
38. Paulmann M, Mockenhaupt M. Severe drug hypersensitivity reactions: clinical pattern, diagnosis, etiology and therapeutic options. *Curr Pharm Des*. 2016;22:6852-6861.
39. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol*. 2011;127:218-222.
40. Atanaskovic-Markovic M, Gaeta F, Medjo B, Gavrovic-Jankulovic M, Cirkovic Velickovic T, Tmusic V, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children – our 10-year experience in allergy work-up. *Pediatr Allergy Immunol*. 2016;27:533-538.
41. Goodyear HM, Laidler PW, Price EH, Kenny PA, Harper JI. Acute infectious erythemas in children: a clinico-microbiological study. *Br J Dermatol*. 1991;124:433-438.
42. Folster-Holst R, Kreth HW. Viral exanthems in childhood–infectious (direct) exanthems. Part 2: other viral exanthems. *J Dtsch Dermatol Ges*. 2009;7:414-419.
43. Onodi-Nagy K, Kinyo A, Meszes A, Garaczi E, Kemeny L, Bata-Csorgo Z. Amoxicillin rash in patients with infectious mononucleosis: evidence of true drug sensitization. *Allergy Asthma Clin Immunol*. 2015;11:1.
44. Rongioletti F, Fiorucci C, Parodi A. Psoriasis induced or aggravated by drugs. *J Rheumatol Suppl*. 2009;83:59-61.
45. Park JJ, Choi YD, Lee JB, Kim SJ, Lee SC, Won YH, et al. Psoriasiform drug eruption induced by anti-tuberculosis medication: potential role of plasma-cytoid dendritic cells. *Acta Derm Venereol*. 2010;90:305-306.
46. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. *Am J Clin Dermatol*. 2008;9:1-14.
47. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. *Allergy*. 1999;54:999-1003.
48. Brockow K, Przybilla B, Aberer W, Bircher AJ, Brehler R, Dickel H, et al. Guideline for the diagnosis of drug hypersensitivity reactions: S2K-Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) in collaboration with the Association of German Allergologists (AeDA), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Swiss Society for Allergy and

Immunology (SGAI), the Austrian Society for Allergology and Immunology (OGAI), the German Academy of Allergology and Environmental Medicine (DAAU), the German Center for Documentation of Severe Skin Reactions and the German Federal Institute for Drugs and Medical Products (BfArM). *Allergo J Int*. 2015;24:94-105.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.