



Drug Allergy and Cutaneous Adverse Reactions

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Contents

- 1 Introduction
- 2 Clinical Reaction Types
 - 2.1 Urticaria and Angioedema
 - 2.2 Exanthems
 - 2.3 Multiforme-Like Drug Reaction
 - 2.4 Lichenoid Eruption
 - 2.5 SDRIFE
 - 2.6 Fixed Drug Eruption
 - 2.7 Acute Generalized Exanthematous Pustulosis
 - 2.8 Drug Reaction with Eosinophilia and Systemic Symptoms
 - 2.9 Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
- 3 Management of Cutaneous Adverse Reactions
 - 3.1 General Considerations
 - 3.2 Specific Treatments
- 4 Allergologic Testing in SCAR
- References

Abstract

Allergy or hypersensitivity to drugs often affects the skin and sometimes also mucosa. While immediate type reactions show a rather homogeneous pattern, delayed type reactions reveal a high variability. In both cases it may not always be easy to differentiate drug reactions from non-drug-induced skin conditions. Furthermore, the different types of cutaneous adverse reactions may be difficult to distinguish in the beginning. This accounts predominately for delayed hypersensitivity reactions that can occur after a variety of medications and present with

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manifold lesions. Most of these cutaneous adverse reactions are mild, but some are severe with high morbidity and mortality. In the clinical setting, it is important to recognize the signs that point to a more severe condition early on in order to initiate appropriate management. In addition, it is crucial to identify the potentially culprit medication on the basis of a detailed medication history and by evaluating the relevant exposure times of certain drugs that differ substantially between the various reaction types. After the acute stage of the adverse reaction is managed successfully, further allergologic testing may be undertaken to confirm the offending drug.

Keywords

Cutaneous adverse drug reactions · Delayed hypersensitivity · Drug allergy · Immediate hypersensitivity · Severe cutaneous adverse reactions

Abbreviations

AGEP	Acute generalized exanthematous pustulosis
BSA	Body surface area
DRESS	Drug reaction with eosinophilia and systemic symptoms
FDE	Fixed drug eruption
GBFDE	Generalized bullous fixed drug eruption
ICU	Intensive care unit
MPE	Maculopapular exanthema
SCAR	Severe cutaneous adverse reactions
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis

1 Introduction

A variety of skin reactions toward drug ingestion or application are known, which differ in clinical pattern and pathogenesis. Some reactions follow the classical allergic pathway as described by Coombs and Gell, others reveal a different, sometimes unknown mechanism. Urticaria and angioedema may be manifestations of drug hypersensitivity, either IgE-mediated (immediate or type I hypersensitivity) or non-IgE-mediated through direct mast cell activation. Whereas this clinical pattern of immediate hypersensitivity reactions is rather homogeneous, that of delayed cutaneous hypersensitivity reactions (type IV hypersensitivity) is very heterogeneous in terms of lesions, severity, and time course. Some of these delayed drug reactions can be explained through sensitization, for others the mechanism remains unclear (Brockow et al. [2019](#)).

Cutaneous reactions to drugs are common, affecting 2–3% of hospitalized patients, and are a significant cause of outpatient morbidity. It is estimated that 1 in 1,000 hospitalized patients has a serious cutaneous drug reaction (Bigby 2001).

The following chapter will present the various types of drug reactions with focus on delayed and severe hypersensitivity. However, immediate type reactions will be briefly discussed as well.

2 Clinical Reaction Types

2.1 Urticaria and Angioedema

Urticaria is characterized by an eruption of hives (wheals), which are erythematous, circumscribed, raised, pruritic lesions, often with central pallor. Individual lesions may enlarge, coalesce with others, and typically disappear within a few hours. Angioedema is caused by swelling of the deeper dermis and subcutaneous tissue that may be accompanied by urticaria in up to 50% of cases. Angioedema may be disfiguring if it involves the face and lips, or life-threatening if laryngeal edema or tongue swelling leads to airway obstruction.

Antibiotics, esp. penicillins and cephalosporins, are common causes of IgE-mediated drug allergy. However, the infection requiring antibiotic treatment may also induce urticaria.

Other drugs may induce urticaria/angioedema due to direct mast cell activation by a non-IgE mediated mechanism. Most frequently implicated are opiate analgesics like morphine or codeine. The concomitant use of opiates and vancomycin may increase the risk of the so-called red man syndrome, which can be observed after rapid infusion of vancomycin. It is induced by direct mast cell activation and may also present with urticaria (Kanani et al. 2018).

Nonsteroidal anti-inflammatory drugs (NSAIDs) can trigger urticaria/angioedema through direct mast cell activation but also through other mechanisms such as abnormalities of the complement cascade (inherited and acquired abnormalities of complement metabolism) and increased activity of vasodilatory kinin pathways. Angioedema (in the absence of urticaria) has been reported to occur in 2 to 10 of 10,000 new users of angiotensin-converting enzyme (ACE) inhibitors and typically affects mouth and tongue (Stone and Brown 2017). The assumed mechanism is an impaired bradykinin degradation by ACE leading to elevated blood levels of the vasoactive peptide bradykinin.

Despite the name “immediate reaction type” eruptions like urticaria and/or angioedema can also occur accelerated, i.e. hours after exposure, or delayed, i.e. days after exposure.

Anaphylaxis is the most severe and potentially life-threatening form of immediate type I hypersensitivity and includes pruritus, urticaria, angioedema, laryngeal edema, wheezing, nausea, vomiting, tachycardia, and sometimes even shock. Drugs are not the most common cause of anaphylaxis but have been reported as the third frequent trigger (Simons et al. 2013).

2.2 Exanthems

The most frequent cutaneous reactions to drugs are exanthems of various kinds. They represent more than 75% of all drug eruptions. They are described as morbilliform or macular and/or papular eruptions (Bigby 2001; Ardern-Jones and Friedmann 2011). Many frequently prescribed and commonly used medications have been reported as the cause of such cases. Furthermore, it is well known that certain antibiotics, e.g. aminopenicillins, have a higher risk to induce an exanthematous eruption in the presence of a viral infection. In addition, many viral infections show an exanthem and parainfectious eruptions are also frequent. Therefore, the differential diagnosis may be difficult.

2.3 Multiforme-Like Drug Reaction

This eruption is frequently misdiagnosed as erythema (exsudativum) multiforme (E(E)M) or Stevens-Johnson syndrome (SJS). It presents with targetoid lesions that may be confluent (Fig. 1c). The histopathology reveals rather dermal than epidermal



Fig. 1 Various types of cutaneous adverse reactions. (a) Acute generalized exanthematous pustulosis (AGEP). (b) Drug reaction with eosinophilia and systemic symptoms (DRESS). (c) Multiforme-like drug eruption. (d) Fixed drug eruption (FDE) with local blisters. (e) Generalized bullous fixed drug eruption (GBFDE)

changes, which have been called “the dermal type of EM.” Mucosal involvement, if present, is mild and skin blisters may occur due to edema but not due to apoptosis like in EM or SJS/TEN (Roujeau and Mockenhaupt 2019).

Whereas EM minus or majus (with hemorrhagic erosions of mucous membranes) is most frequently (if not always) induced by infection (typically herpes simplex virus or mycoplasma pneumoniae), multiforme-like drug eruption is induced by medication, e.g. NSAIDs and diuretics and has also been observed in the context of targeted therapies (Ziemer et al. 2007).

2.4 Lichenoid Eruption

The violaceous or hyperpigmented, flat-topped, pruritic papules that typically affect the ankles and the volar surface of the wrists in lichen planus may also be seen in lichenoid drug eruptions. This type of reaction usually develops months or even years after beginning of drug use. It may spread over the entire body, but typically spares the mucosa. Beta-blockers, ACE inhibitors, methyl dopa, penicillamine, quinidine, antimalarials, and thiazide diuretics have been reported as the most frequent causes (Inoue et al. 2017). Recently, TNF-alpha inhibitors, tyrosine kinase inhibitors, and further targeted therapies have also been observed to induce lichenoid reactions, some with bullous lesions that may imitate Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (Reschke et al. 2019). The mechanism of this reaction pattern remains unknown.

2.5 SDRIFE

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously also called baboon syndrome, is an infrequent type of drug-induced eruption (Häusermann and Bircher 2007). It typically occurs a few hours to a few days after the initiation of the offending drug. The eruption presents as a well-demarcated V-shaped erythema in the gluteal-perianal or inguinal-perigenital area, often with involvement of intertriginous folds. Systemic symptoms are not present. In some cases, SDRIFE may resemble a specific pattern of fixed drug eruption, whereas in other cases pustules may occur in the intertriginous areas, which may spread like in AGEP (Brockow et al. 2019; Häusermann and Bircher 2007). Amoxicillin, ceftriaxone, penicillin, clindamycin, and erythromycin have been reported as inducing agents in up to 50% of cases. Iodinate contrast media, pseudoephedrine, acetyl salicylic acid, mitomycin C, phenothiazines, valacyclovir, and many other drugs have also been implicated (Thyssen and Maibach 2008).

2.6 Fixed Drug Eruption

Fixed drug eruption is a distinctive reaction characterized by erythematous and/or edematous plaques with a grayish-violaceous center or bulla in the acute stage and by a dark pigmentation in the chronic phase (Fig. 1d). Affected sites include mouth (lips and tongue), genitalia, face, and acral areas (Brockow et al. 2019). The defining features of this eruption include postinflammatory hyperpigmentation and recurrence of lesions at exactly the same sites with re-exposure of the drug (Brahimi et al. 2010).

Patients with generalized bullous fixed drug eruption (GBFDE) can be misdiagnosed as having SJS/TEN, but in GBFDE mucosal involvement is usually absent or mild and the clinical course is favorable with resolution within 2 weeks after drug discontinuation (Fig. 1e) (Cho et al. 2014). The reaction occurs typically after 1–2 days of taking the inducing medication. Drugs frequently involved include NSAIDs, antibacterial agents, such as sulfamethoxazole, tetracyclines, dapsone, barbiturates, paracetamol (acetaminophen), and metamizole (Mahboob and Haroon 1998).

2.7 Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is a rare disorder characterized by the sudden occurrence of erythema and superficial pustules accompanied by fever. The cutaneous eruption typically starts in the face or intertriginous areas and spreads within a few hours. Small, non-follicular pustules arise on edematous erythema with burning and/or itching and the histopathology reveals spongiosis and subcorneal agglomeration of granulocytes (Fig. 1a). A scoring system was developed that helps to confirm the diagnosis of AGEP or rule it out (Table 1) (Sidoroff et al. 2001).

The time between beginning of drug use and reaction onset is remarkably short with 1–2 days for most of the inducing drugs. However, for other medications the onset of symptoms may be delayed for 1–2 weeks (Momin et al. 2009). Antibiotics, particularly penicillins and macrolides, are thought to play a role in 80% of cases (Sidoroff et al. 2007).

2.8 Drug Reaction with Eosinophilia and Systemic Symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) – in Japan also referred to as drug-induced hypersensitivity syndrome (DIHS) – is a severe reaction characterized by fever (38 to 40°C), malaise, lymphadenopathy, skin eruption, and organ involvement. The latter includes affection of liver, kidney, lung, heart, as well as the presence of hypereosinophilia and/or atypical lymphocytes. A diagnostic scoring system was designed to enable confirmation or exclusion of DRESS. However, it is important to apply it correctly and e.g. only count points for liver

Table 1 Diagnostic score for AGEP (Sidoroff et al. 2001)

Morphology	
Pustules	
<i>Typical</i>	+2
<i>Compatible (with disease)</i>	+1
<i>Insufficient</i>	0
Erythema	
<i>Typical</i>	+2
<i>Compatible (with disease)</i>	+1
<i>Insufficient</i>	0
Distribution pattern	
<i>Typical</i>	+2
<i>Compatible (with disease)</i>	+1
<i>Insufficient</i>	0
Post-pustular desquamation	
<i>Yes</i>	+1
<i>No/insufficient</i>	0
Course	
Mucous membrane involvement	
<i>Yes</i>	−2
<i>No</i>	0
Acute onset (≤ 10 days)	
<i>Yes</i>	0
<i>No</i>	−2
Resolution (≤ 15 days)	
<i>Yes</i>	0
<i>No</i>	−4
Fever $\geq 38^{\circ}\text{C}$	
<i>Yes</i>	+1
<i>No</i>	0
$\text{PNN} \geq 7,000/\text{mm}^3$	
<i>Yes</i>	+1
<i>No</i>	0
Histology	
Other disease	−10
Not representative/no histology	0
Exocytosis of PNN	+1
Subcorneal and/or intraepidermal non-spongiform pustules or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform pustules or NOS pustules without papillary edema	+2
Spongiform subcorneal and/or intra-epidermal pustules with papillary edema	+3

NOS not otherwise specified, *PNN* polynuclear neutrophils

Final score for AGEP: ≤ 0 points: excluded (not AGEP); 1–4 points: possible; 5–7 points: probable; 8–12 points: definite case of AGEP

Table 2 Diagnostic score for DRESS (Kardaun et al. 2007)

Score	−1	0	+1	+2	Min	Max
Fever $\geq 38.5^{\circ}\text{C}$	No	Yes			−1	0
Lymphadenopathy		No/U	Yes		0	+1
Eosinophilia Eosinophils % eosinophils if WBC < 4,000			700–1,499/ μl 10–19.9%	$\geq 1,500/\mu\text{l}$ $\geq 20\%$	0	+2
Atypical lymphocytes		No/U	Yes		0	+1
Skin involvement Skin rash (% body surface) Rash suggests DRESS Histology suggests DRESS	No No	No/<50% U U	$\geq 50\%$ Yes		−2	+2
Organ involvement ^a Liver Kidneys Lungs Muscle/heart Pancreas Others		No/U	Single organ Yes Yes Yes Yes Yes Yes	2 or more	0	+2
Resolution ≥ 15 days	No	Yes			−1	0
Laboratory					0	+1
Hepatitis A,B, C						
EBV, CMV						
Mycoplasma, chlamydia						
ANA						
Blood culture						
If none positive and ≥ 3 negative			Yes			
Total score					−4	+9

U unknown/unclassifiable, *Min* minimum, *Max* maximum (score points), WBC white blood cells, EBV Epstein-Barr virus, CMV Cytomegalovirus, ANA antinuclear antibodies

Final score for DRESS: <2 points: excluded (not DRESS); 2–3 points: possible; 4–5 points: probable; >5 points: definite case of DRESS

^aAfter exclusion of other explanations; 1 organ = 1, 2 or more organs = 2

involvement, if the liver enzymes are twofold elevated on at least 2 different dates (Table 2) (Kardaun et al. 2007). The skin eruption is extensive and covers at least 50% of the body surface area (BSA), sometimes even $\geq 90\%$ (Fig. 1b). In such a state of erythroderma or exfoliative dermatitis, the skin eruption may lead to further complications, such as chills, fluid and protein loss (Ushigome et al. 2013).

In most cases, the reaction begins 2–6 weeks after the initiation of the inducing drugs. Aromatic antiepileptic agents (carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin), allopurinol, antibacterial sulfonamides including sulfasalazine, and vancomycin are the most frequent causes of DRESS (Kardaun et al. 2013).

2.9 Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), nowadays summarized as or called epidermal necrolysis (EN) due to common pathogenesis and causes, is a severe, often life-threatening condition with extensive morbidity and mortality. EN is characterized by epidermal necrosis and sloughing of skin and mucous membranes (Fig. 2 a–e). The amount of skin detachment related to the BSA distinguishes SJS from TEN: detachment is limited to less than 10% in SJS (Fig. 2a) and exceeds 30% in TEN (Fig. 2b) whereas detachment between 10 and 30% defines SJS/TEN-overlap (Table 3) (Bastuji-Garin et al. 1993; Mockenhaupt and Roujeau 2019).

EN is frequently caused by medications. However, approximately 25% of all cases and 50% of pediatric cases are not drug-induced. Most of these may be triggered by infection, predominantly viral respiratory infection and flu-like illness (Mockenhaupt and Roujeau 2019).

The time latency between beginning of drug use and reaction onset varies between 4 days and 4 weeks for different culprit agents. Allopurinol, certain



Fig. 2 Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). (a) Confluent macules with blister formation in SJS. (b) Extensive skin detachment in TEN. (c) Eye involvement with conjunctivitis and blepharitis. (d) Hemorrhagic erosions of lips and oral mucosa. (e) Erosions of genital mucosa in a young man

Table 3 Consensus definition of SJS/TEN (Bastuji-Garin et al. 1993)

Criteria	EM majus	SJS	SJS/TEN overlap	TEN with maculae	TEN on large erythema (without spots) ^a
Skin detachment (%)	<10%	<10%	10–30%	>30%	>10%
Typical target lesions	+	–	–	–	–
Atypical target lesions	Raised	Flat	Flat	Flat	–
Maculae	–	+	+	+	–
Distribution	Mainly limbs	Widespread	Widespread	Widespread	Widespread

EM erythema multiforme, SJS Stevens-Johnson syndrome, TEN toxic epidermal necrolysis

^aRecently these cases are thought to be forms of generalized bullous fixed drug eruption (GBFDE)

antiepileptic drugs (carbamazepine, lamotrigine, phenobarbital, phenytoin), antibacterial sulfonamides, nevirapine, and oxacam NSAIDs have been shown to carry the highest risk for EN (Mockenhaupt et al. 2008).

AGEP, DRESS, SJS/TEN, and severe cases of GBFDE are referred to as severe cutaneous adverse reactions (SCAR). They are rare, but potentially life-threatening. All age groups may be affected, but elderly patients more frequently.

3 Management of Cutaneous Adverse Reactions

3.1 General Considerations

Most drug reactions are of milder nature, but some are severe and prone to subsequent complications. In the beginning, it can be difficult to differentiate a benign rash from a severe condition. Therefore, the patient should be followed closely and clinical and laboratory investigations may have to be performed repeatedly. Whenever a severe reaction is suspected, basic investigations are recommended, such as assessment of internal organ involvement and comorbidity status through full blood count (FBC), urea and electrolytes (U&E) including magnesium/phosphate/bicarbonate, liver function tests (LFT), coagulation studies, glucose, chest X-ray, HIV, ESR, CRP (Arden-Jones and Mockenhaupt 2019).

To confirm the diagnosis and exclude differential diagnoses, samples for mycoplasma serology, swabs from lesional skin for virology and bacteriology should be performed when appropriate. Furthermore, a skin biopsy (lesional skin or just adjacent to a blister) should be taken for routine histopathology and in blistering eruptions also direct immunofluorescence to exclude bullous autoimmune disease (Ziemer and Mockenhaupt 2011).

Furthermore, photographs of the skin eruption should be taken to show the specific features and the extent of involvement (Mockenhaupt and Roujeau 2019).

Whenever a skin eruption is considered as being drug-induced, the potentially culprit agent should be identified and withdrawn. The group of SCAR reveals various timelines for onset of symptoms after beginning of drug use with the longest typically seen in DRESS (2–8 weeks) and the shortest in AGEP and GBFDE (1–2 days for most cases), whereas in cases of EN the offending drug is typically started 4–28 days before reaction onset (Fig. 3) (Cho et al. 2014; Mahboob and Haroon 1998; Sidoroff et al. 2007; Kardaun et al. 2013; Mockenhaupt et al. 2008).

The skin eruption of DRESS may be identical to that of a typical benign maculopapular eruption, however, distinct in the systemic features. In addition to the more delayed onset, DRESS usually shows a more florid and extensive eruption, often associated with facial swelling. The mortality of DRESS is mainly due to organ failure (e.g., of the liver) and has been reported as 2–6% (Kardaun et al. 2013). However, long-term morbidity after the acute stage can arise as a consequence of viral reactivation (HHV6/7; EBV; CMV) or induction of autoimmune phenomena (Ushigome et al. 2013).

The occurrence of a non-follicular pustular eruption should point to AGEP. However, numerous small pustules may also be seen in DRESS, but they are mainly follicular. AGEP typically presents as a rapidly arising erythema on which pustules appear, often localized on head, neck, and upper torso and/or predominantly in the body folds. Fever and neutrophilia are present and generalized pustular psoriasis is the main differential diagnosis (Sidoroff et al. 2001; Paulmann and Mockenhaupt 2019).

Blisters leading to epidermal detachment within a skin eruption considered as a hypersensitivity reaction are a key indicator of EN (Bastuji-Garin et al. 1993; Mockenhaupt and Roujeau 2019), but GBFDE should also be considered (Cho et al. 2014). EN, however, is associated with severe hemorrhagic erosions of mucous membranes (typically lips, oral mucosa, eyes, nose, genitalia, and bronchi). Although GBFDE also induces full-thickness epidermal necrosis histologically, the margins of erythematous areas are much more clearly defined than in EN, where detachment can be induced by trauma or friction in skin areas that may not appear affected (positive Nikolsky sign). Furthermore, mucosal involvement is limited and typically does not affect the ocular surface. In addition, mild mucositis may occur as well in DRESS and AGEP (Paulmann and Mockenhaupt 2019).

3.2 Specific Treatments

In AGEP systemic features of fever and neutrophilia are evident, but in most cases they resolve quickly when the culprit drug is withdrawn. Topical or oral corticosteroids may be considered in the acute stage, especially for inflamed or itchy areas of skin. The pustules resolve with a typical post-pustular desquamation, for which emollients can be helpful. Internal involvement, which is reflected by elevation of liver and kidney parameters, has been observed in up to 20% of mainly

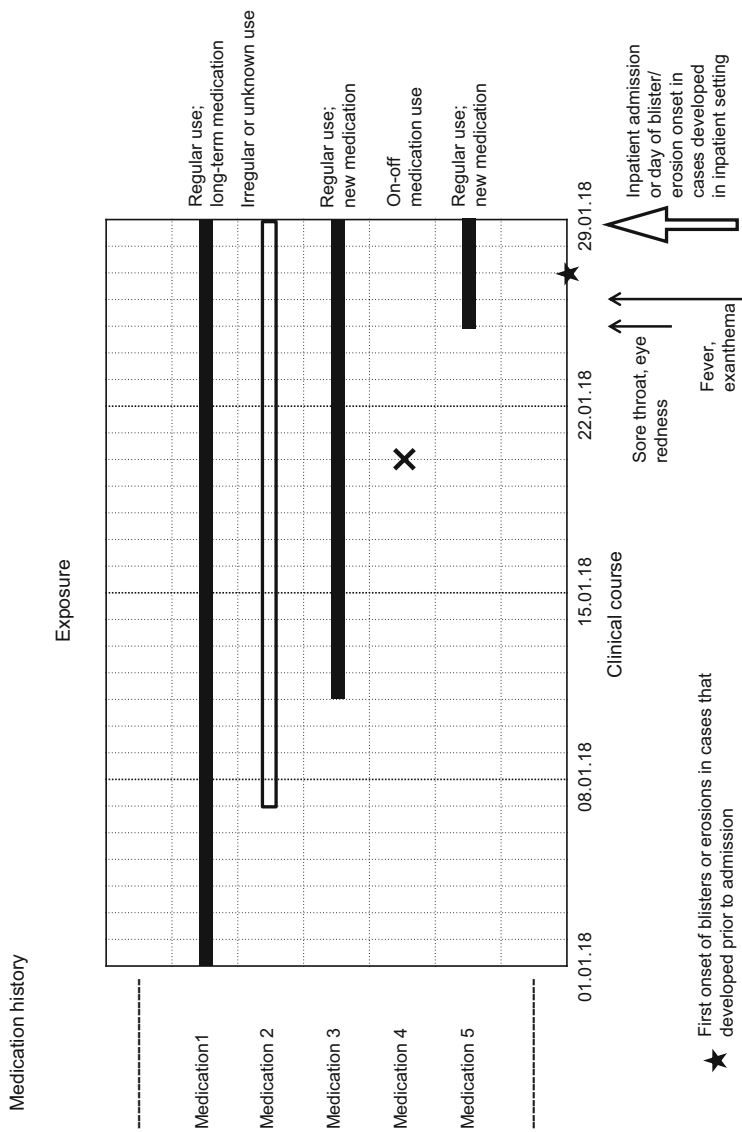


Fig. 3 Timeline of events (X-axis) and medication history (Y-axis) (Paulmann and Mockenhaupt 2019)

Table 4 SCORTEN (Bastuji-Garin et al. 2000)

Factor	Score	Weight/score value ^a
Age	≥40 years	1
Malignancy	Yes	1
Body surface area detached (day 1)	≥10%	1
Tachycardia	≥120/min	1
Serum urea	≥10 mmol/l	1
Serum glucose	≥14 mmol/l	1
Serum bicarbonate	<20 mmol/l	1
	Possible score	0–7

^aThe higher the total score value, the poorer is the prognosis of the patient

elderly patients. However, these elevated values are of transient nature and resolve without specific treatment (Hotz et al. 2013).

Therapy in cases of DRESS should be adjusted to the individual presentation of clinical features and various specialists should be involved accordingly. There is consensus among experts that treatment with corticosteroids is beneficial, topically applied in mild cases, but systemically administered in most cases of DRESS (Funck-Brentano et al. 2015). A dose of 1–2 mg/kg of prednisolone per day is recommended, but the duration of treatment has to be adjusted for each patient. It has been shown that patients who experience reactivation of HHV6/7 (also EBV/CMV) may have a prolonged and complicated course of their disease with repeated flare-ups. Therefore, the corticosteroid dose may have to be tapered very slowly in cases with viral reactivation (Shiohara and Kano 2017). For cases resistant to steroid therapy, successful use of ciclosporin and other immunosuppressants has been reported, whereas IVIG did not prove beneficial (Kirchhof et al. 2016; Joly et al. 2012).

EN can rapidly progress and has the highest mortality of all types of SCAR. Mortality increases with the amount of skin detachment and age of the patient. A useful measurement of prognosis is the “severity score of EN” called SCORTEN (Table 4) (Bastuji-Garin et al. 2000). It should be applied within 24 h after admission, but an analysis of daily scores over the first 5 days revealed that prognostic correlation was best on day 3 (Guégan et al. 2006). Patients with extensive skin detachment should be managed in an intensive care unit (ICU) or burn center, but the precise threshold will be dependent upon local practice. UK guidelines suggest that ICU transfer is appropriate at >10% (Creamer et al. 2016), whereas in Germany the assessment is based on evaluation of the overall medical status and may not be required until detachment of the BSA reaches 30%.

Higher room temperature with increased humidity and pressure relieving mattresses are helpful. Trauma to the affected skin should be minimized, and supportive care includes fluid replacement, nutrition, and analgesia (Mockenhaupt and Roujeau 2019; Creamer et al. 2016). Management of skin detachment may either be conservative (local disinfection and anti-adhesive gauze dressings) or surgical (removal of necrotic or loose skin and the so-called burn-bath). The most common

complication of EN is sepsis secondary to infection most often acquired through catheters and central venous lines. Prophylactic antibiotics are not recommended due to the risk of masking septicemia. Instead, regular microbiological swabbing from multiple sites of the skin and catheters may identify potential pathogenic bacterial organisms, which then can be treated appropriately (Mockenhaupt and Roujeau 2019).

Adequate treatment of affected mucous membranes should involve the relevant specialist with expertise in management of EN. This seems to be of major importance for eye involvement and it has been shown that early intervention with amniotic membrane grafting provides better outcomes (Sharma et al. 2000).

Immunomodulating therapy in EN has been discussed controversially for decades. However, some larger studies could identify a positive effect of short-term steroid use on disease outcome, which was not seen for intravenous immunoglobulins (IVIG) (Schneck et al. 2008; Zimmermann et al. 2017). In recent years different studies and systematic reviews came to the conclusion that ciclosporin A has beneficial effects in terms of disease progression and outcome (Valeyrie-Allanore et al. 2010; González-Herrada et al. 2017; NG et al. 2018).

A randomized controlled trial comparing the TNF-alpha inhibitor etanercept and systemic corticosteroids revealed a better outcome for etanercept. However, this study included mainly mild cases, the steroid therapy was done for as long as 3 weeks, suggesting a higher risk for complications in that group, and the clinical results were not statistically significant (Wang et al. 2018).

Supportive care in GBFDE is essentially the same as that in EN, but immunomodulating treatments have not been evaluated in studies. The majority of cases are less progressive and show a more benign clinical course, but a mortality comparable to that of EN with the same amount of skin detachment has been observed in one study. However, cases of GBFDE with fatal outcome concerned mainly patients who were substantially older and who had a previous event (Lipowicz et al. 2013).

4 Allergologic Testing in SCAR

If the inducing agent has been readily identified by taking a thorough and detailed medication history, no further testing is needed. The drug must be avoided lifelong. In some cases of SCAR the drug history is so complicated that it is impossible to identify the offending medication with any probable likelihood. Causality assessment should be performed by an expert in drug reactions, but one of the problems is that such specialists are often involved weeks, months, or even years after the acute event. As described above, the clinical reaction type with the typical exposure window of inducing medication is of major importance for evaluation of causality.

Skin tests, especially patch test, have been demonstrated to be useful in delayed hypersensitivity reactions. A patch test can also be safely performed in severe reactions, but the correct positive outcome seems to be highly variable. In EN, for example, it provided informative results in no more than 23% of cases. In AGEP and

DRESS the rate of correct positive patch test results was substantially higher but differed between various substances (Barbaud et al. 2013). Allopurinol, a frequent inducer of both DRESS and EN, is not illegible for patch test due to its low lipophilic potency and thus poor skin penetration. This supports the fact that extensive knowledge and specific expertise are required for skin testing in the field of drug reactions (Ardern-Jones and Mockenhaupt 2019). Intradermal testing is routinely used to investigate IgE-mediated drug allergy, when prick test was negative, and is also recommended for use in milder cutaneous adverse reactions. Because severe and even fatal reactions have been reported even when only small doses were applied, intradermal testing in cases of SCAR needs to be done with caution (Brockow et al. 2019; Phillips et al. 2019).

In vitro testing for investigation of SCAR seems to be the ideal approach, but many available tests, e.g. lymphocyte proliferation assay (LPA; syn. lymphocyte transformation test, LTT) and drug-induced cytokine assay (IFN- γ , ELISpot) remain experimental and are not yet used in routine practice. Furthermore, interpretation of the results is often difficult (Trubiano et al. 2018; Porebski 2017).

In recent years a strong association between various HLA-alleles and certain types of SCAR has been identified. Such associations are specific for certain reactions, drugs, and ethnicities. HLA tests are not designed for identification of the culprit drug in adverse reactions but may decrease the risk of SCAR in individuals before taking the decision for certain drug therapy. Thus, the number of carbamazepine-induced EN cases in Hong Kong was substantially reduced when patients tested positive for HLA-B*15:02 were not administered carbamazepine (White et al. 2018).

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