

# Approach to Severe Cutaneous Adverse Drug Reactions

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## Opinion Statement

Severe cutaneous adverse drug reactions (SCARs) can occur at any age and can be life threatening, although some drugs have been more frequently reported than others. The spectrum of SCARs includes acute generalized exanthematous pustulosis (AGEP), drug

reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome (HSS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Immediate withdrawal of the offending drug is the mainstay treatment in SCARs, and rechallenge often leads to recurrent reactions. Cross reactivity and multiple sensitivities have also been reported. The identification of the offending medication at the onset of the disease is therefore essential to avoid future exposures to the same or chemically related compounds. Various algorithms can be useful to identify the culprit drug in the acute stage. Delayed onset from the initiation of treatment differs in the various clinical entities. Therefore, a prompt, accurate diagnosis is crucial for proper identification of the offending agent. After resolution of the disease, cutaneous tests and *in vitro* tests can be useful for confirmation of drug causality and investigation of possible cross-reactivity. SCARs are rare diseases, given the incidence is extremely low. Multidisciplinary and international teams are required to study these diseases. Further research is needed to fully understand etiopathogenesis and for the development of specific treatments.

## Introduction and epidemiology

Cutaneous adverse drug reactions represent a variety of clinical conditions ranging from mild exanthematic reactions to severe life-threatening diseases [1, 2•]. Severe cutaneous adverse drug reactions (SCARs) include acute generalized exanthematous pustulosis (AGEP), drug reactions with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome (HSS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) [3].

AGEP is characterized by the acute development of numerous nonfollicular sterile pustules on an erythematous background. Fever and leukocytosis are usually present, and it frequently affects adults [4•].

DRESS includes skin eruptions, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ involvement (liver, kidney, lungs) [5]. It is characterized by a delayed onset and a prolonged course, with frequent relapses. Terms such as anticonvulsant hypersensitivity syndrome or allopurinol hypersensitivity syndrome, and, in the past, drug-induced pseudolymphoma [5, 6] have been used to describe the disease. The Japanese Research Committee on Severe Cutaneous Adverse Reactions (JSCAR) proposed the term DIHS [7]. DRESS/DIHS can occur in children; however, it most often affects adult patients [8].

SJS and TEN are severe mucocutaneous diseases characterized by subepidermal blisters and skin sloughing. They are considered severity variants of the same disease, differing only in the percentage of body surface area

(BSA) affected [9], and renaming them as epidermal necrolysis (EN) has been proposed [10••]. The current classification labels cases as SJS when skin detachment affects less than 10% of the BSA, those with more than 30% as TEN, and SJS/TEN overlap if the detachment ranges between 10% and 30% [11••]. We will use SJS/TEN to refer to this condition.

SCARs are rare diseases. Although reliable epidemiological data for AGEP are not available, an incidence of fewer than 10 cases per million inhabitants per year [3] and a death rate of approximately 4% have been estimated [4•, 12], although mortality is probably lower [13]. The incidence of DRESS/DIHS was estimated at 9–10 cases per million inhabitants per year in Asians [14, 15•]. The true incidence is difficult to determine because of the variable presentations and a lack of unified criteria for the condition. Moreover, the frequency could be increasing because of milder forms of the disease being reported [16–18]. Mortality rates of 5%–10% were found in retrospective studies [8, 16]. However, in a prospective study, only 1.7% of patients died during the acute phase [19••]. Finally, an incidence of 1.53–1.89 cases per million inhabitants per year was reported for the spectrum of SJS/TEN [12]. Albeit rare, the high mortality highlights the relevance of the disease. A recent cohort study reported mortality rates at 6 weeks after onset of 12%, 29%, and 46% for SJS, SJS/TEN overlap, and TEN, respectively [20]. The incidence of SJS/TEN is approximately 100-fold higher among HIV-infected individuals than in the general population [21]. The specific incidence of SCARs for most culprit drugs is

unknown, though for anticonvulsants it has been estimated at 1 to 10 per 10,000 new users [12].

The low incidence of SCARs makes their identification almost impossible in the pre-authorization phase in clinical trials. For this reason, SCARs are frequently

the cause of regulatory actions [22]. The low frequency of these reactions makes the study of the pathomechanisms involved difficult, requiring multicentric and international collaboration networks such as RegiSCAR ([www.regiscar.org](http://www.regiscar.org)) for their study.

## Clinical presentation and etiology

AGEP is characterized by the presence of multiple pinhead-sized nonfollicular pustules on an erythematous background, with predominant affection of the head and folds. The onset is acute and usually accompanied by a high fever and neutrophilia. Mucous membranes are seldom involved, but organ affection can be found in some cases. A postpustular desquamation pattern in collarettes is a typical feature. In the majority of patients, AGEP usually resolves spontaneously without sequelae shortly after drug discontinuation [23••, 24].

AGEP is caused by drugs in approximately 90% of cases [25]. There are isolated reports of AGEP associated with parasitic infections, spider bites, and herbal medications [25–29]. The drugs most frequently involved in AGEP are antibiotics, including macrolides and anti-infective sulfonamides, hydroxychloroquine, terbinafine, and diltiazem [4•]; however, extensive lists of various other medications have been reported [13, 24]. Exposure time is usually less than 15 days. Interestingly, two different patterns were observed: for exposures to antibiotics, the median duration of treatment was 1 day, whereas for all other associated drugs the median was 11 days [4•].

Cutaneous signs of DRESS are a widespread morbilliform rash, accompanied by infiltrated purpuric plaques and edema. The eruption progresses more or less rapidly to a diffuse, confluent, and infiltrated erythema. Facial edema develops in approximately one-half of cases [19••]. Inflammation and mucous membrane pain is present in nearly 50% of patients, usually at a single site (most often the mouth or pharynx), and does not progress to erosion. In 20%–30% of patients, erythema progresses to exfoliative dermatitis. Vesicles, tension blisters induced by dermal edema, or pustules can also occur [15•]. Lymphopenia can be seen at the beginning of the reaction. Other hematological alterations can be observed, but eosinophilia and the presence of atypical lymphocytes are characteristic features [8, 15•]. Hypogammaglobulinemia can be present at the onset of the disease [30]. Fever, malaise, lymphadenopathy, and skin eruption are the most common initial symptoms, although they are not invariably present. Fever usually precedes the rash and can be part of the prodromal symptoms [15•, 31•]. Diffuse lymphadenopathy is reported in 30%–60% of cases [8].

Involvement of at least one internal organ occurs in approximately 90% of patients; in 50%–60% two or more organs are involved, most frequently the liver, kidneys, and lungs [19••, 32, 33]. Other organs such as the gastrointestinal tract, pancreas, thyroid, brain, muscle, heart, peripheral nerves, and eyes can be affected [8].

Sequential reactivation of several herpes viruses has been reported [15•]. Human herpes virus-6 (HHV-6) infection has been detected in 40%–60% of the cases tested [34].

The onset of symptoms is highly variable, with patients developing 2–3 features followed by a stepwise development of further manifestations, often after the withdrawal of the culprit drug.

In most patients, the reaction begins 2–8 weeks after the introduction of the offending medication [19••]. Flu-like symptoms, pruritus, hypogammaglobulinemia, eosinophilia, fever, lymphadenopathy, and visceral involvement can precede exanthema by up to 4 weeks [35]. The skin eruption and visceral involvement generally resolve gradually. The average time to recovery is 6–9 weeks [8]. In up to 20% of cases, the disease can persist for several months, with a succession of remissions and relapses. Factors associated with a prolonged course include more severe liver involvement, atypical lymphocytosis [36], and HHV-6 reactivation [34]. Mortality has been associated with liver or kidney failure [15•]. Severe hepatitis is responsible for the majority of deaths associated with DRESS [37, 38]. Other symptoms such as tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleeding, and systemic inflammatory response syndrome were associated with a poor outcome in patients with DRESS [39].

The development of an autoimmune disease as an adverse long-term sequela of DRESS has been reported [40]. The time to diagnosis can be from several months up to several years, making it difficult to establish a direct association with the DRESS episode.

Drug causality is determined as highly probable in approximately 80% of DRESS cases [8, 19••]. In a study performed in Europe, anticonvulsants, allopurinol, sulfonamides, and antibiotics (especially vancomycin and minocycline) accounted for 96% of cases [19••, 41]. Other drugs frequently associated with DRESS are nevirapine, mexiletine, and abacavir [8, 15•], although hypersensitivity reactions to nevirapine and abacavir show some peculiar symptoms different from classical DRESS/DIHS [3, 42, 43].

Epidermal detachment with the appearance of burned skin and mucosal involvement is characteristic of SJS/TEN, but internal organ involvement (lungs, digestive tract, and kidneys) is also found. A prodromal phase with fever, malaise, and sore throat is characteristic. The first cutaneous lesions appear on the trunk or face typically after 4–28 days of drug intake and extend progressively to the rest of the body. Spots, atypical flat target lesions, and positive Nikolsky sign are the primary cutaneous features. Spots can coalesce and subepidermal blisters can appear under necrotic skin. Two or more mucous membranes are affected, with the development of oral ulcers and hemorrhagic crusts on the lips as well as severe conjunctival affection. Lymphopenia is often found, mainly affecting CD4+ T cells [44–46]. Electrolytic alterations (metabolic acidosis, low serum bicarbonate) cause increased morbidity and mortality.

SJS/TEN is a self-limiting disease. The acute phase lasts 8–12 days. Re-epithelialization begins in most cases after a few days and typically requires 2–4 weeks. After resolution, hyper- or hypopigmentation usually develops and can decrease over time. In some patients, partial or complete nail loss may occur. However, the sequelae of the mucosa, especially the ocular, have the most impact on the patient's quality of life and make SJS/TEN a chronic condition [47•].

A drug reaction is most frequently the etiological cause. More than 200 drugs have been reported to be related to SJS/TEN [48,49•]. In a recent study [50•], anticonvulsants, allopurinol, sulfonamides, NSAIDs, and antibiotics were the most frequently involved; however, 2% of patients did not receive any systemic medication prior to the reaction, and in 13% of cases drug causality was found to be unlikely or very unlikely. Idiopathic cases of SJS/TEN are more common in children, and only a very small percentage of these can be reliably related to infections such as herpes simplex virus and *Mycoplasma pneumoniae* [51, 52]. A variant of coxsackievirus A6 can induce severe mucocutaneous blistering reactions indistinguishable from SJS/TEN, mainly in children [53••].

## Pathophysiology

SCARs are type IV hypersensitivity reactions mediated by T cells [54]. The plurality of phenotypes has led to the subclassification of type IV hypersensitivity into four subgroups, considering the cytokine patterns and the participation of accessory subpopulations of leukocytes [55]. In particular, DRESS is usually considered a type IVb hypersensitivity reaction with a Th2 cytokine pattern and the participation of eosinophils; SJS/TEN is considered a type IVc hypersensitivity reaction with predominant participation of CTLs and NK cells as effector cells, and AGEP is regarded as a type IVd reaction in which IL-8/CXCL8 production by drug-specific T cells stimulates the recruitment of neutrophils to the skin. Th17 cells can also participate in AGEP [56].

The delayed reaction and the reproduction of the clinical picture upon re-exposure of the patients to the same drugs suggest prior sensitization and persistence of immunological memory. *In vitro* studies confirm specific T cell responses to incriminated drugs [57]. Various models for drug recognition by drug-specific T cells have been proposed [58••].

The participation of cytotoxic lymphocytes in SJS/TEN was supported by the finding of these subpopulations in blister fluids [59], which were able to kill target cells in a drug-dependent manner [60]. Later, Chung et al. found that granulysin, a cytotoxic molecule expressed by cytotoxic lymphocytes, was highly expressed by blister fluid-infiltrating cells [61]. These authors and other groups [45] have also found the presence of NK cells in the blister fluids. However, various effector leukocytes and downstream mediators participate in the final phenotypes of SCARs [62, 63].

Reactivation of herpes virus infection is considered specific to DRESS [64, 65]. Cross-reactivity between virus- and drug-specific memory T cells has been suggested to explain not only DRESS relapses [15•] but also cutaneous reactions in SJS/TEN [66•].

Genetic analyses performed to search for biomarkers have identified human leukocyte antigen (HLA)-I molecules as the most relevant genes, reinforcing the hypothesis of a drug-specific immune cell response [67]. Interestingly, the HLA-I alleles identified have proven to be not only drug-specific, but in some instances disease- and ethnicity-specific. The most emblematic example is the strong association of HLA-B\*1502 and SJS/TEN

with carbamazepine in Southeastern Asian populations (odds ratio =58.1), but not in patients of European ancestry. In contrast, HLA-A\*3101 is a risk factor for DRESS (but not for SJS/TEN) from carbamazepine in both populations [68••, 69••]. Disease-specific associations of HLA-B\*3801 and A\*24:02 for lamotrigine-induced SJS/TEN or DRESS have been described [70]. The allele HLA-B\*5701 is strongly associated with abacavir hypersensitivity. Conversely, HLA-B\*5801 confers a predisposition to develop SJS/TEN and DRESS/DIHS from allopurinol. [71].

A single study found certain associations of HLA alleles and AGEP [23••]. A possible genetic basis for a small subset of patients with AGEP with mutations in IL36RN has been found [72].

The allelic variant CYP2C9\*3, which leads to reduced metabolism and increased serum concentrations of phenytoin, has been identified in patients with SCARs to phenytoin [73].

## Histopathology

The histologic hallmark of AGEP is the formation of subcorneal and/or sometimes intraepidermal pustules. Other features include epidermal spongiosis and edema of the papillary dermis. Necrosis of single keratinocytes, a leukocyte infiltrate including neutrophils and eosinophils with perivascular accentuation, is also frequently observed [74].

Histopathological examination of DRESS skin biopsies reveals a variable combination of spongiosis, acanthosis, interface vacuolization, perivascular lymphocytic infiltrate in the superficial dermis, and variable presence of eosinophils, erythrocytes, and dermal edema [75]. In a recent study, the most frequent pattern was interface dermatitis [76], although more than one pattern was frequently observed. Atypical lymphocytes were present in approximately one-third of cases.

Full-thickness necrosis of all epidermal layers is the pathognomonic feature of SJS/TEN, with a scarce dermal mononuclear infiltrate. In early biopsies, only scattered necrotic keratinocytes can be found [77] with a perivascular or dermoepidermal lymphocyte infiltrate [78].

## Diagnosis

Prodromes of SCARs and initial cutaneous exanthematic lesions can be indistinguishable from mild reactions or viral infections. Diagnostic criteria for SCARs have recently been reviewed, as well as the differential diagnosis of the clinical presentations [48, 79, 80].

A scoring system for the diagnosis of AGEP has been published by the RegiSCAR group [23••], with those cases scored with  $\geq 8$  points labeled as definite (Table 1). However, this score was developed primarily for retrospective evaluation. The diagnosis of AGEP is suspected in patients presenting the following: (1) rapid development of a febrile pustular eruption a few hours or days after beginning a drug treatment; (2) clinical finding of dozens to hundreds of pinhead-sized, nonfollicular pustules on a background of edematous erythema with accentuation in skin folds and flexures; (3) marked neutrophilic leukocytosis ( $>7000/\mu\text{l}$ ); (4) pustule smear and culture negative for

**Table 1. AGEP validation score (RegiSCAR) [23••]**

|                                                                                   |                                                                                     |                 | Score |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------|-------|
| Morphology                                                                        | Pustules                                                                            | Typical         | +2    |
|                                                                                   |                                                                                     | Compatible      | +1    |
|                                                                                   |                                                                                     | Insufficient    | 0     |
|                                                                                   | Erythema                                                                            | Typical         | +2    |
|                                                                                   |                                                                                     | Compatible      | +1    |
|                                                                                   |                                                                                     | Insufficient    | 0     |
|                                                                                   | Distribution/pattern                                                                | Typical         | +2    |
|                                                                                   |                                                                                     | Compatible      | +1    |
|                                                                                   |                                                                                     | Insufficient    | 0     |
|                                                                                   | Postpustular desquamation                                                           | Yes             | +1    |
|                                                                                   |                                                                                     | No/insufficient | 0     |
| Course                                                                            | Mucosal involvement                                                                 | Yes             | -2    |
|                                                                                   |                                                                                     | No              | 0     |
|                                                                                   | Acute onset ( $\leq 10$ days)                                                       | Yes             | 0     |
|                                                                                   |                                                                                     | No              | -2    |
|                                                                                   | Resolution ( $\leq 15$ days)                                                        | Yes             | 0     |
|                                                                                   |                                                                                     | No              | -4    |
|                                                                                   | Fever $\geq 38^{\circ}\text{C}$                                                     | Yes             | +1    |
|                                                                                   |                                                                                     | No              | 0     |
| Histology                                                                         | PMN $\geq 7000/\mu\text{l}$                                                         | Yes             | +1    |
|                                                                                   |                                                                                     | No              | 0     |
|                                                                                   | Suggestive of other disease                                                         |                 | -10   |
|                                                                                   | Not representative/no histology                                                     |                 | 0     |
|                                                                                   | Exocytosis of PMN                                                                   |                 | +1    |
|                                                                                   | Non-follicular unspecific pustules                                                  |                 | +2    |
|                                                                                   | Subcorneal and/or intraepidermal pustule with spongiotic epidermis and dermal edema |                 | +3    |
| Total score $\leq 0$ : no case; 1-4: possible; 5-7: probable; $\geq 8$ : definite |                                                                                     |                 |       |

bacteria; (5) rapid resolution of the rash after drug discontinuation. Histological examination of a skin biopsy is necessary to confirm the diagnosis and to rule out other pustular eruptions.

AGEP should be differentiated from generalized acute pustular psoriasis (von Zumbusch type). Criteria that favor a diagnosis of generalized acute pustular psoriasis include a history of psoriasis, longer duration of fever and pustular eruption, and absence of drug exposure [23••]. Severe cases of AGEP presenting with atypical target lesions and confluent pustules mimicking a positive Nikolsky sign can be difficult to differentiate from SJS/TEN [81]. Features that favor a diagnosis of SJS/TEN include a longer latency between drug exposure and clinical manifestations, severe involvement of the mucous membranes, and histological

findings of full-thickness epidermal necrosis. Nonetheless, there are isolated reports of overlap cases with clinical and histological features of both AGEP and SJS/TEN [82]. Pustules can also occasionally occur in patients with DRESS. However, DRESS is characterized by a much longer latency, a more severe and prolonged clinical course, eosinophilia or atypical lymphocytosis in the peripheral blood, signs and symptoms of visceral involvement, and different histology. Cases with features of both DRESS and AGEP have been reported [83].

Two scoring systems have been developed for the diagnosis of DRESS/DISH (Tables 2 and 3). The JSCAR group score [84] classifies the reactions into typical or atypical, with reactivation of HHV-6 as mandatory for a typical DISH. The score developed by RegiSCAR classifies the reaction as possible, probable, or definite DRESS [31•, 85••]. The diagnosis of DRESS is suspected in patients receiving a drug treatment and presenting the following: (1) skin eruption (morbilliform or diffuse, confluent, and infiltrated); (2) fever; (3) facial edema; (4) enlarged lymph nodes. The clinical suspicion can be substantiated by a history of exposure to a high-risk medication in the previous 2–6 weeks, studies demonstrating organ involvement, and a skin biopsy. The initial laboratory evaluation tests include a complete blood cell count (to investigate eosinophilia and atypical lymphocytes), liver function tests, serology for viral hepatitis to exclude viral infection in patients with abnormal liver tests, and serum creatinine and urinalysis to investigate kidney involvement. Because not all the features develop simultaneously, periodic examinations are recommended.

There is no consensus on the definition of internal organ involvement in DRESS. Detailed criteria for the scoring system proposed by RegiSCAR have been published [85••].

Histological findings, although not specific, can exclude other SCARs. Testing for herpes virus infections can be useful because viral infection/reactivation could be the cause of a prolonged course and increased risk of complications.

Other SCARs, viral or bacterial infections, hypereosinophilic syndrome, or lymphoma can present with clinical symptoms mimicking DRESS [79]. Dermal edema can lead to skin detachment that mimics SJS/TEN; however, overlap cases have been reported [86].

**Table 2. DIHS diagnostic score (JSCAR) [7]**

1. Maculopapular rash developing >3 weeks after starting treatment with a limited number of drugs
2. Prolonged clinical symptoms upon drug discontinuation
3. Fever ( $>38^{\circ}\text{C}$ )
4. Liver abnormalities ( $\text{ALT} > 100$ )\*
5. Leukocyte abnormalities (at least 1 present)
  - a) Leukocytosis ( $>11 \times 10^9/\text{l}$ )
  - b) Atypical lymphocytosis ( $>5\%$ )
  - c) Eosinophilia ( $>1.5 \times 10^9/\text{l}$ )
6. Lymphadenopathy
7. HHV-6 reactivation (2nd–3rd week)

\*This can be replaced by other organ involvement  
7 criteria: Typical DIHS; 5 criteria: atypical DISH

**Table 3. DRESS diagnostic score (RegiSCAR) [31•]**

| Score                                                              | −1                                                     | 0     | 1                                               | 2           | Min | Max |
|--------------------------------------------------------------------|--------------------------------------------------------|-------|-------------------------------------------------|-------------|-----|-----|
| Temperature $\geq 38.5^{\circ}\text{C}^*$                          | N                                                      | Yes   |                                                 |             | −1  | 0   |
| Lymphadenopathy                                                    |                                                        | No/U  | Yes                                             |             | 0   | 1   |
| Eosinophilia                                                       | -                                                      | No/U  | 700–1499                                        | $\geq 1500$ | 0   | 2   |
| -Eosinophils/ml                                                    |                                                        |       | 10%–19.9%                                       | $\geq 20\%$ |     |     |
| -% (if WBC < 4000)                                                 |                                                        |       |                                                 |             |     |     |
| Atypical lymphocytes                                               |                                                        | No/U  | Yes                                             |             | 0   | 1   |
| Skin Involvement                                                   | No                                                     | No/U  | >50%                                            |             | −2  | 2   |
| - % BSA                                                            | No                                                     | U     | Yes                                             |             |     |     |
| - Rash suggests DRESS**                                            |                                                        | Yes/U |                                                 |             |     |     |
| - Histology suggests DRESS                                         |                                                        |       |                                                 |             |     |     |
| Organ involvement                                                  |                                                        | No/U  | Single organ                                    | 2 or more   | 0   | 2   |
| L/K/L/M/H/P/O                                                      |                                                        |       | Yes/Yes/Yes/Yes/Yes/Yes                         |             |     |     |
| Resolution $\geq 15$ days                                          | No                                                     | Yes   |                                                 |             | −1  | 0   |
| Serology/PCR/<br>VHA,B,C; EBV; CMV;<br>Mycoplasma/chlamydia<br>ANA |                                                        |       | Yes if none positive<br>and at least 3 negative |             | 0   | 1   |
| Blood culture                                                      |                                                        |       |                                                 |             |     |     |
| Total score                                                        | <2: excluded; 2–3: possible; 4–5 probable; >5 definite |       |                                                 |             | −4  | 9   |

\*38°C if axillary

\*\*At least two of the following: facial edema, infiltrated plaques, scaling, purpura

SJS/TEN is suspected in patients with skin eruptions and mucosal involvement. Flu-like prodromal symptoms precede the mucosal lesions from 1–3 days. Photophobia, conjunctival itching or burning, and difficulty swallowing can be early symptoms of mucosal involvement. In some patients, an exanthematous eruption can precede the development of severe skin symptoms. Clinical findings include atypical flat target lesions or maculae (starting in the face and upper trunk and spreading symmetrically), skin pain, positive Nikolsky sign, skin detachment, and erosions in mucous membranes. Criteria for diagnosis of SJS, TEN, and SJS/TEN overlap are shown in Table 4 [11••]. Differential diagnosis includes mainly erythema multiforme major (EMM), staphylococcal scalded skin syndrome, autoimmune bullous diseases, and generalized bullous fixed drug eruption (GBFDE). EMM is the primary differential diagnosis for SJS [87••]. In GBFDE, mucosal involvement is usually absent. Moreover, large red or brown plaques with overlying bullae are separated by large areas of healthy skin. Skin biopsy usually shows a moderate mixed infiltrate.

Severe cases of AGEP or DRESS can also mimic some features of SJS/TEN (see above). Histological examination of cutaneous lesions is important for accurate diagnosis, and immunofluorescence tests are critical for differential diagnosis of autoimmune bullous diseases.

The SCORTEN scale, a prognostic score algorithm that includes variables such as age, active malignancy, extent of epidermal detachment, tachycardia,

**Table 4. Consensus definition of severe blistering diseases (modified from [11••])**

| Features            | EEMM                      | SJS                             | SJS/TEN overlap                 | TEN with maculae (spots)        | TEN on widespread erythema (without spots) |
|---------------------|---------------------------|---------------------------------|---------------------------------|---------------------------------|--------------------------------------------|
| Skin detachment     | <10%                      | <10%                            | 10-30%                          | >30%                            | >10%                                       |
| Typical targets*    | Yes                       | -                               | -                               | -                               | -                                          |
| Atypical targets    | Raised                    | Flat                            | Flat                            | Flat                            | -                                          |
| Maculae (spots)     | -                         | Yes                             | Yes                             | Yes                             | -                                          |
| Dissemination       | Predominantly extremities | Predominantly trunk/generalized | Predominantly trunk/generalized | Predominantly trunk/generalized | Predominantly trunk/generalized            |
| Mucosal involvement | Mild                      | Severe**                        | Severe**                        | Severe**                        | Severe**                                   |

\*Raised lesions with three concentric zones  
 \*\*Two sites

urea plasma levels, glycemia, and low bicarbonate, has been developed to evaluate the severity of SJS/TEN on admission [88]. Its use is now controversial because of improved supportive care in most centers.

## Drug causality assessment in the acute phase

Withdrawal of the suspected medication(s) is the mainstay of treatment for SCARs and therefore an urgent requirement for improving the immediate prognosis. A proper identification of the drug responsible for the disease is therefore essential.

Several methods have been proposed to assess the causal relationship between an adverse event and a suspected medication. Most of these belong to one of three categories: (1) expert clinical judgment; (2) Bayesian approaches; (3) algorithms. Clinical judgment is the first mandatory step, largely used in daily practice. However, an expert decision presents pitfalls, such as subjectivity and lack of standardization. Bayesian approaches require much more information than is usually available and thus have obvious limitations for their routine application in daily practice. Algorithms are much easier to apply and are the preferred method [89]. Most combine five criteria: temporal sequence, dechallenge, rechallenge, previous reporting, and the existence or not of other potentially causal alternatives [90, 91]. Several National Pharmacovigilance Systems have also developed their own algorithms, all based on the essential five criteria mentioned above [92, 93]. When compared with clinical judgment, causality algorithms represent the highest levels of observed agreement: high (nearly 100%) sensitivity and positive predictive value, but low (no more than 37.5%) specificity and negative predictive values [89].

When evaluating drugs involved in SCARs, it is important to keep in mind substantial differences in the induction/latency periods in these diseases.

Therefore, an early accurate diagnosis and thorough anamnesis are crucial in order to pinpoint the culprit drug. Moreover, in some DRESS cases, multiple drug sensitizations occur to drugs that are introduced during the course of the disease. ALDEN [50•] is an example of a specific algorithm developed by the RegiSCAR study group to evaluate drug involvement in SJS/TEN cases.

## Management and treatment

There are three key aspects of management: (1) immediate withdrawal of the culprit drug, which is the mainstay treatment; (2) supportive measures and monitoring of peripheral blood cell counts and serum chemistry with evaluation of hepatic and renal functions; (3) pharmacological treatment.

AGEP is a self-limiting disease with a favorable prognosis. Patients with severe forms of AGEP are usually hospitalized for treatment. Older or compromised patients with fever and widespread eruption can require fluid, electrolytes, and nutritional support. For symptomatic relief of pruritus and skin inflammation, topical corticosteroids are used. In the pustular phase, antiseptic solutions can be used for prevention of bacterial superinfection. In the desquamation phase, emollients are helpful in restoring skin barrier function [94].

In DRESS cases, sequential blood tests might be necessary because symptoms and signs can appear progressively. We also suggest avoiding introducing new medications, if possible, during the course of DRESS and in patients in whom DRESS is suspected because of the risk of multiple drug sensitizations [95•]. A recent study [96••] suggests that topical steroids are a better choice in the management of mild cases of DRESS because systemic steroids have been associated with an increase in infections, herpes virus reactivation, and relapses. For more severe cases, there is consensus on treating with systemic corticosteroids [3]. Optimal doses and duration have not been established. Initial doses are usually maintained until remission starts and then are progressively tapered. Antiviral agents can be useful for cases of well-documented viral reactivation leading to severe complications [3].

If blisters or mucosal erosions develop, SJS/TEN should be suspected. Complete guidelines for the management and treatment of patients with SJS/TEN have been recently published [48, 49••, 97••]. Serologies for mycoplasma, herpes virus, and enteroviruses can be important to rule out an infectious disease, especially in children. A cutaneous biopsy is mandatory. Supportive care in specialized wards is the mainstay of treatment in SJS/TEN and includes thermoregulation, airway protection, fluid replacement, nutritional support, pain management, venous thromboembolism prophylaxis, and monitoring of infection. Transfer to a specialized burn unit with experienced nursing staff improves survival. Ophthalmological assessment is necessary within the first 24 h of admission [98]. In females (children and adults), gynecological assessment is recommended at admission [99] and during hospitalization. Similarly, urological assessment is recommended for men. Respiratory tract evaluations should be performed by an otorhinolaryngologist [100] for early detection of bronchial epithelium lesions. For skin management, no specific dressing has

proven better outcomes in SJS/TEN. Debridement is discouraged [49••]. Suctioning blister fluid as well as leaving the blister roof minimizes infection and acts as a natural dressing. SJS/TEN has a major psychological impact on patients and their family; psychological assessment and support should be continuous. Beyond supportive care, there are no established therapies for SJS and TEN. Several immunosuppressive or immunomodulatory therapies have been used in clinical practice, including systemic corticosteroids, intravenous immune globulin (IVIG), cyclosporine, plasmapheresis, GM-CSF, N-acetylcysteine, cyclophosphamide, and anti-tumor necrosis factor therapies [10••, 48, 49••, 101, 102]. However, none have been studied in randomized trials except thalidomide, which was found to be harmful [103].

The use of systemic corticosteroids in SJS/TEN remains controversial [104, 105]. Early observational studies indicated a higher frequency of complications and increased mortality for patients with TEN treated in burn units with corticosteroids. Subsequent studies suggested that a short course of moderate to high doses of systemic corticosteroids might not be harmful and could have a beneficial effect if administered early in the course of the disease. However, an updated mortality analysis of the RegiSCAR cohort and a systematic review of case series did not confirm a survival benefit for patients treated with systemic corticosteroids. Steroid pulse therapy has recently been proposed with initial encouraging results, although the experience is still limited. Interestingly, the exposure to corticosteroids before the onset of SJS/TEN did not affect the disease severity and mortality; however, corticosteroids prolonged the latency period from drug initiation to onset and progression of the disease [106].

Data surrounding the use of IVIG for SJS/TEN are limited and conflicting. A large European cohort study could not demonstrate a significant survival advantage for patients treated with IVIG compared with supportive care only [104]. A 2015 meta-analysis of 13 studies of patients who received IVIG found a nonsignificant difference in the mortality among SJS/TEN patients treated or not with IVIG [107].

The use of cyclosporine has recently attracted much attention. Several studies have suggested important mortality benefits, probably linked with an early arrest of disease progression, in the absence of significant toxicity [108–111, 112••]. Etanercept has been used successfully in a small number of patients [113].

## Confirmation of causality

Diagnosis of drug causality in SCARs is often a problem, given rechallenge is not feasible [114]. In polymedicated patients, it can be difficult to identify the culprit agent based exclusively on chronological criteria. *In vivo* and *in vitro* tests are currently used upon resolution of the disease [115].

Regarding *in vivo* tests, epicutaneous drug patch tests (DPTs) can be helpful because they imply only a moderate re-exposure of patients to offending drugs. Two European guidelines [116••, 117] have been published. Systemic corticosteroids must be discontinued at least 1 month before testing, and topical corticosteroids should not be applied in the

week before testing. DPTs appear to have a good specificity but a low sensitivity. In a recent study, DPTs were positive in 56.7% of 134 cases. Intradermal tests (IDTs) can also be useful if a negative result with a patch test is obtained and a suitable injectable form is available [115, 117]. DPT and IDT sensitivity appear to depend on the drug involved and the clinical features under evaluation. Because the sensitivity of both procedures is not optimal, there is a risk of eliciting an adverse reaction even for patients with negative skin test results. IDTs appear to be more sensitive than DPTs, but less specific.

Positive DPTs have been reported in 7 of 14 patients with SJS/TEN [118] and in 26 of 45 AGEP cases [116••]. In DRESS cases, overall positive rates for patch tests range from 32.1% to 64%, or 51.5% in the case of anticonvulsants. Particularly for carbamazepine, the positive rate rose to more than 70% [116••, 119, 120•]. Only isolated data on IDTs in DRESS have been reported [121, 122]. DPTs do not appear to be very sensitive for SJS/TEN, as only 2 of 22 patients, and 4 of 17 tested [116••, 118] had positive results. Nevertheless, sensitivity could also be dependent on the drug tested. Ten positive DPTs for carbamazepine were obtained in 16 patients with SJS/TEN [120•].

*In vitro* tests have the advantage of being absolutely safe and are useful for analysis of cross-reactivity. A positive result reflects specific sensitization of the patient to the test drug, which is a risk factor but does not prove causality; however, it can support the diagnosis and can also pinpoint the responsible agent if the patient took several drugs. The lymphocyte transformation test (LTT) is the most widely used [123, 124].

There is controversy over the specificity and sensitivity of the LTT in general. In the largest group of patients reported [125••], 78% sensitivity and 85% specificity were calculated. Some reports suggest that the results might depend on the drug and the clinical entity. The lack of a gold-standard diagnostic test, along with the paucity of large-scale studies, precludes accurate determination in SCARs.

In AGEP and DRESS, most information is derived from small studies [82, 93, 121, 125••, 126–135]. In an analysis of 41 Spanish DRESS cases, 74% sensitivity and 78% specificity of LTT were reported [136]. Low sensitivity has been reported for LTT in SJS/TEN [137]. Some authors suggest that performance of the test during the acute phase in SJS/TEN would improve the results [130, 138]. However, only 50% of the patients tested positive. In a study performed in 26 Spanish cases of SJS/TEN after complete resolution of the clinical symptoms, 19 tested positive. Moreover, high rates of false-positive results were obtained during the acute reaction (T Bellón, unpublished). Although LTT requires a specialized laboratory and skilled personnel, and is not standardized for each drug, there is consensus among laboratories regarding protocol and cutoff for positivity [124].

Flow cytometry analysis of lymphocyte proliferation can be used as an alternative. Few reports have been published on SCARs [126, 139].

Standard proliferation assays have been supplemented by the analysis of the secretory or cytotoxic potential of effector cells and upregulation of cell surface activation markers such as CD69 [140]. The analysis of cytokine release by ELISA or ELISPOT upon drug stimulation of PBMCs is used by several laboratories. However, there is no consensus on the protocol or

criteria for positivity. Moreover, various cytokines could be involved in different clinical entities [123, 141]. Positive ELISPOT assays for IFN- $\gamma$  production have been reported in DRESS cases [142, 143]. Recently, 13 allopurinol-induced DRESS cases were reported with positive IFN- $\gamma$  ELISPOT, whereas 21 control donors tested negative [144]. Similarly, 8 of 11 SJS/TEN patients tested positive. Interestingly, the results of this study were independent of the time of sampling and appear not to be influenced by corticosteroid treatment.

## Future use of medication and prevention

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Since re-exposure can induce another episode of AGEF, patients with DRESS or SJS [145–150] should be counseled to avoid the offending medication and be provided with a written list of the generic and brand names of the drug. The advice to avoid the culprit drug and other chemically related medications should be extended to other family members, especially in cases when a risky HLA allele has been identified.

HLA genotyping has proven to be useful for certain drugs in populations in which the risk allele is prevalent. Testing for HLA-B\*1502 in Asians and HLA-B\*5701 in all populations is recommended by regulatory agencies worldwide before treatment with carbamazepine and abacavir, respectively, and has proven to be effective [58••]. HLA-B\*B5801 testing has also proven useful in Taiwan for patients treated with allopurinol [151].

## Conclusions

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- SCARs can compromise the life of the patient.
- Early diagnosis and withdrawal of the responsible drug is essential.
- Diagnosis and management of SCARs require a multidisciplinary approach.
- Prompt inspection of skin biopsies should be encouraged for a rapid differential diagnosis.
- Identification of culprit drugs and avoiding them in the future is of utmost importance.
- SCAR prevention strategies should be implemented.

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## Compliance with Ethical Standards

### Conflict of Interest

Drs. Bellón, Cabañas, González-Herrada, Ramírez, González-Ramos, López San Martín, González-Valle, Fiandor, Lerma, Roustán, and de Abajo declare that they have no conflicts of interest.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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