



Severe Cutaneous Adverse Drug Reactions: Presentation, Risk Factors, and Management

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Abstract

Purpose of Study Immune-mediated adverse drug reactions occur commonly in clinical practice and include mild, self-limited cutaneous eruptions, IgE-mediated hypersensitivity, and severe cutaneous adverse drug reactions (SCAR). SCARs represent an uncommon but potentially life-threatening form of delayed T cell-mediated reaction. The spectrum of illness ranges from acute generalized exanthematous pustulosis (AGEP) to drug reaction with eosinophilia with systemic symptoms (DRESS), to the most severe form of illness, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Recent Findings There is emerging literature on the efficacy of cyclosporine in decreasing mortality in SJS/TEN.

Summary The purpose of our review is to discuss the typical presentations of these conditions, with a special focus on identifying the culprit medication. We review risk factors for developing SCAR, including HLA alleles strongly associated with drug hypersensitivity. We conclude by discussing current strategies for the management of these conditions.

Keywords Severe cutaneous adverse drug reaction (SCAR) · Acute generalized exanthematous pustulosis (AGEP) · Drug reaction with eosinophilia and systemic symptoms (DRESS) · Stevens-Johnson syndrome (SJS) · Toxic epidermal necrolysis (TEN) · HLA-associated drug hypersensitivity

Introduction

Adverse drug reactions occur commonly in clinical practice and range from mild, self-limited reactions to severe,

life-threatening medical emergencies. Depending on the presentation, adverse drug reactions are managed by a host of clinical specialties, including pediatricians and primary care physicians as well as dermatologists and allergists and clinical immunologists. Adverse drug reactions vary from expected side effects and non-immune mediated intolerances, to immune-mediated reactions, including IgE-mediated immediate hypersensitivity and non-IgE-mediated immune reactions. Severe cutaneous adverse reactions (SCAR) encompass a spectrum of delayed type hypersensitivity reactions mediated by the adaptive immune system. A universal feature of these conditions is the integral role of T cells, which infiltrate skin lesions and are key effector cells in the pathogenesis of end-organ damage. Unlike IgE-mediated reactions, sensitization is not necessary, and drug reacting T cells can expand upon their initial encounter with the culprit drug and lead to clinical manifestations [1]. Given the severity of these reactions, early recognition and treatment is essential in improving clinical outcomes. We will review the most common forms of SCAR, discuss genetics and predictive tests to minimize the risk of reactions, and discuss the most recent evidence to guide management.

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AGEP

Acute generalized exanthematous pustulosis (AGEP) is the mildest form of SCAR and develops rapidly after the initiation of medical therapy, typically within a few hours and up to 5 days. Although information on epidemiology is poorly understood, prevalence is estimated to be between 0.35–5/million [2]. In AGEP, non-follicular pustules appear on the subcorneal skin or intraepidermally, often on the face but also on the trunk. The palms and soles are rarely affected. The pustules are sterile, i.e., they are not contaminated by bacterial or fungal infection and contain large numbers of neutrophils. Pustules can be accompanied by neutrophilia and fever. CD4+ T cells have been identified at the periphery of lesions and secrete high levels of CXCL8, which is a strong chemoattractant of neutrophils [3]. Withdrawal of the culprit drug typically leads to resolution of symptoms within days to 2 weeks. AGEP is associated with a favorable prognosis with rare long-term sequelae and minimal mortality.

DRESS

Drug reaction with eosinophilia and systemic symptoms (DRESS) presents with a skin rash, along with immune-mediated end-organ damage. According to prospective surveys from the hospital setting, the prevalence of DRESS is estimated to be between 1/1000 to 1/10,000 drug exposures [4, 5]. Patients typically present with a maculopapular skin eruption along with fever, lymphadenopathy, peripheral eosinophilia, and evidence of end-organ involvement. The RegiSCAR study group proposed patients meet at least three of the following criteria to make a diagnosis of DRESS: (1) acute skin rash, (2) fever ($> 38^{\circ}\text{C}$), (3) lymphadenopathy of at least two sites, (4) involvement of at least one internal organ, (5) lymphocytosis ($> 4 \times 10^3/\mu\text{L}$) or lymphocytopenia ($< 1.5 \times 10^3/\mu\text{L}$), (6) blood eosinophilia ($> 10\%$ or $700/\mu\text{L}$), and (7) thrombocytopenia ($< 120 \times 10^3/\mu\text{L}$). Based on this scoring system, patients were classified into definite, probable, possible, or no diagnosis of DRESS [6]. The timely diagnosis of DRESS can be difficult because of the late onset of symptoms after the introduction of the culprit drug. Although symptoms usually develop after 2 to 8 weeks of treatment, a delay of up to 3 months between initiation of therapy and presentation of symptoms has been reported. Affected organs can include the liver, kidney, lungs, and heart. Organ damage is the major cause of morbidity and mortality, and in severe cases, organ transplantation should be considered [7]. In affected organs, CD3+ lymphocytes and eosinophils are felt to contribute to lesions. CD8+ and CD4+ infiltrating T cells have been shown to release inflammatory and cytotoxic mediators within lesions. Moreover, reactivation of herpes viruses (EBV, HHV-6, HHV-7, and HSV) can occur shortly after the start of

the disease. The role of this viral reactivation in the pathogenesis of DRESS remains debatable. DRESS requires long-term observation of the patient because unlike other SCARs, DRESS can recur after initial stabilization of the disease [8, 9]. Mortality rates of up to 10% have been reported in DRESS, and this is frequently due to liver failure or secondary infection. Higher mortality rates may also be associated with certain medications, such as allopurinol [10].

SJS/TEN

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a spectrum of the most severe form of SCAR. In these cases, large areas of epidermis become rapidly necrotic with resulting skin detachment. In SJS, there is less than 10% epidermal detachment, whereas TEN involves more than 30% of body surface area. SJS/TEN overlap is used to describe cases in between these two extremes. Depending on the country of origin, the overall incidence of SJS/TEN ranges from 1.9 cases per million in Europe [11] to 6.5 cases per million in Asia [12] to approximately 12 cases per million in the USA [3]. The main features of SJS and TEN are as follows: (i) dark purple macular lesions, (ii) blister formation and skin detachment (Nikolsky sign), (iii) involvement of mucosal surfaces. Histologically, SJS and TEN are both characterized by extensive cell death in the epidermis with a surprisingly sparse infiltration of inflammatory cells in the underlying dermis. Large numbers of CD8+ T cells and other cytotoxic cells (NK, NKT) are found within lesions [13]. SJS/TEN is also characterized by large concentrations of cytotoxic molecules in lesions, such as perforin, granzyme B, and granulysin [14–16]. Other inflammatory markers, such as $\text{IFN}\gamma$, $\text{TNF}\alpha$, soluble Fas ligand, and NK-activating molecules, can also be found within lesions [17]. It is important to clinically distinguish SJS from erythema multiforma majus (EMM), which is associated with underlying microbial infection, rather than due to a drug hypersensitivity reaction. EMM has a different pathophysiology resulting in necrosis occurring below the epidermis [11]. Unlike SJS/TEN, recurrence of EMM is fairly common. SJS and TEN are life-threatening conditions that require immediate medical care. Studies suggest SJS has a mortality of 10%, with global mortality rates as high as 30–40% in patients with TEN [18]. Mortality rates in the USA have been shown to be as high as 19.4% [19]. In addition to mortality, survivors also often experience a myriad of long-term sequelae, including changes in pigmentation and scarring of the skin, sicca symptoms, visual impairment, including blindness, periodontal disease, gastrointestinal ulceration, and vaginal and urethral stenosis, as well as increased autoimmunity [19, 20•].

SCAR-Associated Drugs and Non-Genetic Risk Factors

Although many medications have been reported to induce SCAR, and all medications must be considered, certain drugs are associated with a higher risk of reaction. Historically, anti-epileptic agents have been associated with a higher risk of inducing SCAR. In the European SCAR registry (REGISCAR), carbamazepine has been identified as the most common cause of DRESS [10] and the second most common cause of SJS/TEN [21]. Other anti-epileptics such as phenytoin have also been associated with SCAR. The risk of SCAR associated with various medications depends on multiple variables, including both genetic (discussed below) and non-genetic risk factors. Host factors that increase the risk of SCAR include underlying malignancy or the presence of systemic lupus erythematosus, along with underlying infections such as tuberculosis and HIV. Individuals with HIV infection have a 1000-fold increased risk of SCAR as compared to the general population [22]. Underlying infection not only increases the risk of SCAR, but may also lead to a more severe phenotype of illness, including an increased likelihood of ophthalmological complications [23]. Additionally, prescribing habits also affect the risk of SCAR. For example, doses of allopurinol greater than or equal to 200 mg daily have been associated with a higher risk of developing SJS/TEN [21]. In addition to allopurinol and aromatic anti-epileptic agents, other commonly associated drugs with SCAR include antimicrobial agents (cotrimoxazole, vancomycin, aminopenicillin, minocycline, sulfasalazine, dapsone) and NSAIDs (celecoxib, ibuprofen) (Table 1).

Genetics and Predictive Tests

Clinical data suggests that many SCAR reactions involve immune mechanisms, and genetic association studies have identified strong linkage between drug hypersensitivity reactions to several drugs and specific HLA alleles (Table 2). The strongest of HLA associations are HLA-B*57:01 with abacavir hypersensitivity syndrome (odds ratio = 960) [24, 25], HLA-B*15:02 with carbamazepine-induced SJS and TEN in Asian populations (OR > 1000) [26, 27], and HLA-B*58:01 with allopurinol-induced hypersensitivity syndrome and SJS/TEN (OR = 580) [28]. Carbamazepine DRESS/drug-induced hypersensitivity syndrome (DIHS) was associated with HLA-A*31:01 in European Caucasians (OR = 58) [29]. Dapsone DRESS/DIHS was associated with HLA-B*13:01 in Han Chinese (OR = 20) [30].

HLA alleles associated with SCAR that exhibit high odds ratio values show high negative predictive values (NPV > 99%), indicating that the adverse reaction occurs almost exclusively in individuals expressing a specific HLA allele (e.g.,

Table 1 Commonly associated drugs with SCAR

AGEP	DRESS	SJS/TEN
Latency periods		
Hours to days	2–6 weeks	1–4 weeks
Medications		
Penicillins	Allopurinol	Allopurinol
Macrolides	Carbamazepine	Carbamazepine
Diltiazem	Lamotrigine	Lamotrigine
Antimalarial agents	Phenytoin	Nevirapine
	Sulfasalazine	NSAIDs
	Vancomycin	Phenobarbital
	Minocycline	Phenytoin
	Dapsone	Sulfamethoxazole
	Sulfamethoxazole	Sulfasalazine

HLA-B*58:01 for allopurinol) [31••]. However, positive predictive values are significantly lower (PPV ranging from 0.9 to 55%). These data suggest that specific HLA alleles are necessary, but not sufficient to predict drug-specific SCAR with 100% accuracy (sensitivity and specificity). Genes encoding proteins involved in drug metabolism have been associated with SCAR, although with significantly lower levels of association. Genetic variants associated with SCAR that influence drug metabolism include P450 genes such as CYP3A4 [32], CYP2C9 [33], myeloperoxidase [34], and glutamate-cysteine ligase catalytic subunit gene GCLC [35].

Since individuals at high levels of risk can be identified (e.g., HLA-B*57:01 for abacavir), there are several examples in which pharmacogenomic testing and drug avoidance have been successful to prevent SCAR. A double-blind, prospective, randomized study involved 1956 HIV infected patients from 19 countries who had not previously received abacavir [36••]. Patients were given either standard of care (including therapy with abacavir) or HLA-B*57:01 screening, with exclusion of HLA-B*57:01-patients from abacavir treatment. In addition to clinical diagnosis of hypersensitivity reaction to abacavir, epicutaneous patch testing was also used as immunological confirmation of abacavir hypersensitivity. The study demonstrated that HLA-B*57:01 screening and drug avoidance effectively decreased toxicity by preventing hypersensitivity. The number needed to screen to avoid one abacavir-induced drug hypersensitivity reaction was 13. The FDA has indicated the need to add a Boxed Warning about the recommendation to test all patients for the HLA-B*57:01 allele before starting or restarting therapy with abacavir or abacavir-containing medications [37]. This screening practice is cost effective, reliable, and has quick turn-around time, and has thus been widely adopted by prescribing providers.

The Singapore Health Sciences Authority evaluated two common HLA allele-drug pairs associated with SCAR. Genotyping for HLA-B*15:02 for new users of

Table 2 Specific HLA alleles associated with SCAR

Drug and syndrome	HLA allele	HLA carriage rate	Disease prevalence	OR	NPV	PPV	NNT to prevent "1"
Abacavir ABC HSR	B*57:01	5–8% Caucasian < 1% African 2.5% African American	8% (3% true HSR and 2–7% false-positive diagnosis)	960	100% for patch test confirmed	55%	13
Allopurinol SJS/TEN and DRESS/DIHS	B*58:01	9–20% Han Chinese 1–6% Caucasian	0.1–0.4%	> 800	100% in Han Chinese	3%	250
Carbamazepine SJS/TEN	B*15:02	10–15% Han Chinese < 0.1% Caucasian	< 0.1–0.6%	> 1000	100% in Han Chinese (with other B75 serotype)	3%	1000
Dapsone DRESS/DIHS	B*13:01	2–20% Chinese 28%	1–4% Han Chinese	20	99.8%	7.8%	84

Specific HLA alleles have been strongly associated with SCAR. However, there may be a low probability that subjects with a positive screening test for the associated HLA allele will develop SCAR (e.g., PPV 3% for allopurinol). Statistics from (White et al. 2018)

carbamazepine in patients of Southeast Asian descent/ethnicity became a diagnostic standard in 2013 and widespread screening reduced the number of cases in Singapore from 18 per year to one case in the 4 years since implementation [31•]. Genotyping for HLA-B*58:01 for new users of allopurinol was not mandated due to lower efficacy and/or higher costs of alternative gout medications. It is expected that HLA types will be better integrated into electronic medical records in a manner that alerts physicians of patients at high risk for specific drug induced SCAR.

Management—General Principles

There is significant heterogeneity in the management of SCAR between treating specialties as well as regionally between institutions. Given the high rates of morbidity and mortality, early admission to a specialty intensive care unit that can provide a multidisciplinary approach to patient care should be considered. Burn units are often considered the preferred site of management of SCAR because of their expertise in managing skin involvement. Appropriate management of the affected skin can minimize temperature dysregulation, insensible fluid loss, and hemodynamic instability. Palmieri et al. demonstrated differences in treatment of TEN between burn centers and non-burn facilities. Burn centers provided more enteral nutrition, while using less prophylactic antibiotics and systemic corticosteroids. This study and others suggest that early referral to a burn center leads to improved outcomes in the management of TEN [38–41].

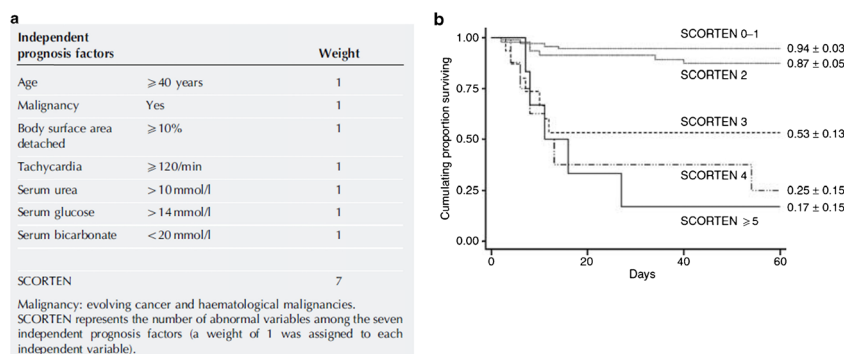
Identification and immediate discontinuation of the culprit drug remains the most important step in the management of

SCAR. Early withdrawal of the offending agent has been shown to decrease mortality in both SJS and TEN [42]. Although one can focus on common offending agents of SCAR (Table 1), all medications initiated within 8 weeks must be considered, including over-the-counter preparations. Validated drug causality assessment tools exist for all adverse drug reactions, as well as specifically for SJS/TEN, and may help with identification of the culprit medication [43, 44]. Additional principles of management include IV fluid resuscitation, providing adequate nutrition, pain control, and prophylaxis against thromboembolic complications and ulcer formation. Attempts at prevention of long-lasting sequelae, such as strictures of mucosal surfaces, may include early urologic/gynecologic examination, and possible use of urinary catheterization and/or vaginal molds/dilators [45]. If possible, oral feeding is preferred to parenteral nutrition and may help prevent esophageal adhesions. Prophylactic antibiotics are not recommended. For SJS/TEN, SCORTEN is a validated severity-of-illness score that should be calculated for all patients on days 1 and 3 of hospitalization. In addition to predicting prognosis and mortality, the SCORTEN can help triage patients to the correct inpatient setting [46•] (Fig. 1).

Management of AGEF

Approximately 90% of cases of AGEF are caused by medications, most commonly antibiotics. The remaining 10% are caused by underlying infection or thought to be idiopathic. Since AGEF is a self-limited condition with a favorable prognosis, management is based on withdrawal of the culprit drug, which typically leads to rapid resolution of symptoms, followed

Fig. 1 **a** SCORTEN Score. **b** Survival curves based on SCORTEN score on day 1



by conservative management aimed at controlling symptoms. Despite the absence of supporting studies, expert recommendations suggest using topical corticosteroids with or without systemic antihistamines [47, 48]. Systemic corticosteroids have not been shown to shorten disease duration and are generally not recommended in AGEp [49].

Management of DRESS

Mild cases of DRESS may be successfully treated with topical corticosteroids [50]. Although systemic corticosteroids do not appear to have detrimental effects and have not been demonstrated to increase the risk of infection, no randomized trials have shown a mortality benefit in the setting of DRESS. It remains unclear if systemic steroids decrease end-organ involvement or shorten disease duration in DRESS. Nevertheless, given the favorable risk/benefit analysis, most clinicians routinely use systemic corticosteroids for more severe cases or if there is evidence of end-organ involvement [10, 51]. There are case reports of IVIg in DRESS, but the utility remains uncertain, and most experts therefore do not recommend use of IVIg in DRESS [52, 53]. Lastly, given the notable safety concerns associated with antiviral agents (ganciclovir, forcartet, cidofovir), and the lack of supporting literature regarding efficacy, antiviral agents are not recommended in the treatment of DRESS.

Management of SJS/TEN

Like all clinical phenotypes of SCAR, discontinuation of the culprit agent is the most important step of management in SJS/TEN. These patients require a multidisciplinary approach by clinicians well versed in the management of these potentially life-threatening conditions.

Organ Specific Therapy

There is no consensus on the optimal management for skin and wound care, and different institutions use different approaches. A conservative and more commonly used approach recommends leaving denuded skin intact, since this serves as a natural barrier and biologic dressing. Surgical debridement is typically only considered in the presence of infection or if conservative management fails. A more aggressive surgical approach involves early debridement to remove detached epidermis that may become infected, followed by physiologic wound closure using dressings and/or grafting. Dorafshar et al. showed both strategies have similar mortality outcomes [54]. There was no information on whether one approach is superior to the other in regard to duration of illness or prevention of long-term sequelae. For additional skin care, large bullae may be aspirated and expressed. The application of emollients to the skin may help support barrier function and therefore decrease insensible fluid loss while facilitating re-epithelialization [55].

Up to 74% of patients with SJS/TEN experience ocular involvement in the acute phase, with others experiencing long-term ocular complications [56]. Patients with ocular involvement should have an ophthalmology consultation. Ocular and conjunctival lubrication and hygiene should be maintained for the duration of therapy. Topical corticosteroids are routinely used to manage acute inflammation and have been suggested to improve ocular outcomes as compared to ocular lubrication alone [57]. Broad spectrum topical antibiotics are also commonly used and should be based on local resistance patterns. To date, there is no convincing evidence to show that systemic steroids or IVIg improve ocular outcomes in SJS/TEN. Additionally, although a small, retrospective study, Yip et al. showed no difference in ocular outcomes with IVIg as compared to patients treated with systemic steroids [58]. Lastly, there is literature to support the use amniotic membrane transplant to improve ocular outcomes in the acute phase of SJS/TEN [59, 60]. Potential benefits include

decreased inflammation, leading to enhanced re-epithelialization and decreased scarring. At specialized centers, this procedure can be performed at the bedside under local anesthesia. Although not technically challenging, it is time consuming and can take up to 90 min per eye.

Systemic Therapy

There are no therapeutic regimens with unequivocal benefits in SJS/TEN. Given the difficulty of conducting large, randomized trials in these relatively uncommon yet life-threatening conditions, most of the literature is limited to case reports and case series. Numerous therapies have been reported to provide benefit, and these include G-CSF [61–63], plasmapheresis [64–66], N-acetylcysteine [67–69], and cyclophosphamide [70]. Thalidomide was studied in a double-blind, randomized, placebo-controlled study, but the study was stopped early due to increased mortality in the thalidomide group [71]. Thalidomide should therefore not be used in SJS/TEN. Tumor necrosis factor α agents (etanercept and infliximab) have also been reported to improve outcomes in TEN [72]. Paradisi et al. reported a case series of ten patients [73•]. Although there was no control group, the average SCORTEN for the group was 3.6, and seven of ten patients had a SCORTEN ≥ 3 , suggesting a predicted mortality of 50%. These ten patients were treated with a single dose of subcutaneous etanercept 50 mg and experienced average re-epithelialization by 8.5 days. Importantly, despite the 50% predicted mortality, no patients died. Based on this case series, therapy with tumor necrosis factor α antagonists deserves further investigation.

There is an increasing emerging literature on the use of cyclosporine in SJS/TEN. Several case series and case-controlled studies suggest a likely mortality benefit of cyclosporine in SJS/TEN. Singh et al. first suggested decreased time to re-epithelialization and decreased hospital length of stay [74]. Recently conducted critical reviews have reaffirmed the mortality benefit of cyclosporine in SJS/TEN [75•, 76••]. Roujeau et al. conclude that the time has come to integrate cyclosporine into early management of SJS/TEN, possibly in conjunction with systemic steroids [77•].

Although systemic corticosteroids are frequently used in SJS/TEN, their mortality benefits and clinical utility remain debatable. Again, the entire body of literature on systemic steroids consists of case reports and case series, with no well-designed randomized trials, and results are equivocal. A recent retrospective case series of 70 patients found a lower than expected mortality rate in patients treated with systemic corticosteroids [78]. Advocates suggest using high-dose systemic steroids early in the course of illness, while being cautious regarding adverse effects, most notably the increased risk of infection and resulting septicemia. Lastly, IVIg is also commonly used in SJS/TEN. IVIg is believed to work through

inhibition of Fas-Fas ligand interaction, thus leading to decreased cellular apoptosis through anti-Fas activity. Although multiple case series have suggested mortality benefit of IVIg in SJS/TEN, meta-analyses have not confirmed these findings [79, 80]. The lack of mortality benefit of IVIg persisted regardless of using a low-dose (< 3 g/kg) versus high-dose (> 3 g/kg) regimen. Other studies have suggested mortality benefits when combining systemic corticosteroids and IVIg [81]. Again, critical appraisal of the literature regarding combination therapy with IVIg and systemic steroids has led to equivocal results [82, 83•].

In summary, despite several case reports and case series, there is a paucity of high-quality data to confidently guide systemic therapy in SJS/TEN. To date, systemic steroids, and particularly cyclosporine, are the most promising therapies for SJS/TEN. Well-designed, controlled studies would be beneficial, but are difficult to conduct in these conditions. Management should continue to primarily focus on prompt identification and withdrawal of the culprit drug, followed by a multidisciplinary approach to supportive therapy in a facility well versed in these conditions.

Drug Re-Challenge

Once a medication has been identified to cause SCAR, typical management consists of strict avoidance. Most conditions have alternative therapies utilizing medications with a dissimilar chemical structure. With that being said, in special cases, re-challenge may be considered. There is minimal existing literature to address many questions, such as the utility of diagnostic testing (patch testing, lymphocyte transformation assays), along with the appropriate timing and dosing schedule of a re-challenge. Nevertheless, there is emerging literature suggesting re-challenge may be feasible even in life-threatening SCAR [84]. Drug re-challenge may be particularly safe with good outcomes in children, since many initial reactions are due to the underlying illness, rather than medication itself [85]. If drug re-challenge is considered, it must be pursued in a controlled environment by physicians experienced in the management of adverse reactions to medications.

Conclusions

Severe cutaneous adverse drug reactions have a range of clinical presentations, ranging from AGEP to DRESS, with the most severe form being SJS/TEN. There are well defined risk factors for SCAR, including certain commonly associated medications and genetic predispositions. Management of SCAR is based on prompt withdrawal of offending drug and a multi-disciplinary approach. To date, there is minimal high-quality data to make definitive recommendations regarding

optimal therapeutic regimens. Although systemic steroids and/or IVIg are commonly used, there is emerging literature regarding the efficacy of cyclosporine in SJS/TEN, and this warrants further investigation.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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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- Of major importance

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