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Update in Diagnosis and Management of Severe Cutaneous Adverse Reactions: Emerging Therapies and Evolving Presentations

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Introduction

Severe cutaneous adverse drug reactions (SCARs) represent some of the most critical and potentially life-threatening conditions encountered in dermatology. These reactions include Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)—also referred to as Drug-Induced Hypersensitivity Syndrome (DIHS), Acute Generalized Exanthematous Pustulosis (AGEP), and Generalized Bullous Fixed Drug Eruption (GBFDE). All of these are classified as T-cell mediated hypersensitivity reactions.[1]

The development of SCARs is influenced by a complex interplay of genetic predisposition, variations in drug metabolism, and, in some cases, concurrent infections. In this update, I will review the latest advances in the diagnosis and management of SCARs, highlighting emerging patterns of presentation, differential diagnoses, and therapeutic strategies that are impacting clinical practice.

Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

SJS and TEN are both diseases of drug-induced epidermal necrosis, differing mainly by the extent of cutaneous involvement. SJS and TEN are type IVa hypersensitivity reactions mediated primarily by type 1 cytotoxic lymphocytes and natural killer cells.[2] The global incidence of SJS and TEN remains relatively stable, with an estimated 1–2 cases per million individuals per year. Despite their rarity, these conditions carry significant morbidity and mortality, warranting careful attention to risk stratification. Several factors are associated with an increased risk of developing SJS/TEN. Immunosuppression is a notable risk factor—whether due to malignancy, acquired immunodeficiency syndrome, or immunosuppressive therapies. Advanced age and systemic lupus erythematosus have also been linked to a higher incidence of these conditions. In addition, certain populations, particularly individuals of Black and Asian descent, appear to have a heightened susceptibility, potentially due to genetic and pharmacogenomic factors.[1,3]

Co-trimoxazole and lamotrigine remain the drugs with the highest incidence rates of SJS/TEN. Although the onset typically occurs within 4 days to 4 weeks, it can extend up to 8 weeks for drugs with longer half-lives, such as allopurinol, phenytoin, carbamazepine, or lamotrigine.

Due to the ethical challenges of conducting randomized, double-blind, controlled clinical trials and the lack of standardized outcome measures, there are no consistent treatment guidelines for SJS/TEN. Consequently, consensus recommendations for therapy primarily focus on supportive care.[4] Over the years, corticosteroids, intravenous immunoglobulin (IVIG), and cyclosporine have been used for treating SJS and TEN, with clinical results remaining controversial. In 2017, a meta-analysis of immunomodulating therapies for SJS and TEN suggested that careful use of corticosteroids (administered early, pulsed and/or in particular populations) or cyclosporine appeared most promising, with a possible mortality benefit. However, IVIG did not show any mortality benefit.[5] In 2018, Chung et al. performed an impactful randomized controlled trial of 96 patients with SJS/TEN who were treated with etanercept or traditional corticosteroids.[6] This study found that etanercept shortened the time of skin healing in patients with moderate to severe disease compared with corticosteroids and resulted in fewer gastrointestinal side effects. A more recent network meta-analysis in 2021 showed that a combination of IVIG and corticosteroids reduced mortality in SJS/TEN and TEN. While other therapies and their combinations may also be effective, further evidence is required to confirm these findings.[7] Several studies have shown that TNF-alpha inhibitors, either alone or in combination with other therapies, can improve disease outcomes. In 2022, a small cohort study of 25 patients showed that etanercept combined with methylprednisolone (15 patients) decreased acute disease duration and accelerated the skin healing time compared to systemic steroids alone (10 patients).[8] Additionally, a Cochrane review in 2022 concluded that treating SJS/TEN with etanercept rather than systemic steroids may decrease mortality. However, there is currently insufficient evidence for cyclosporine, systemic steroids, and IVIG.[9] A recent and exciting therapeutic development in TEN was reported in a study published in Nature in November 2024. The study showed upregulation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway in TEN, then effectively treated mouse models of TEN using pan-JAK (tofacitinib) and JAK1 (abrocitinib, upatacitnib) inhibitors. They subsequently safely and effectively treated seven human patients with SJS/TEN and TEN using JAK inhibitors, with patients showing rapid cutaneous re-epithelialization and recovery.[4] While more studies are required, this represents a very exciting potential future application of JAK inhibitors.

Special Populations

Updates have been made for three specific special populations: the management of pediatric epidermal necrolysis, the diagnosis and management of epidermal necrolysis in patients on immune checkpoint inhibitors, and the management of epidermal necrolysis in pregnancy.

In the pediatric population, the incidence rates of SJS/TEN are reported to be slightly higher than in adults. However, this may be due to the erroneous inclusion of cases of erythema multiforme major and reactive infectious mucocutaneous eruption (RIME) misdiagnosed as SJS/TEN.[2] Ramien et al. described useful distinguishing features between RIME and epidermal SJS/TEN, stressing that mucous membranes are more severely affected than the skin in RIME, with 47% of cases showing sparse skin findings and 34% having absent skin findings.[10] Additionally, in children presenting with mucosal eruptions, prodromal respiratory symptoms, and lack of significant drug exposure the diagnosis is most likely RIME.[10] SJS/TEN generally has a better prognosis in children than in adults. TNF-alpha inhibitors, such as etanercept and infliximab, have been reported to be successful in treating SJS/TEN pediatric populations. These treatments have shown success both as monotherapy and in combination with IVIG, with IVIG and systemic corticosteroids, or with cyclosporine and systemic corticosteroids. A systematic review by Sachdeva et al. examined ten studies including 12 pediatric patients with a mean age of 9.5 years and mean body surface area involvement of 52.2%, all treated with TNF-alpha inhibitors for SJS/TEN.[9] The complete remission rates with infliximab and etanercept were 80% and 85.7%, respectively. Only one patient died (treated with infliximab and systemic corticosteroids) due to the severity of the disease. This mortality rate is lower than previously reported rates.[9]

SJS/TEN rarely occurs during pregnancy. While the effects of pregnancy on SJS/TEN are not well understood, it has been reported to have a milder course. The largest cohort study to date on SJS/TEN in pregnancy retrospectively identified 650 hospitalizations for SJS/TEN and compared them to pregnant patients admitted for reasons other than SJS/TEN. The findings were reassuring, showing milder disease and a higher survival rate compared to the general population with SJS/TEN. Additionally, apart from a higher preterm delivery rate, there was no difference in fetal outcomes, such as live birth and stillbirth. Risk factors for SJS/TEN in pregnancy included genitourinary infections, human immunodeficiency virus (HIV), herpes simplex virus (HSV), mycoplasma infection, malignancy, and cutaneous autoimmune conditions. Most episodes had occurred in the third trimester.[11]

Immune-check-point inhibitors (ICI), an emerging class of drugs for the treatment of cancer, have been found to have many potential cutaneous adverse reactions including SJS/TEN (<1% of reactions).[12] It is important for physicians to recognize that SJS/TEN induced by ICIs may have an atypical or blunted presentation. The latency period from drug initiation to eruption onset can span several months, and sudden desquamation may be preceded by a slowly progressing lichenoid or morbilliform eruption.[12] A 2023 retrospective cohort study looked at the differences between SJS/TEN induced by PD-1/PD-L1 inhibitors and those induced by gout and seizure medications. The study showed a delayed onset (4–7 weeks versus a 15-week median onset for PD-1/PD-L1 inhibitors). Additionally, the incidence was higher for PD-1/PD-L1 inhibitors (6.1 cases/10,000 starts in one year versus 1.9–2.8 cases/10,000 starts for other medications). Similar to studies with other drugs, non-white patients were more commonly affected. No significant difference in disease severity was identified.[13]

Molina et al. have proposed reclassifying these reactions as 'Progressive Immunotherapy Related Mucocutaneous Eruption (PIRME)' while others in the literature have referred to these reactions as 'TEN-like'.[14,15] In the PIRME concept introduces a '2-hit hypothesis' based on observations that all the patients in their case series first started an ICI and then had a second drug introduced. They suggest that the ICI reduces immune tolerance to the second drug, leading to a heightened sensitivity and development of a more severe eruption than would typically occur from a drug that would otherwise have had a more benign eruption. Given the '2-hit hypothesis', the group also proposed that in some situations, restarting the ICI may be considered.[14] There are reports of patients being rechallenged with ICIs without recurrence of the eruption; however, this approach must be taken with caution given the potentially life-threatening nature of SJS/TEN and the lack of evidence. Systemic therapies

reported for ICI-induced SJS/TEN reactions include corticosteroids, cyclosporine, and TNF-alpha inhibitors.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS is characterized by fever, rash (with typical facial edema), internal organ involvement, and the potential for subsequent onset of autoimmune disease. It is a potentially fatal type IVb hypersensitivity reaction primarily involving the activation of T helper 2 (Th2) lymphocytes and viral reactivation.[2,16]

Similar to SJS/TEN, high quality therapeutic studies for DRESS are lacking. The first step in management is drug discontinuation. If systemic therapy is required, corticosteroids remain the first-line treatment.[17] Steroid sparing agents with reported success include cyclosporine, IVIG, and anti-interleukin (IL-5) agents. Additionally, antiviral therapies may play a role in treatment based on the disease's pathophysiology if a viral reaction is suspected.

In the early stages of DRESS, the expansion of T-reg cells induces immunosuppression, which increases the risk of viral reactivation. Additionally, drugs such as valproic acid and amoxicillin can stimulate viral replication. Viruses that have been reported to have reactivated in DRESS include human herpesvirus 6 (HHV6), human herpesvirus 7 (HHV7), Epstein-Barr Virus, and cytomegalovirus.[17] Although the exact mechanism is unclear, viral reactivation in DRESS has been associated with a more severe disease course, prolonged disease, and severe internal organ involvement, as well as autoimmune sequelae such as myocarditis, hepatitis, and pancreatitis, among others. The viruses may modulate the immune response to the drugs or may directly infect and damage immune cells. If viral reactivation is suspected, antivirals such as intravenous ganciclovir or valganciclovir may be added to the more conventional systemic therapies for DRESS, which include systemic steroids, cyclosporine, or a combination of systemic steroids and IVIG.[17]

More recently JAK-STAT pathway activation has been identified in patients with DRESS and there have been case reports of tofacitinib successfully treating recalcitrant DRESS.[17,18]

Genetic polymorphisms are associated with increased risk of DRESS with specific drugs in specific populations. For many years, patients have been screened for *HLA-B5701* prior to initiating abacavir. Other organizations recommend screening for *HLA-3103* prior to initiating carbamazepine, *HLA-1301* prior to dapsone and *HLA-5801* prior to allopurinol. Additionally, *HLA-B*58:01* testing is routinely conducted in some Asian countries.[17]

An interesting article published in the *Journal of the American Academy of Dermatology* (JAAD) in 2024 pointed out the differences in the presentation of DRESS based on the culprit drug. Beta-lactams were found to have the shortest median latency, less than the classically reported 21 days, while allopurinol had the longest latency at 36 days. Sulfonamide-induced DRESS was almost always associated with a fever (87%), however, only 40% of patients exhibited eosinophilia. Cephalosporin-induced dress was found to have longer hospital stays with most patients requiring an ICU admission, whereas non-steroidal anti-inflammatory drug (NSAID)-induced DRESS had the shortest hospital stays. Cephalosporins and vancomycin had the highest fatality rates. Although vancomycin-induced DRESS is commonly known for renal involvement, this study found it is most commonly associated with liver involvement.[19]

Acute Generalized Exanthematous Pustulosis (AGEP)

AGEP is estimated to occur in 1–5 individuals per million each year and is characterized by an abrupt onset of numerous sterile pustules accompanied by erythema, typically appearing with a short latency period following antibiotic use. After antibiotics, hydroxychloroquine is the second most common culprit, with some cases presenting a delayed onset.[20] AGEP is felt to be a T-cell mediated disease in which CD8+ lymphocytes produce large quantities of IL-8. More recently, IL-36 has been implicated in its pathogenesis.[21] AGEP generally has a good prognosis, typically self-resolving in a couple of weeks, except in

the elderly or chronically ill patients. It is more commonly observed in women and patients with a higher body mass index.[20] A localized variant of AGEP, known as acute localized exanthematous pustulosis (ALEP), has been reported. In ALEP, the eruption is localized to one or a couple of locations, most often the face. This variant follows a similar time course and is triggered by the same drugs (most commonly antibiotics), however, it is less likely to have systemic involvement.[20]

If systemic treatment is required, oral corticosteroids are typically used first; however, cyclosporine has demonstrated similar efficacy. In recalcitrant cases, secukinumab and infliximab have been reported as successful options. Since 2024, there have been two case reports of AGEP being successfully treated with the anti-IL-36 receptor monoclonal antibody spesolimab.[21,22]

Generalized Bullous Fixed Drug Eruption (GBFDE)

GBFDE is commonly associated with the use of NSAIDs. While it can resemble SJS/TEN, diagnostic clues include the presence of islands of normal skin, previous exposures to the drug with milder reactions, shorter latency periods, milder mucosal involvement, and typically no ocular involvement.[2,23]

Conclusion

SCARs remain among the most critical and challenging conditions for dermatologists to manage. With the rapid development of new therapies, including immunotherapies, the clinical patterns of these reactions are evolving. Dermatologists must stay abreast of these changes to ensure safe, effective, and comprehensive patient care. The presentation of drug reactions can vary significantly depending on the offending agent and patient-specific factors. Despite advances in our understanding of these syndromes, there is still no consensus regarding the optimal first-line systemic therapies. Notably, JAK inhibitors have emerged as promising therapeutic candidates for severe drug reactions such as SJS, TEN, and DRESS, although further clinical studies are needed to validate their safety and efficacy.

Highlights

SJS/TEN

- Mainstay of care remains **early drug withdrawal + supportive measures.**
- Etanercept shows promising efficacy (faster healing, fewer gastrointestinal side effects versus corticosteroids).
- **JAK inhibitors** are emerging as a new therapeutic option with mechanistic support via JAK/STAT activation.

DRESS

- **HHV-6, HHV-7, EBV, CMV** are often reactivated—antiviral therapy should be considered.
- Genetic markers: *HLA-B57:01* (abacavir), *HLA-B58:01* (allopurinol), and others depending on the population.
- JAK inhibitors are also being explored for **recalcitrant DRESS**.

AGEP

- **IL-36** is emerging as a central cytokine; **spesolimab** (IL-36R antagonist) has shown early success in 2024 case reports.
- **Hydroxychloroquine**-induced cases may have longer latency.
- ***Localized variant:*** **ALEP** (e.g., facial involvement without systemic disease).

GBFDE

- Can mimic SJS/TEN.
- ***Key clues:*** islands of skin-sparing, milder mucosal/ocular involvement, prior mild episodes to same drug.

ICI-Induced Reactions / PIRME

1. May present as **blunted SJS/TEN**, with delayed onset, preceded by lichenoid eruptions.
2. "2-hit hypothesis": immune checkpoint inhibition followed by a second drug triggers SCAR.
3. Potential rechallenge with ICIs in very selected cases.

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