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Dermatologic Emergencies CME Part III: Drug reactions

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ABSTRACT

This section reviews the triad of life-threatening drug reactions including Stevens-Johnson/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).

Key words: *Stevens-Johnson syndrome/toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic symptoms; Acute generalized exanthematous pustulosis*

Severe cutaneous adverse reactions (SCARs) to drugs are potentially life-threatening and associated with various clinical patterns and morbidity. Severe cutaneous adverse reactions (SCARs) affect approximately 1 in every 1000 inpatients. Early recognition and diagnosis of SCARs are essential for improving prognosis and limiting long-term sequelae [1,2].

• STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome are rare mucocutaneous reactions of differing severity most commonly triggered by medications. Although the estimated incidence is low, the condition is a potentially fatal medical emergency and appropriate management is crucial for survival [3,4].

SJS/TEN represents a spectrum of reactive disorders classified according to the percentage of the affected body surface area. SJS is defined as skin involvement of < 10%, TEN is defined as skin involvement of > 30%, and SJS/TEN overlap as 10%–30%. SJS/TEN usually occurs within 7–21 days after initiation of the implicated drug. More than 100 drugs have been implicated in triggering this reaction. The most frequent culprits are sulfonamides, aromatic antiepileptic drugs, allopurinol, oxicam NSAIDs, lamotrigine, and nevirapine [5,6]. The increased risk of hypersensitivity reactions to certain drugs may be linked to specific human leukocyte antigen (HLA) alleles, immunosuppression, slow acetylation, and concomitant administration of radiotherapy and anticonvulsants [7,8].

A prodrome of fever, malaise and upper respiratory tract symptoms usually precede the eruption by several days. Erosive and hemorrhagic mucositis may result from mucous membrane involvement of the eyes, nose, mouth, and genitalia. SJS/TEN is characterized by cutaneous pain and confluent macular erythema that progresses to epidermal necrosis [9]. Extensive detachment of the epidermis sheets leads to areas of denuded oozing dermis that readily bleeds and can become secondarily infected. Septicemia is a leading cause of morbidity and mortality in the acute phase [10]. Patients surviving the acute phase of TEN have a significant risk of morbidity, including ocular lesions, cutaneous scarring, and mucosal involvement with secondary development of strictures, dental, genitourinary, gastrointestinal, respiratory, and psychological complications. The mortality rate of SJS varies between 1% and 5%, while TEN ranges from 25% to 30% [11,12].

Although a SJS/TEN diagnosis is suggested by physical signs, skin biopsy from lesional skin adjacent to a blister is usually necessary to support the clinical assessment. A second perilesional biopsy may be sent unfixed for

How to cite this article: Shanshal M. Dermatologic Emergencies CME Part III: Drug reactions. Our Dermatol Online. 2022;13(4):495-502.

Submission: 18.06.2022; **Acceptance:** 01.10.2022

DOI: 10.7241/ourd.20224cme.3

direct immunofluorescence to exclude other types of blistering dermatoses. Epidermal necrosis seen histologically on frozen sections has high sensitivity and low specificity for the diagnosis of toxic epidermal necrolysis [13,14]. Although not readily available at this time, new experimental diagnostic tools that measure serum granulysin and high-mobility group protein B1 (HMGB1) offer the potential to differentiate early TEN from other less severe drug reactions [15,16].

A prognosis score called the Severity of Illness Score for Toxic Epidermal Necrolysis (SCORTEN) was developed to assess the severity of the disease and predict mortality in acute TEN. SCORTEN has been validated for use on days one and three of hospitalization [17] (Table 1).

Treatment

The mainstay of treatment for TEN involves immediate discontinuation of the culprit drug(s), specialized care in an intensive care unit or burn center, wound care, and supportive care (Fig. 1). There are no RCT data on the impact of immunomodulatory therapies in the management of TEN. The most commonly reported systemic medications that can be considered on a short-term basis include intravenous immunoglobulin (IVIG) [18], cyclosporine [19,20], pulse corticosteroids [21,22], and TNF-α inhibitors [23-25], but there is insufficient data to support their use.

Practical pearls

- Despite the lack of evidence-based treatment, a meta-analysis of 96 studies showed that the supportive care is the most crucial step in the management of SJS/TEN with the superiority of corticosteroids and cyclosporine to other management protocols [29]
- ABCD-10 mortality score is a less well-known scoring system than SCORTEN that can predict the in-hospital mortality where one point is given for (Age above 50 years, epidermal detachment > 10, serum bicarbonate < 20 mmol/L, active cancer) and 3 points for dialysis before admission [30]

Table 1: Severity of illness score for toxic epidermal necrolysis (SCORTEN) [26]

1 point for each of the 7 criteria:
Age >40 years
Heart rate >120 bpm
Cancer or hematologic malignancy
BSA involved on day 1 >10%
Serum urea >10 mmol/l
Serum bicarbonate <20 mmol/l
Serum glucose >14 mmol/l
Total score (mortality rate)
0-1 (3.2%)
2 (12.2%)
3 (35.5%)
4 (58.3%)
≥ 5 (90.0%)

Table 2: Systemic complications of DRESS [49,50]

Lymphatic	Lymphadenopathy is common, and it can be limited or generalized. Histopathologically, two distinct variants are seen, the benign and pseudolymphomatous variants
Hematologic	Marked leukocytosis with atypical lymphocytosis and hypereosinophilia is typical. There is often leukopenia or lymphopenia that precedes leukocytosis. There may be thrombocytopenia, anemia and rarely hemophagocytic syndrome
Liver	Varying degrees of hepatitis, hepatosplenomegaly may occur with elevated liver enzymes. In severe cases, hepatic necrosis may lead to liver failure, coagulopathy, and sepsis. Phenytoin, minocycline, and dapsone are commonly implicated in liver damage.
Kidney	Manifestations range from asymptomatic to mild hematuria and proteinuria. Rarely, severe interstitial nephritis and renal failure requiring short-term supportive haemodialysis may develop. Allopurinol is the most common offending drug, followed by carbamazepine and dapsone.
Pulmonary	Lung involvement may manifest as impaired pulmonary function, acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress syndrome. Minocycline is the most common drug causing lung pathology.
Heart	DRESS syndrome associated myocarditis is potentially fatal. Ampicillin and minocycline are the most commonly implicated drugs.
Central nevus system	Meningitis and encephalitis can occur and could be related to HHV-6 reactivation.
Gastrointestinal	Gastroenteritis and dehydration, acute gastrointestinal bleeding, colitis and pancreatitis
Endocrine	Usually long-term sequelae. The thyroid gland is the most commonly affected gland resulting in thyroiditis or sick euthyroid syndrome, type 1 diabetes mellitus, and bilateral edema and infiltration of the salivary glands
Long term complications	Some DRESS patients may develop long-term sequelae, especially autoimmune diseases and end-organ failure

• DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also referred to as drug-induced hypersensitivity syndrome, is potentially life-threatening, multi-organ adverse drug reaction develops 2 to 6 weeks after drug initiation (DRESS has a later onset and longer duration than other drug reactions) [31]. DRESS encompasses a combination of cutaneous rash, hematological manifestations and internal organ

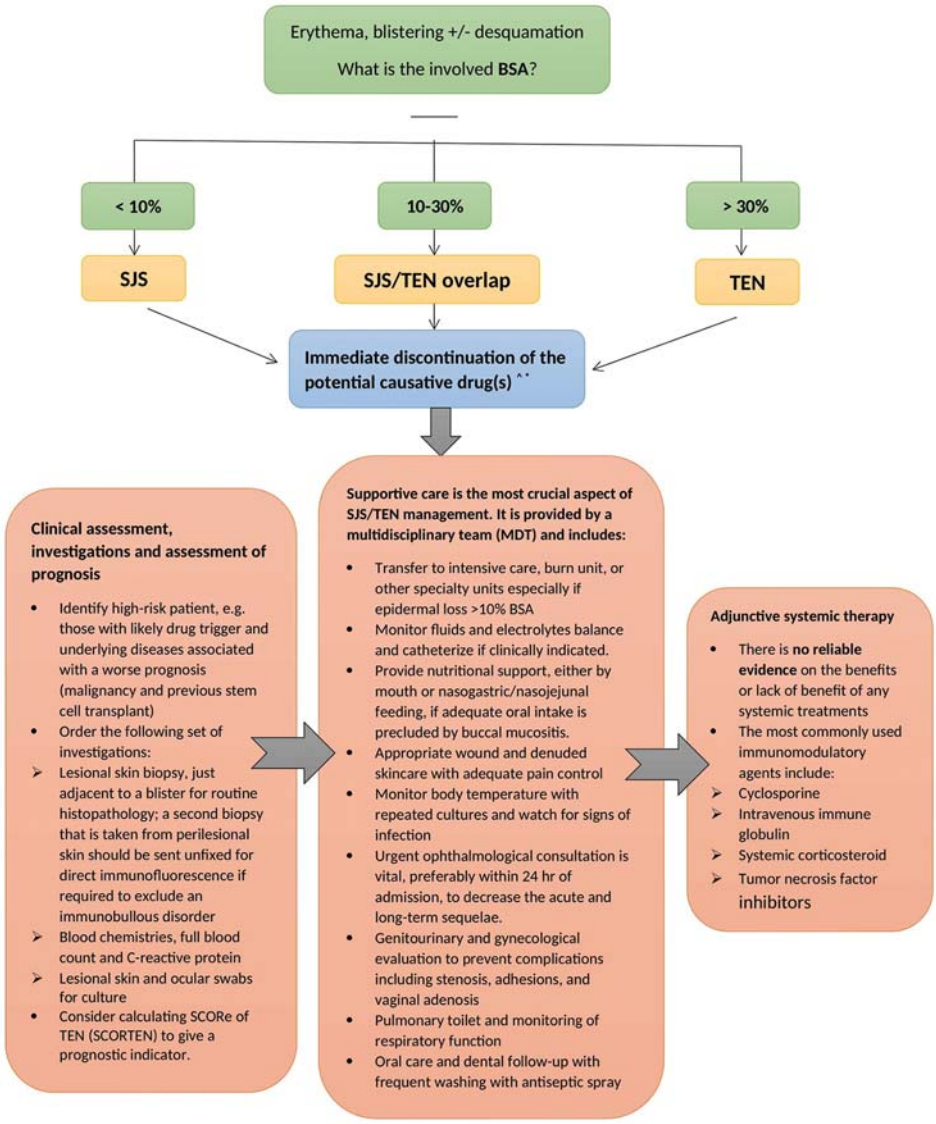

Figure 1: Stevens-Johnson syndrome/toxic epidermal necrolysis. Suggested algorithm for the management of SJS/TEN [27,28]. ^-Earlier withdrawal of implicated drug(s) is associated with a better overall prognosis. *-ALDEN (ALgorithm of Drug causality in Epidermal Necrolysis) is an online tool that can be used to predict the likely causality of a drug reaction.

marked derangement [32,33]. The reaction is triggered by an interplay between predisposing drugs and reactivation of human herpesviruses (HHV), especially HHV-6, in genetically susceptible individuals [34-37]. In addition to aromatic anticonvulsant drugs, which are the most common offenders, many other drugs have been reported to trigger DRESS, including dapsone, minocycline, allopurinol, vancomycin, trimethoprim–sulfamethoxazole, abacavir, and nevirapine [38-40].

The dermatological manifestations of DRESS can be diverse, but they are most often presented as morbilliform cutaneous eruptions. The classic cutaneous distribution involves the face, upper trunk, and extremities; however, it may involve the entire surface of the skin [41]. Significant facial edema is a frequent finding that can sometimes be mistaken for angioedema [42,43].

The associated systemic involvement includes fever, lymphadenopathy, hematologic abnormalities, and multi-organ manifestations. The liver is the most frequently affected visceral organ in ~60% . 80% of patients, followed by renal, pulmonary, and cardiac manifestations. Other organs that could be involved to a lesser degree include the central nervous system, gastrointestinal and endocrine organs [44,45]. DRESS has a 10% mortality rate, most commonly from fulminant hepatitis with hepatic necrosis (Table 2).

The diagnosis of DRESS syndrome is mainly clinical. The patient should undergo extensive evaluation to establish the diagnosis and assess the severity of internal organ involvement (Fig. 2).

Treatment

Early withdrawal of the offending drug is essential, but this may not result in a rapid or complete recovery. Symptoms can take several weeks to resolve. Systemic corticosteroids show promising results for severe reactions and may help prevent autoimmune complications at the resolution stage. Adjunctive high dose intravenous immunoglobulin (IVIG) or steroid-sparing immunosuppressive agents may be used in conjunction with corticosteroids for severe and unresponsive cases of DRESS [46-48].

Practical pearls

- Gradual loss of regulatory T cells (Tregs) that play a role in the development of late-onset autoimmune reaction and organ damage can be alleviated by administration of systemic corticosteroids at the acute stage; hence steroid use may play a role in the prevention of long-term sequelae
- Renal function should be closely monitored in allopurinol-induced DRESS due to the associated chronic renal complications
- The liver is the most common internal organ involved in DRESS, and elevation of liver enzymes is the most common laboratory finding; however, it usually resolves without long-term complications

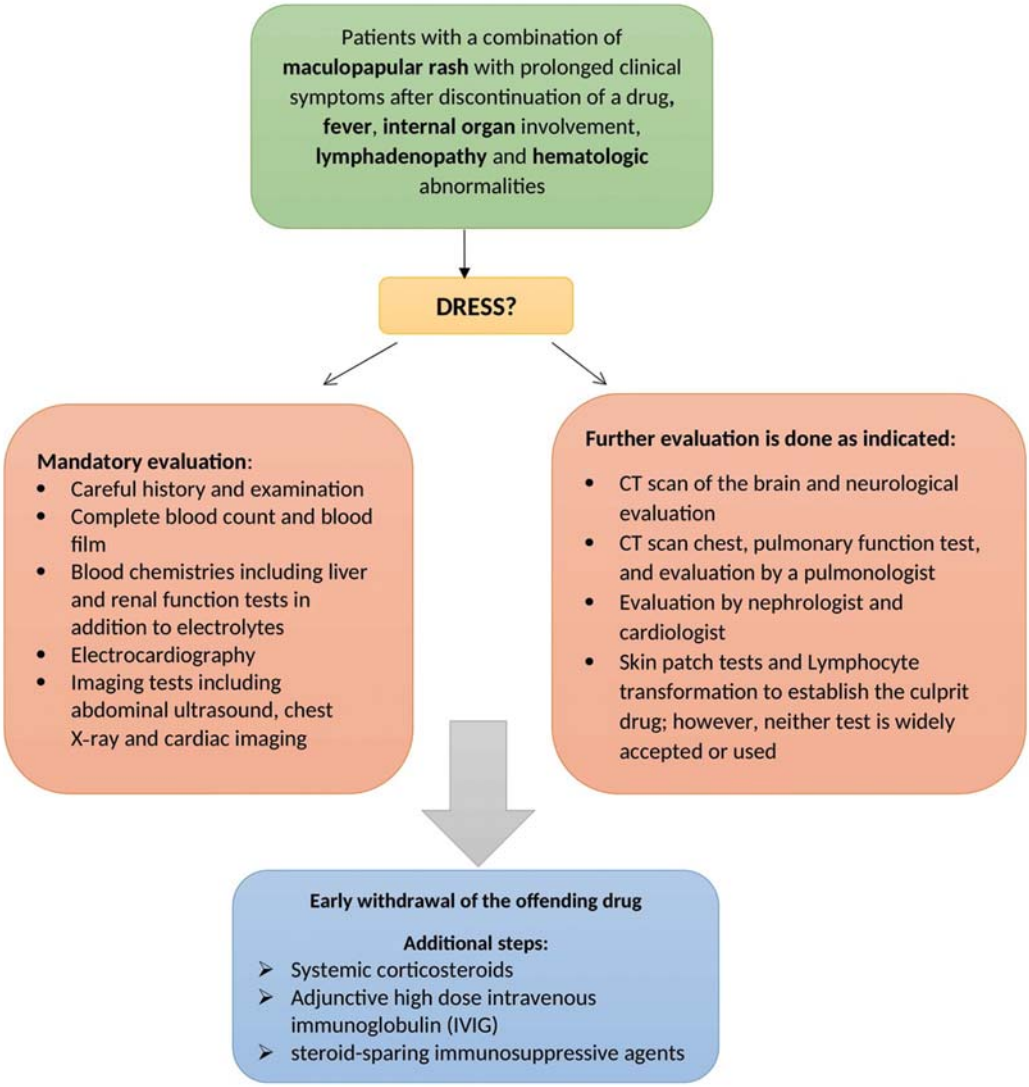

Figure 2: Drug reaction with eosinophilia and systemic symptoms (DRESS). Diagnostic workup for drug reaction with eosinophilia and systemic symptoms[51].

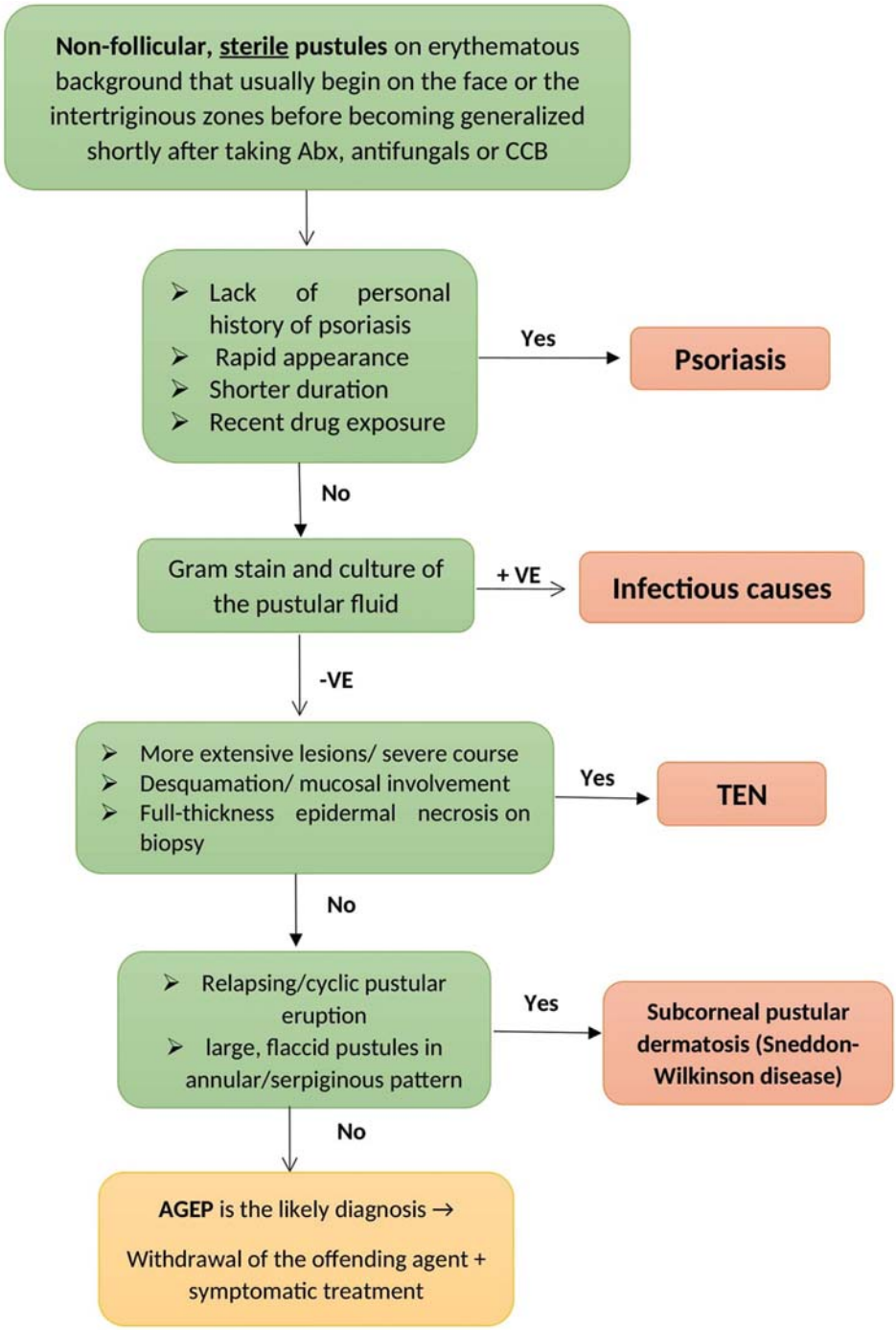

Figure 3: Acute generalized exanthematous pustulosis (AGEP) Flowchart of approach to generalized pustular eruption.

Pitfalls in the diagnosis of DRESS

- Long latency period
- Diversity and absence of specific symptoms
- The similarity to other drug eruptions and viral exanthemas
- Delayed response after withdrawal of the culprit drug

• ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP) is a rare but acute severe pustular reaction that can occur within a few hours to a few days of drug exposure (earlier than other immunological drug reactions). Drugs account for approximately 90 percent of AGEP

cases. The most important culprits include β-lactam antibiotics, macrolides, clindamycin, antifungals, and calcium channel blockers, especially diltiazem, but viral infections can also trigger this reaction [52-54].

AGEP is characterized by numerous pinpoints, primarily non-follicular, sterile pustules arising within large areas of edematous erythema. The rash usually begins on the face or major skin folds and rapidly extends to the trunk and limbs. Lesions typically last for 1 to 2 weeks and are followed by superficial desquamation [55,56]. In most cases, the course of AGEP is characterized by fever, leukocytosis, and elevated inflammatory markers. Systemic involvement occurs in the minority (17%-20%) of patients, primarily involving hepatic, renal, or pulmonary injury [57,58]. The overall prognosis in AGEP is good with a 1%-5% mortality rate, primarily in elderly patients and those of a poor general condition [59-61].

Patients with suspected AGEP should undergo Gram staining and pustular fluid culture to exclude potential infectious causes and the possibility of bacterial superinfection. The principal differential diagnosis of AGEP is acute generalized pustular psoriasis (Fig. 3). Lack of personal history of psoriasis, rapid appearance, shorter duration of fever and pustular eruption and recent drug exposure all favor a diagnosis of AGEP [62-64]. A skin biopsy may be warranted to distinguish the two conditions, with AGEP histopathology usually showing spongiform subcorneal and/or intraepithelial pustules, necrotic keratinocytes, an oedematous papillary dermis and perivascular infiltrate with neutrophils and some eosinophils [65].

Treatment

AGEP is a self-limiting disease with a favorable prognosis in most cases. Management includes removal of the offending drug, infection prevention, monitoring for systemic complications, and supportive symptomatic treatment for pruritus and fever [66,67].

Practical pearls

- DRESS and AGEP can be associated with the development of pustules but AGEP has a shorter latency period of few days compared to 2-6 weeks of DRESS.
- The mucous membrane and internal organ involvement are significantly lower in AGEP.

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Source of Support: This article has no funding source.
Conflict of Interest: The authors have no conflict of interest to declare.