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Clinical Manifestations and Prognosis Factors in Severe Cutaneous Adverse Drug Reaction (SCADR)

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Abstract
Severe Cutaneous adverse drug reaction (SCADR) is a severe skin reaction due to the use of drugs that can be life-threatening. This article describes the clinical manifestations and prognosis factors that affect SCADR patients. The most common types of SCADR were Stevens-Johnson Syndrome (SSJ) and Toxic Epidermal Necrolysis (TEN). The drugs that most often trigger are antibiotics and anticonvulsants. The main clinical manifestations include erythematosa skin lesions, epidermal necrolysis, and mucosal involvement. Significant prognosis factors include the extent of the affected skin area, internal organ involvement, and SCORTEN score. Patients with high SCORTEN scores have a greater risk of mortality. Early treatment and discontinuation of trigger drugs are key factors in improving clinical outcomes. The conclusion is early recognition of clinical manifestations of SCADR as well as assessment of prognosis factors can be helpful in patient management and reduce the risk of serious complications. The study also highlights the importance of educating medical personnel in detecting and managing severe drug reactions
Keywords: SCADR, clinical manifestations, prognosis factors

INTRODUCTION

Cutaneous adverse drug reaction is the most frequent manifestation of drug sensitivity with highly variable causative agents (Zhang et al., 2019). Cutaneous adverse drug reaction (CADR) is an unwanted reaction that can alter the structure or function of the skin, with or without systemic involvement after administration of the drug at normal doses. The skin is the organ most often affected by drug reactions. This reaction manifests as a series of dermatological symptoms that can cause discomfort and reduce the patient's quality of life. Cutaneous adverse drug reaction has a wide range of diseases based on severity from mild to severe, namely severe cutaneous adverse drug reaction (SCADR) (Mustafa et al., 2018).

Cutaneous adverse drug reaction requires great attention in clinical management because it can affect the discontinuation of treatment, reduce the patient's quality of life and in severe cases can result in a life-threatening condition. Understanding the mechanisms, risk factors, prognosis factors and management of adverse drug reactions to the skin is essential for healthcare professionals to provide safer and more effective care to patients. The prevalence of CADR varies depending on the medication and the patient's prognosis factors. Some people may be more susceptible to these reactions due to genetic factors or underlying medical conditions (infection, inflammation, malignancy). Identifying clinical manifestations of CADR early is essential for rapid intervention and minimizing its impact on patient well-being (Damayanti et al., 2019).

Severe cutaneous adverse drug reaction is a delayed hypersensitivity reaction mediated by the body's immune system which mainly includes drug reactions namely Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), which is the most severe form of SCADR. Each subtype of SCADR has different clinical manifestations.

Typical symptoms of DRESS are fever (>38°C), periorbital and facial edema, lymphadenopathy (cervical, axillary, or inguinal region) and involvement of several organs. Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis is characterized by skin and mucosal involvement as well as pain, erythema, epidermolysis and positive Nikolsky signs. Acute Generalized Exanthematous Pustulosis is characterized by acute fever, pustules with a base of erythematosis and leukocytosis (Deng et al., 2023).

The diversity of clinical manifestations and causative drugs often leads to misdiagnosis and delays in SCADR diagnosis. Severe cutaneous adverse drug reactions contribute to high morbidity and mortality although rare. The mortality rate reaches 10% for DRESS, 5%-30% for SJS/TEN and <5% for AGEP. Severe cutaneous adverse drug reaction can cause dysfunction of multiple organs, severe acute complications, death and lifelong sequelae (Bellón, 2019). Identification of risk factors, SCADR management and appropriate prognosis factors are essential to reduce mortality and improve prognosis.

Previous research by Zhang et al. (2019) highlighted the variability in causative agents and clinical manifestations of SCADR, emphasizing the need for early identification and intervention. However, their study primarily focused on epidemiological data without delving deeply into the underlying immune mechanisms or genetic predispositions. Another study by Bellón (2019) explored the immunological pathways involved in SCADR but lacked comprehensive clinical data to correlate these mechanisms with patient outcomes. These gaps underscore the necessity for research that bridges mechanistic insights with clinical applications to improve diagnostic accuracy and therapeutic strategies.

This study aims to fill these gaps by integrating a critical analysis of clinical manifestations, genetic risk factors, and prognostic indicators in SCADR. By synthesizing data from diverse patient populations and incorporating recent advancements in immunogenetics, this research provides a more holistic understanding of SCADR. The findings will enhance early detection, risk stratification, and personalized management, ultimately reducing morbidity and mortality. Additionally, this study underscores the importance of educating healthcare professionals on SCADR recognition and management, thereby improving patient outcomes and quality of life.

The incidence of CADR is 1-5% in developing countries. This CADR condition can occur in 2-3% of hospitalized patients. The increase in CADR cases ranges from 2-5% in developing countries. The highest incidence of CADR occurs between the ages of 41 and 50 years and the three most common causes are anti-epileptic drugs (39%), allopurinol (15%), antibiotics (22%) with the most antibiotics being penicillin, macrolides, sulfa and dapsone (Lady Aqnes Kurniawati et al., 2021).

Stevens Johnson syndrome and TEN are estimated to reach 1-6 cases per million population per year and 0.4-1.2 cases per million population per year. In the United States, the incidence of SJS and TEN is 1.5-9.6% per 1,000,000 inhabitants per year. In France, the incidence and mortality of SJS and TEN are 6.5 and 0.9 per 1,000,000 inhabitants per year, in China, the incidence of SJS and TEN reaches 1.8% of the hospital population. In Singapore, 0.7% of the CADR is SJS and TEN. A previous study conducted at Dr. Soetomo Hospital Surabaya reported that adverse drug reactions occurred in 6.5% of hospitalized patients with a mortality rate of 2% (Del Pozzo-Magaña & Liy-Wong, 2024). Globally, mortality rates for SJS and TEN are so high that in-depth analysis of epidemiological data is required. Several incidents of SJS and TEN in hospitals have been reported in Indonesia, one of which is a study by Osdatilla et al. in 2023 which reported the number of patients diagnosed with SSJ at 48.57%, followed by SSJ-NET at 40.0% and NET at Dr. Moewardi Surakarta Hospital for the period January 2019 – December 2022 (Putri et al., 2024).

Drug reaction with eosinophilia and systemic symptoms is estimated to have an incidence

of between 1 case in 1,000 to 10,000 drug exposures. In children, it is likely to be lower than in adults. Drug reactions with eosinophilia and systemic symptoms are believed to occur more frequently than other severe reactions caused by drugs, such as SJS/TEN, but less often than food-induced anaphylactic reactions (Manieri et al., 2023).

Acute generalized exanthematous pustulosis is a rare drug reaction on the skin characterized by the acute onset of extensive sterile pustule formation. The incidence is estimated to be around 1-5 cases per one million people per year in the world and is considered a self-limiting reaction. The epidemiology of AGEP in Asia has not yet been fully characterized. Cases of AGEP can occur at any age and seem to be more common in women (Lee et al., 2014).

Research Methods

This study uses a retrospective method by analyzing the medical records of SCADR PATIENTS (SJS/TEN, DRESS, AGEP) from several hospitals in Indonesia for the 2019-2023 period. Data is collected from complete medical records, laboratory results, and supporting examinations such as skin biopsies. Samples were selected based on confirmed diagnosis criteria and completeness of data. Statistical analysis included Chi-square tests and logistic regression to evaluate prognostic factors such as drug type, comorbidities, and SCORTEN scores. This research has received ethical approval and maintains the confidentiality of patient data. The main limitation is the retrospective nature which has the potential to give rise to selection bias..

RESULTS AND DISCUSSION

Antimicrobial drugs also often cause CADR even to a milder degree. Among the antimicrobial groups, sulfa drugs such as cotrimoxasol, beta-lactam drugs such as penicillin and cephalosporins, fluoroquinolones, nitro-imidazole and tuberculosis drugs are antibiotics that often cause CADR. Anti-pain and analgesic medications such as paracetamol can also cause CADR in some cases. Anti-osteoporosis drugs that often cause CADR are bisphosphonates and strontium ranerate (Chen et al., 2021).

Individual factors also affect the occurrence of SCADR, in addition to the drug factor itself. The condition of a person who is suffering from malignancy, the presence of autoimmune diseases such as systemic lupus erythematosus (SLE) and the presence of infections such as tuberculosis and human immunodeficiency virus (HIV) can also increase the risk of SCADR up to 1000 times when compared to other normal people. A study found that SCADR occurs in 16.9% of HIV patients who have low immunity. The presence of infection can also cause the SCADR reaction that occurs to be more severe and increase the likelihood of complications, in addition to increasing the likelihood of SCADR itself (Maharani et al., 2020).

Table 1. Medications often associated with SCADR

AGEP	DRESS	SJS/TEN
Penisillin	Allopurinol	Allopurinol
Macrolides	Karbamazepin	Karbamazepin
Diltiazem	Lamotrigin	Lamotrigin
Antimalarial agents	Phenytoin	Nevirapin
	Sulfasalazin	Nonsteroidal anti-inflammatory drugs (OAINS)
	Vancomycin	
	Minoskilin	Phenobarbital
	Dapson	Phenytoin
	Sulfametoxazol	Sulfametoxazol
		Sulfasalazin

Source: Processed from the EuroSCAR study (Bellón, 2019) and clinical data from Deng et al. (2023).

SCADR patients are more elderly or patients who are taking a lot of medications. The occurrence of SCADR in this case is related to the interaction between drugs due to polypharmacy. Decreased kidney or liver function in elderly patients can also interfere with pharmacokinetics and pharmacodynamics of drugs so that it can increase the risk of ADR (Machoń et al., 2022).

Severe cutaneous adverse drug reaction is closely related to immune mechanisms, which have a strong bond with genetics. Some specific human leukocyte antigen (HLA) alleles are reported to have strong associations with sensitivity to certain drugs. Human leukocyte antigens A*02:02 and A*51:01 increase the risk of SCADR, while HLA-A*02:01 has protective properties against SCADR. [19] Human leukocyte antigen B*57:01 has a hypersensitivity reaction with abacavir. Human leukocyte antigen B*15:02 has an association with the occurrence of SJS/TEN in Asian populations due to carbamazepine. Human leukocyte antigen B*31:01 is directly related to carbamazepine-induced CADR in all populations. Human leukocyte antigen B*58:01 causes hypersensitivity up to allopurinol-induced SJS/TEN. Dapson can also cause DRESS, which is often associated with the HLA-B*13:01 allele. Identifying risk factors and understanding their pathogenesis can help optimize therapy. The general risk factor is. immune-mediated related to the genetic polymorphism of the HLA allele, this variant can differ by population, drug and phenotype and is not dependent on metabolism. The next risk factor is non-immune-mediated, where this reaction can be caused by genetic abnormalities in genes that encode enzymes involved in drug metabolism as well as patients, diseases and drug-related variables.

The EuroSCAR study evaluated the drug's risk in causing SJS and TEN. The drugs with the highest risk include allopurinol, carbamazepine, cotrimoxazole, other sulfonamide antibiotics, sulfasalazin, lamotrigine, nevirapin, OAINS, phenobarbital and phenytoin. Drugs with medium risk include cephalosporins, macrolides, quinolones, tetracyclines and OAINS in addition to the high-risk category. Low-risk drugs include beta-blockers, angiotensin-converting enzymes, calcium-channel blockers and sulfonamide-based thiazide diuretics, anti-diabetic sulfonylureas, insulin and OAINS. Epidemiological studies of SJS and TEN in Southeast Asia show that the main causative drugs are carbamazepine (17%), allopurinol (15%), sulfonamide antibiotics (12%), phenytoin (9%), OAINS (8%), lamotrigin (2%), phenobarbital (1%) and ß-lactam antibiotics (13%).

The common pharmacological agent that triggers DRESS involves aromatic anticonvulsants responsible for 35% of cases, followed by allopurinol occurring in 18% of cases, sulfonamides in 12% of cases and other antibiotics in 11% of cases. Antiretroviral drugs such as nevirapin and abacavir are commonly reported to be associated with DRESS, although hypersensitivity reactions to abacavir generally show an earlier onset and different symptoms than classical DRESS.

Many causative factors cause AGEP, more than 90% of cases are related to the consumption of drugs. Aminopenicillin, pristinamicin, sulfonamides, quinolones, hydroxychloroquine, terbinafine and diltiazem are the drugs that are most commonly responsible for AGEP. Some specific cases can be triggered by bacterial, viral or parasitic infections (for example, parvovirus B19, mycoplasma, cytomegalovirus, coxsackie B4, Chlamydia pneumoniae, Escherichia coli and Echinococcus), spider bites, herbal remedies, mercury and even psoralen treatment combined with ultraviolet A (PUVA) light.

Pathogenesis

The general pathogenesis of SCADR is basically mediated by a type IV (slow type) hypersensitivity reaction in which a T cell-mediated drug-specific immune response is responsible for causing SCADR. The hypersensitivity reaction of type IVa underlies the contact

dermatitis reaction, type IVb underlies the reaction of MPE, IVc represents TEN and IVd demonstrates the basic mechanism of AGEP**.** Four subtypes of type IV hypersensitivity are initiated from a reaction mechanism mediated by T cells, including the hapten/prohapten model, the pharmacological interaction model (p-i) and the peptide repertoire model that is able to alter the ability of drugs to activate T cells.

The hapten/prohapten model shows that in the process the drug will bind to peptides by forming covalent bonds either intracellularly, namely in the endoplasmic reticulum, i.e. before processing and presentation to T cells or on the cell surface. An example is hypersensitivity to penicillin (anaphylactic reaction). The p-i model shows that the noncovalent bonds between HLA molecules and T cell receptors result in direct T cell activation. The p-i reaction activates only lymphocytes mediated by cellular immune responses by T cells. Clinically, this can appear as cellular immunity-mediated CADRs such as MPE, SJS/TEN and DRESS. The last model, the peptide repertoire, also shows the presence of noncovalent binding that occurs in the HLA antigen binding gap that is able to alter the peptide ligand repertoire, leading to the presentation of a new peptide ligand recognized as a foreign body and elicit an immune response, for example in hypersensitivity to abacavir**.**

The pathomechanism of the initial stage of SJS/TEN is the binding of drug antigens or metabolites with major histocompatibility complex (MHC) type 1 or cellular peptides to form immunogenic compounds. The pathomechanism of SJS/TEN suggests that there is a balance disorder between pro-inflammatory and immunomodulatory mechanisms.[22] The cause of SJS/TEN involves the pharmacological role of certain drugs in which drug molecules will be recognized by the body's immune system and are able to cause increased regulation or increased production of Fas ligand (Fas-L) by keratinocytes that constituently express Fas, which will lead to the activation of the apoptosis pathway. Certain drugs may interact with cells expressing major MHC class I which will cause the accumulation of CD8+ cytotoxic T cells as well as release perforin and granzyme B that can kill keratinocytes. Molecules of certain drugs can also activate monocytes that can induce the secretion of annexin A1 which has an effect in the induction of necroptosis in keratinocytes. Molecules from certain drugs can also trigger the activation of CD8+ T cells, natural killer cells (NKs) and natural killer T cells (HCVs) to secrete granulicin, which can induce keratinocyte death without the need for cell contact**.**

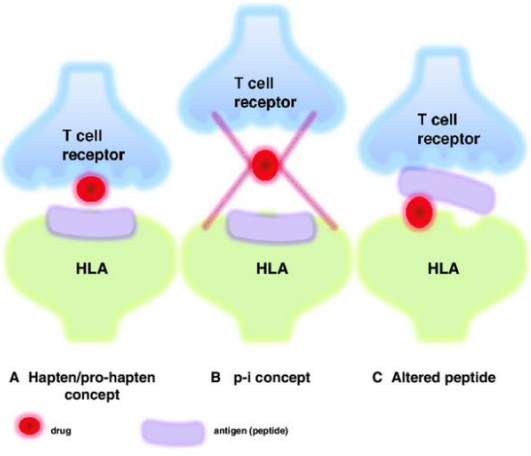

Figure 1. Conceptual model of drug stimulation of T cells in SCADR
Source: Adaptation of: Bellón (2019) with modifications based on current immunogenetic mechanisms (Chen et al., 2021).

The exact pathogenesis of DRESS is still difficult to understand, but in cases related to anticonvulsants, there are three components of complex interactions in the form of a deficiency

or disorder of the enzyme epoxide hydroxylase that detoxifies the associated drug metabolites, reactivation of the Herpesviridae family of viruses and ethnic predisposition to certain human leukocyte antigen (HLA) alleles.[52] The main immune response of DRESS is the Th2 response with the expansion of T cells and cytokines associated with hyper-eosinophilia such as IL-4, IL-5 and IL-13 as well as thymus and activation regulated chemokine (TARC). TARC levels were identified as a potential biomarker of acute phase and a predictor of DRESS activity and appear to correlate with the severity of skin manifestations. Other cytokines and chemokines reported to be elevated in DRESS include TNF-α, interferon (IFN)-γ, IL-2 and IL-6**.**

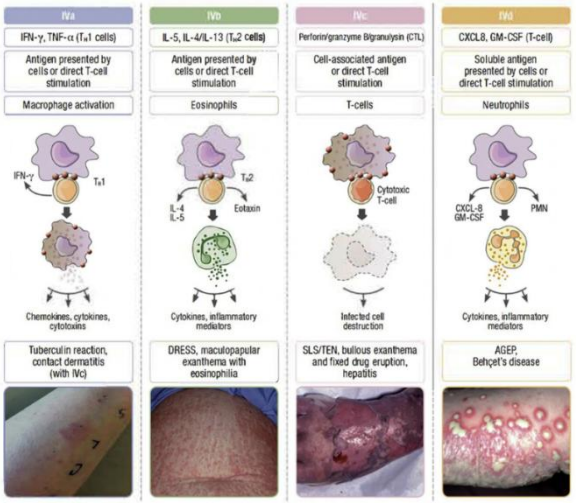

Figure 2. Conceptual model of slow type IV hypersensitivity reaction in SCADR [57]

Virus reactivation from the Herpesviridae family is one of the characteristics of DRESS. Human herpesvirus (HHV)-6 is most commonly reactivated, followed by Cytomegalovirus (CMV), Epstein–barr virus (EBV) and HHV-7. The role, mechanism and timing of viral reactivation in the drug-specific immune response and pathogenesis of DRESS have not been fully clarified, but there is a relationship between reactivation and worsening of clinical symptoms, greater severity or longer duration of disease. Viral reactivation contributes to T cell activity by inducing the synthesis of pro-inflammatory cytokines. Viruses may also participate in interactions between drugs and T cell receptors. One hypothesis is that viral reactivation occurs due to a state of immunodeficiency, in the acute stage of DRESS, the regulatory T cell population is expanded, while the number of B cells and immunoglobulin levels in plasma are reduced, which can facilitate viral reactivation. An alternative hypothesis is that some drugs (e.g. amoxicillin and valproic acid) may directly increase HHV-6 replication. Recent research has also mentioned that the T lymphocytes that develop after exposure to the causative drug are virus-specific memory T cells, which are reactivated after misidentification of the HLA complex with the drug. The detection of HHV-6 in the patient's peripheral blood is considered a marker in DRESS.

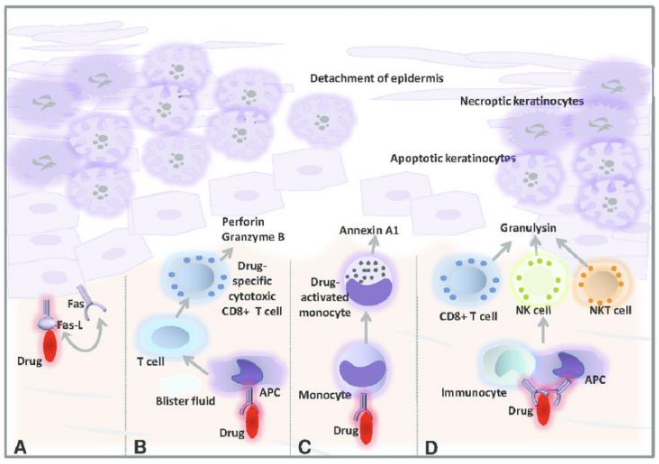

Figure 3. Molecular pathomechanisms in SJS/TEN [22]

Deficiency of metabolic enzymes and overactivity of a drug metabolite is based on a genetic mutation that specifically encodes the enzyme exposyase hydroxylase, an enzyme useful for the detoxification process of drugs that is usually inherited autosomal dominantly. Genetic susceptibility is believed to be one of the factors that can affect the immune response. Several studies have revealed the fact that certain specific HLAs may have a higher binding affinity for certain drugs that trigger adverse immune responses. For example, several studies have highlighted the association between HLA-B*58:01, HLA-B*32:02, HLA-B*31:01 and HLA-B*13:01 with allopurinol, vancomycin, carbamazepine and dapsone-induced DRESS, so that HLA can be used as an additional screening test to improve the evaluation of drug causality and isolate the risk of DRESS.

The presence of polymorphisms in genes encoding drug metabolite enzymes (e.g. cytochrome P450) can lead to the accumulation of drugs or their active metabolites and has been linked as an additional factor in the development of severe phenytogen-induced skin reactions, however these findings suggest that the pathogenesis of DRESS is multifactorial, taking into account not only genetic susceptibility but also the presence of viral reactivation, the patient's ethnic group and immune status. These factors alone may not be enough to trigger DRESS, but when combined, they can work synergistically to increase the risk of DRESS.

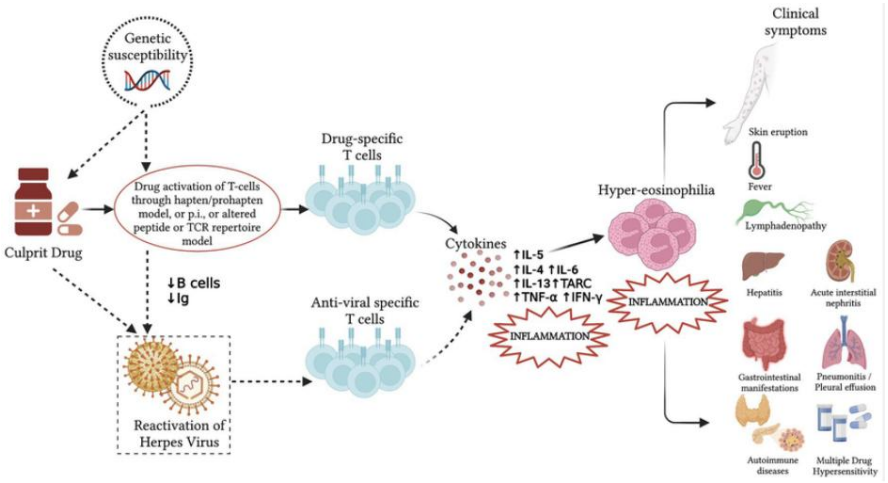

Figure 4. Pathomechanism of DRESS

Source: The diagram is adapted from the study of Manieri et al. (2023) and the findings of the reactivation of the HHV-6 virus (Deng et al., 2023)

The pathogenesis of AGEP is usually described as a T cell-mediated type IVd hypersensitivity reaction with neutrophil inflammation. Activation, proliferation and migration of drug-specific CD4 and CD8 T-cell differentiation clusters play an important role in the development of AGEP. The initial phase involves the stimulation of specific T cells and their migration from the T cells to the skin. The accumulation of T cells and cytotoxic proteins such as granzyme B and perforin can activate the response of HCV where HCV will induce keratinocyte apoptosis through cytotoxic proteins and Phase/FasL interactions resulting in the formation of subcorneal vesicles **(Figure 5).** Recent studies have shown that in addition to TEN, granulicin is also expressed by CD4 and CD8 cells as well as NK cells in different drug reactions including AGEP. HCV cells along with NK cells and activated inflammatory cells (keratinocytes, dendritic cells, macrophages, neutrophils) will release a variety of pro-inflammatory cytokines and chemokines. In vitro tests have shown that drug-specific T cells in AGEP patients produce more CXCL8/IL-8 chemokines (chemokines chemotaxis) which are believed to play a central role in the formation of pustules by recruiting neutrophils. Enhancement of IL-17 and IL-22 and GM-CSF by Th 1 cells in AGEP patients can also participate in potent neutrophilic activity through synergistic effects on CXCL8/IL-8 production and prevent neutrophil apoptosis. IL36-Ra deficiency in some AGEP patients leads to increased expression of various pro-inflammatory cytokines and chemokines such as IL-1, IL-6, IL-12, IL-23, IL-17, TNFα and CXCL8/IL-8 which can further improve neutrophil recruitment and activation.[1]

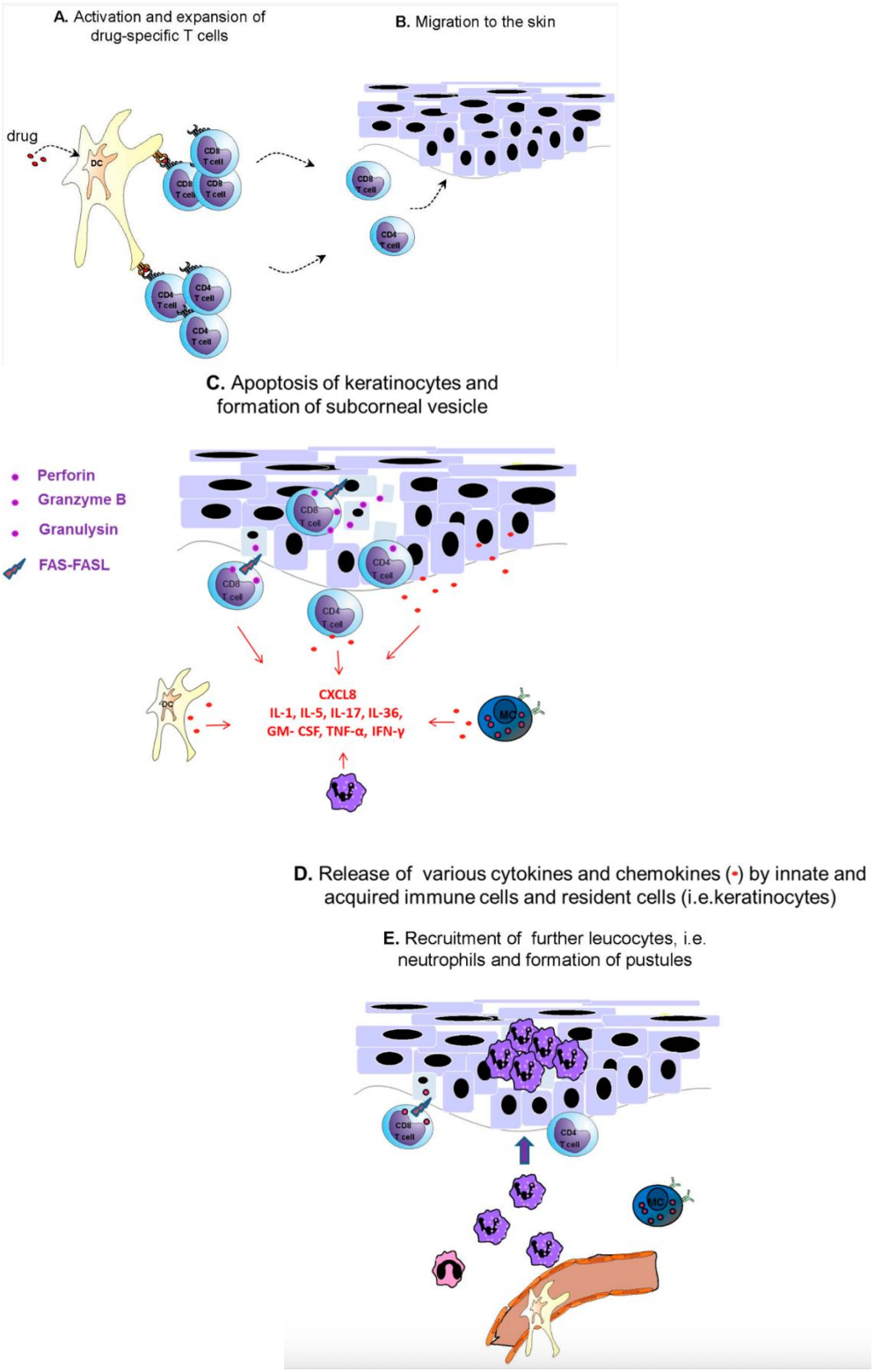

Figure 5. Pathomechanism in acute generalized exanthematous pustulosis (AGEP) [10]

Clinical Manifestations

In the case of SJS/TEN, mucosal involvement is often obtained. The oral mucosa and lips are the most frequent predilections, but not a few patients also get lesions on the genital area. Hyperpigmentation and hypopigmentation of the skin, eye complications (50% of cases)

and nail dystrophy (37.5% of cases) are common symptoms in SJS and TEN. Skin disorders that can be obtained are vesicles or bulas all over the body with tenderness accompanied by positive Nikolsky signs. Nikoslky's sign occurs due to the rapid formation of blisters on the skin and mucosa so that the skin layer is detached. Vesicles on the skin can turn into hemorrhagic erosion as the disease progresses. The disease is also often accompanied by fever**.**

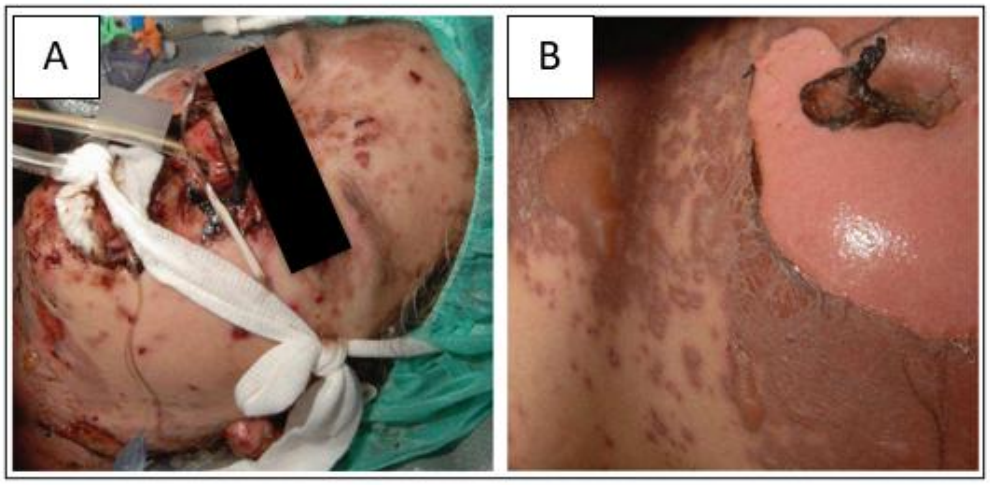

Figure 6. Clinical manifestations of SJS/TEN after administration of carbamazepine. **(A)** Removal of skin by erosion of the face, including involving the lips and conjunctiva. **(B)** TEN with extensive skin involvement is characterized by apoptotic skin release and erosion. [22]

Drug reaction with eosinophilia and systemic symtomps is a form of various symptoms of fever, rash, facial erythema, facial edema, systemic involvement, and eosinophilia. Symptoms include lymphadenopathy (involving the neck, armpit and inguinal region in more than 70% of cases), hepatitis (80% of cases), lung (15% of cases), kidney (interstitial nephritis), heart (myocarditis or pericarditis), pancreatic involvement and haematological abnormalities (e.g. thrombocytopenia, leukocytosis, eosinophilia). The appearance of manifestations on the skin is preceded by a fever of 1 to 2 days. In DRESS, the lesions that form can vary. The lesions will be spread to the face, trunk and extremities **(Figure 7A-E).** Multiorgan involvement can also occur in DRESS accompanied by eosinophilia. The most common skin manifestation of DRESS is a polymorphic maculopapular eruption followed by exfoliation and desquamation. Skin lesions appear on the face with periorbital edema and the face then spreads to the upper body and lower limbs in 25-76% of cases. Pustula, purpura, plaque, erosion, target lesions, urticaria lesions and likenoid lesions are also seen in DRESS patients. [17 33] Oral and lip cavities are often involved in SJS/TEN, and 5% of SJS/TEN patients have lesions on the eyes or genitals without involving the oral cavity or lips, but the pattern of mucosal involvement differs in DRESS. A total of 63.6% of DRESS cases showed oral or lip involvement, 36.4% cases with eye involvement and 36.4% cases with genital lesions.

Acute generalized exanthematous pustulosis is usually characterized by pustules on the surface of the skin that are eremic and edematous. Acute generalized exanthematous pustulosis is a form of SCADR that is not too severe. The manifestation is in the form of acute fever with pustular eruptions in the form of non-follicular sterile pustules with an erythematosa base and accompanied by itching, especially in large folds (axillary folds, inguinal folds). The pustules can fuse and then cause rapidly developing superficial skin desquamation with a short interval between the administration of the drug and the onset of the disease. It is generally triggered by the antibiotics aminopenisillin and macrolides **(Figure 8A-B).** The presence of eosinophils in

inflammatory infiltrates occurs in about 30% of patients. Fever and leukocytosis are the first symptoms followed by isolated non-follicular pustules. Pruritus with or without burning sensation is reported by some patients. Liver dysfunction, renal insufficiency, respiratory distress, agranulocytosis and lymphadenopathy are examples of multi-organ involvement that have been documented in about 17% of cases.

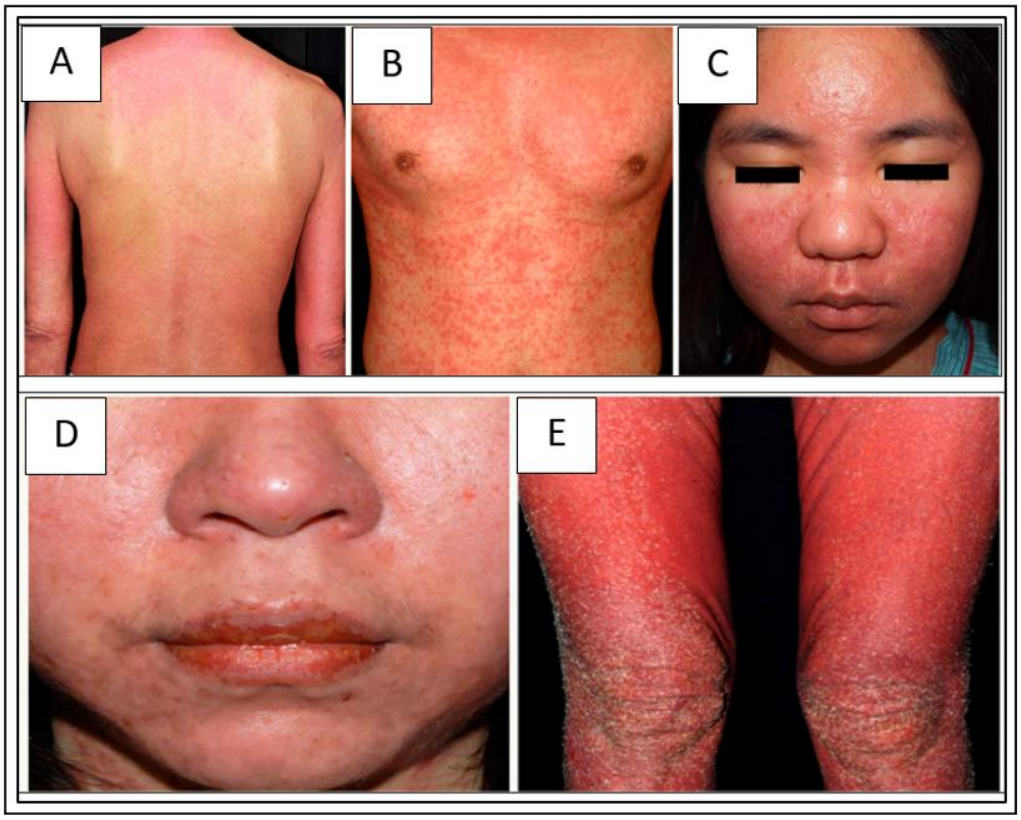

Figure 7A-E. Skin presentation in DRESS patients. **(A)** Extensive papules and purpura plaques on the body and limbs; **(B)** Infiltrative lesions in the body; **(C)** Facial edema with the exception of the area around the eyes; **(D)** Erosion of the lips; **(E)** Desquaamation at the recovery stage. [25]

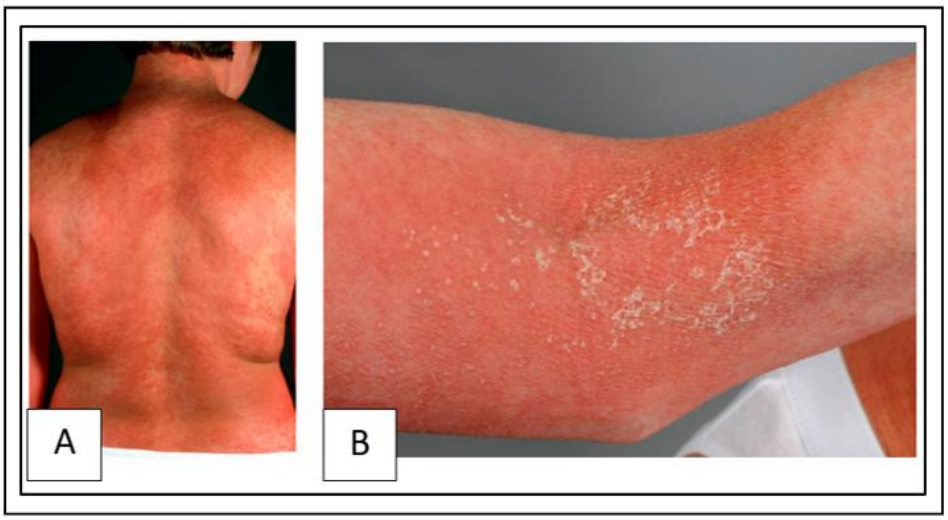

Figure 8A-B. Skin presentation on AGEP. **(A)** Evenly distributed rash with many needle-head-sized pustules on the base that are erythema and edematous; **(B)** Protrusions in folds with desquaamation are usually seen in AGEP.

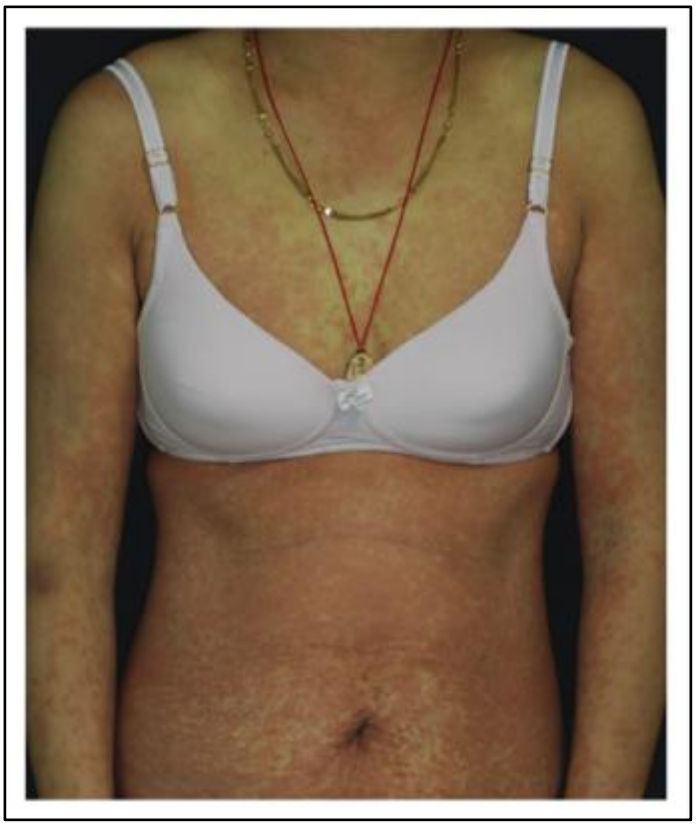

Figure 9. Skin lesions with DRESS after erlotinib therapy for 4 weeks.
Source: Clinical case from Putri et al. (2024), with the consent of the patient's ethics.

Supporting Examination And Enforcement Of Diagnosis

Diagnosis enforcement related to suspicion of side effects due to drugs can be used by the naranjo assessment system. The naranjo score consists of 10 questions that can be asked to patients where each question can be answered with yes, no and unknown. A naranjo score of ≥9 indicates a side effect due to the drug definitively. Values of 6-8 are probable, values 1-4 are possible and values of 0 indicate that the patient's condition is not due to a drug reaction.

Drug skin test can be used as a way to establish a CADR diagnosis. This method can be used to identify causative drugs, cross-reactions between drugs and determine safer drugs that can be used by patients. Drug skin tests should be done within 4 weeks after the loss of CADR and a maximum of 1 year after CADR.[32] Prick test is performed on the patient's arm where the drug is injected and is expected to release specific IgE if the patient is allergic to the substance. An intradermal test is carried out if the prick test result is negative but there is a high suspicion of CADR type 1. The patch test is the least sensitive of the previous two tests, but it can be an option if the ingredient being tried cannot be injected into the skin.

Many studies have explored potential biomarkers for SJS/TEN, including granulisin, FasL, perforin B, microRNA (miRNA), annexin A, calcium binding protein S100A2 (S100A2), IL-15, galectin-7 and high mobility group box 1 (HMGB1) protein. Previous studies have shown that the level of FasL in serum is related to the pathogenesis of SJS/TEN. Th17 cells are found together with CD8+ T cells in the blister fluid of SJS/TEN patients. CD8+ T cells are a source of IL-17, a cytokine that promotes neutrophil recruitment. The involvement of Th17

cells in SJS/TEN is indicated by a decrease in their number in the periphery after improvement of treatment-related diseases. Recent findings suggest that Th17 cells can change their phenotype and become regulatory T cells.

Drug reaction with eosinophilia and systemic symtomps shows a mixed presentation and the asymptomatic lag between drug use and symptom onset becomes a challenge in diagnosis, especially in the early stages. In Japan, dermatologists use the term DIHS (Drug Induced Hypersensitivity Syndrome) instead of DRESS. In 2006, the diagnostic criteria of the Japanese Severe Cutaneous Adverse Reactions to Drugs (J-SCAR) were introduced, covering seven parameters such as maculopapular rash that develops at least 3 weeks after initiating a particular drug group, persistent clinical symptoms 2 weeks after stopping the drug, fever, elevated liver enzymes, hematological abnormalities, lymphadenopathy and HHV-6 reactivation. All seven parameters must be met to diagnose DRESS. Initial diagnostic criteria were proposed by Bocquet et al. in 1996. These criteria include rashes due to medications, hematological changes (eosinophil levels greater than 1500 × 109/L and the presence of atypical lymphocytes) and systemic manifestations (lymphadenopathy, liver, kidney, lung and cardiac involvement). This criterion was replaced by the criteria proposed by the. Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group which is based on clinical and laboratory findings **(Table 2).**

The clinical scoring system of the RegiSCAR group in 2007 became the most commonly used and appears to be more accurate and comprehensive. The inclusion criteria of RegiSCAR require at least three independent features including skin involvement with acute rash, fever, lymphadenopathy in two different locations, internal organ involvement, lymphocytosis or lymphocytosis, blood eosinophilia and thrombocytopenia. The diagnosis of DRESS is determined based on clinical manifestations, laboratory and identification of causative drugs can strengthen the diagnosis.

Patients with suspected clinical symptoms of DRESS need to have laboratory tests including complete blood counts, liver enzymes, blood electrolytes, kidney function tests, urine analysis and thyroid function tests. Thyroid function tests should be repeated after 2 months because autoimmune complications such as diabetes mellitus type 1 and autoimmune thyroiditis, may appear over a longer period of time after the acute stage. Additional diagnostic tests involve polymerase chain reaction (PCR) for specific viruses and serology for hepatitis A, B and C. Skin biopsy may be considered if the diagnosis is in doubt, although the histopathological pattern of DRESS is highly variable and not pathomonical. Skin biopsy findings in the form of a picture of spongiosis, acanthosis, vacuolization, lymphocytic infiltration of the papillary dermis and perivascular dominance, the presence of varied eosinophils and atypical lymphocytes can guide the diagnosis of DRESS.

Table 2. The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system in the Diagnosis of DRESS

Criterion	**Score**			
	−1	0	+1	+2
Fever ≥ 38.5°C (core temperature) or ≥ 38°C (axillary)	No/unknown	Yes		
Enlarged lymph nodes (≥2 locations, >1 cm)		No/unknown	Yes	
Eosinophilia				
Eosinophils		No/unknown	700–1.490	≥1.500
Eosinophils, if		No/unknown	10,0–19,9%	≥20%

leukocytes <4×109/L				
Atypical lymphocytes		No/unknown	Yes	
Skin Engagement				
Skin rash rate (>50% body surface area (BSA))		No/unknown	Yes	
Skin rash on DRESS	Not	Unknown	Yes	
Biopsy on DRESS	Not	Yes/Unknown		
Organ Involvement				
One		No/unknown	Yes	
Two or More		No/unknown		Yes
Resolution ≥15 days	No/unknown	Yes		
At least 3 negative biological investigations to rule out other potential diagnoses		No/unknown	Yes	

Source: RegiSCAR validation criteria (Del Pozzo-Magaña & Liy-Wong, 2024).

Additional examinations according to the patient's symptoms, including abdominal ultrasound, chest X-ray, electrocardiogram, echocardiography, brain computed tomography (CT), neurological evaluation, pulmonary function tests, thoracic CT and other specialist consultations. The clinical severity of DRESS and the risk of recurrence may be related to the presence of fever, prolonged leukocytosis, facial edema, lymphadenopathy with erythroderma and involvement of the visceral organs if any. Patch tests and lymphocyte transformation tests (LTTs) can be used to verify the causality of the drug, patch tests can give positive results in patients with DRESS and should be done 2 to 6 months after symptoms subside. Lymphocyte transformation tests are in vitro tests that measure the activation of serum T cells when exposed to certain drugs, LTTs take the right time between 5 and 8 weeks after the onset of the rash in DRESS syndrome.

Diagnosis of AGEP can be done clinically with the support of histopathological findings and patch tests. The EuroSCAR study group presented a standard assessment system in 2001, namely the AGEP validation score which includes the morphology of skin lesions, fever, clinical development and laboratory and histopathological findings. A patch test can be done after the skin has fully recovered to identify the responsible drug in the case of polypharmacy. The sensitivity of patch tests in AGEP is higher than that of other drug reactions such as SJS or TEN (58% positive for AGEP and 24% positive for SJS/TEN). Positive results often indicate a small pustule at the test site. Histopathological examination should be performed to distinguish AGEP from other pustular eruptions. The histopathological picture shows subcorneal and or intraepithelial spongiform pustules, edematous papillary dermis and perivascular infiltrates with neutrophils and some eosinophils.

Prognostic Mortality Severe Cutaneous Adverse Drug Reactions

Research by Nunthanach in 2021, revealed the differences and similarities between the three SCADR phenotypes. AGEP patients are more commonly found at an older age and have a higher number of neutrophils compared to SJS/TEN and DRESS patients. According to the multivariate analysis of the SJS/TEN phenotype, old age, high NLR and the presence of systemic infections within 7 days of hospitalization were four independent factors that increased

the risk of death in the hospital in the overall SCADR group.

SCORTEN values above 4.6 indicate a predicted mortality rate of >50% in SCADR patients. Prognostic assessment of mortality of SCADR patients can also be determined by the ALLSCAR model. This model was compiled using factors that provide good accuracy for predicting in-hospital mortality in all SCADR phenotypes. The risk of HMR is significantly increased in patients with high SCADR (SJS/TEN and DRESS), even after adjustment of systemic infection status, this supports previous research that states that NLR is an inflammatory marker associated with the severity of SJS/TEN disease. In summary, the new ALLSCAR model consists of four parameters, namely systemic infection, minimum age of 71.5 years, NLR ≥4.08 and SJS/TEN phenotype. Patients with one of these simple parameters produce a higher ALLSCAR score that will have a higher risk of death in hospital. While a low NLR value indicates a favorable prognosis. Acute generalized exanthematous pustulosis has the lowest mortality rate with a prevalence of 2-5%. Steven Johnson syndrome/toxic epidermolysis necrotizing (SJS/TEN) is a SCADR with the highest mortality rate reaching 50%.

CONCLUSION

Cutaneous adverse drug reaction (CADR) is an unwanted reaction that can alter the structure or function of the skin, with or without systemic involvement after administration of the drug at normal doses. Cutaneous adverse drug reaction is the most frequent manifestation of drug sensitivity with highly varied causative agents and is included in the top 10 causes of mortality and is a skin disorder that is often encountered by dermatologists. There are several types of CADR with severe manifestations, including SJS/TEN, DRESS and AGEP or known as SCADR.

There are several risk factors for SCADR, including certain commonly associated medications and genetic predispositions. The prognosis factors of the SCADR type vary. In SJS/TEN, it can be assessed from SCORTEN and ABCD-10 scores. In DRESS, known prognosis factors are in the form of high eosinophilia, comorbid diseases, leukocytosis, coagulopathy, systemic inflammatory response syndrome and reactivation of certain viruses. AGEP can be known through the level of prothrombin time (PT), activated partial thromboplastin time (APTT) of patients who are elongated. SCADR management is based on the discontinuation of trigger drugs and a multidisciplinary approach according to the accompanying clinical manifestations, it is very important to know the clinical manifestations and prognosis factors of SCADR to reduce mortality and morbidity rates so as to improve the patient's quality of life.

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