

Review article

Severe cutaneous adverse drug reactions: a review on epidemiology, etiology, clinical manifestation and pathogenesis

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Keywords: *severe cutaneous adverse drug eruptions; drug hypersensitivity syndrome; exfoliative dermatitis; toxic epidermal necrolysis; Steven Johnson syndrome*

Purpose To review the current progress in epidemiology, etiology, clinical manifestation, and pathophysiology of severe cutaneous adverse drug reactions (SCADRs).

Data sources Data were acquired by using Blackwell-Synergy, PubMed, original articles published in the main Chinese journals and related medical textbooks materials.

Study selection and data extraction Throughout the literature review 49 articles were selected.

Results SCADRs cases are rare, however, the implication is life threatening with significant mortality rates. Epidemiology studies have shown various incidences from different regions, gender, age, race and concurrent illness. There are typical signs and symptoms for each type of SCADRs, but this is not always so. Drugs associated with inducing SCADRs are anticonvulsants, antibiotics, NSAIDs and antirheumatic drugs. In some countries, especially in Asia, traditional drugs are often the cause of SCADRs. Genetic polymorphisms and viral infections are predisposition factors of SCADRs. Patients with certain genetic alleles and underlying diseases are vulnerable to SCADRs. The exact pathogenesis of SCADRs is not well defined. Nonetheless, recent study showed that reactive metabolites and immunological processes have a significant role in SCADRs.

Conclusions The different SCADRs reactions are attributed by different intrinsic factors, such as genetic polymorphisms, gender, age and race as well as extrinsic factors, such as underlying diseases. Different regions and culprit drugs also play a role in the various types of SCADRs.

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As an increasingly more variable array of new drugs are being introduced into the market and improvement in health services result in a prolonged life expectancy, the frequency and quantity of drugs taken also increases significantly. These facts contribute to more cases of adverse drug reactions (ADRs). The most frequent observed are cutaneous reactions and that range from generally trivial manifestation, such as pigmentation, to severe life threatening reactions, such as toxic epidermal necrolysis (TEN), Steven Johnson syndrome (SJS), exfoliative dermatitis (ED) and drug hypersensitivity syndrome (DHS). Their impact is significant in terms of cost and health service resources.¹⁻⁴ Cutaneous or allergic reactions accounts for approximately 14% of ADRs in hospital patients and 3% of all disabling injuries during hospitalization.^{2,3} In this review, we focus on the current progress study in epidemiology, etiology, clinical manifestation, and pathophysiology of severe cutaneous adverse drug reactions (SCADRs).

EPIDEMIOLOGY OF SCADRS

The incidence of adverse cutaneous drug reactions varies from 2%–5% of hospitalized patients and approximately 1 in 1000 hospital patients suffer from life-threatening cutaneous drug reactions.^{3,5,6} The incidence of SJS-TEN is estimated at 2 to 3 cases per million population per year.⁴ In the general population, DHS exposure is

estimated to be between 1 in 10 000 and 1 in 1000.⁷ ED cases in India and the Netherlands were reported between 0.9 per 100 000 and 35 per 100 000.⁸ The higher incidences of ED occurred in parts of Asia because of common practice of traditional medicaments.²

A study by Li et al⁹ at Peking University Third Hospital reported that the incidence of SCADRs in the Haidian district was 1.8 cases per million person per year and the incidence rate for SJS, ED, TEN, DHS were 0.8, 0.6, 0.05 and 0.4 cases per million person per year, respectively. Different patterns were observed in categories of clinical types of SCADRs in different countries (Table 1), where SJS has a higher proportion as compare to other SCADRs in China and Italy. However, Noel et al¹⁰ in India found a higher proportion on TEN.

One study has shown that the mortality rates for SJS were less than 5% whereas the rate for TEN approaches 20%–40%.¹ However, a study by Huff et al found that the number of deaths is up to 18% of patients with SJS, and up to 50% of patients with TEN. In the published reports of the past 50 years, the mortality rates associated

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Table 1. Comparison of the clinical types of severe cutaneous adverse skin reactions in different countries

Clinical type	Italy ⁴	France ⁶	Thailand ⁷	China ⁹	India ¹⁰
SJS	55.32%	10%	37.04%	41.82%	35%
TEN	10.63%	-	28.57%	10.91%	45%
ED	34.04%	40%	40.74%	29.09%	10%
DHS	-	50%	-	18.18%	10%

with ED have consistently remained high, ranging from 20%–60%² and DHS related deaths are 10%.^{12,13}

Onset of SCADRs varies, ranging from hours to 6 weeks after the initiation of therapy but occurs more rapidly with re-challenge.^{1,2,13,14} The mean time from first drug administration to onset of SJS or TEN was 1–28 days. A longer incubation period was observed with thiacetazone ((10±6) days), phenytoin ((12±9) days) and carbamazepine ((11±3) days).^{1,3} DHS appears in 2 to 6 weeks after administration of the causal drugs,^{1,3,13} however this time interval is shorter for abacavir, lamotrigen and nevirapine. ED onset is within 15 to 28 days after the administration of the causal drugs.^{14–16}

SCADRs occur at ages ranging from 3 to 85 years.^{16,17} However, there has been a case reported from Turkey on DHS in a premature infant, because of anticonvulsant drugs.⁷ There have been some reports of the incidence of drug eruptions that increase with patient age. In the UK the percentage of adverse drug eruptions increased from 0.6% for patients aged 0–20 years to 2.7% for patients aged over 50 years. A study by Richard Martin et al¹⁸ found that the overall age relative risk of an adverse drug reaction is between 30 and 59 years of age.

In most cases of ADRs, females are at higher risk than males.^{1,2,18–23} However, a study by Li et al^{6,9} has shown a male predominance in SCADRs, with an exception for the SJS group where females were predominant. A study by Peyrière et al has shown a male predominance in DHS and ED incidence.^{8,24} A serial study conducted in Thailand showed a male predominance as well in SJS and TEN.²⁵

Patients with AIDS have a dramatically increased incidence of TEN and DHS.^{1,2,26} A study by Fiszenson et al⁶ found that of the cases of cutaneous adverse drug reactions, 19% were known to be infected by HIV. Patients with HIV are also prone to exfoliative dermatitis drug eruptions.⁸ Reactivation of Human Herpes Virus 6 may contribute to the development of DHS.¹³ Patients with autoimmune diseases, like lupus erythematosus (LE) and an HLA-linked genetic susceptibility, have been reported to have a higher frequency of drug allergies. LE patients have also been shown to have an increasing incidence in antibiotic allergy.^{1,2,19,27}

CLINICAL MANIFESTATION OF SCADRS

SJS and TEN

Patients initially develop pain, tenderness or a burning sensation in the skin. These symptoms often begin abruptly and are associated with fever and general

malaise. Over the next 1 to 3 days, ill-defined erythematous macules or a diffuse erythema develops over the trunk and extremities. As the red areas enlarge, central dusky necrotic sites develop with subsequent bullae formation. As the disease progresses, sheets of full-thickness epidermis detach, revealing dark red, moist dermis (resembling severe second-degree burns).^{2,28} A positive Nikolsky sign is an important diagnostic clue and precedes the onset of a life-threatening event. SJS involves less than 10% epidermal detachment and TEN involves more than 30% of epidermal detachment. Between 10%–29% epidermal detachment is diagnosed as SJS/TEN overlap. However, there was a report of a case of SJS that only presented with mucous membrane lesions, without skin lesions, in 14 year old boy.²⁹ The presenting sign of mucous membrane involvement occurs in 85% to 95% of SJS and TEN patients, appearing on the conjunctivae, mucous membranes of the nares, mouth, oropharynx, anorectal junction, vulvovaginal region and urethral meatus. Table 2 shows the detailed SJS and TEN differences.

Table 2. SJS and TEN clinical manifestation^{2,28}

Manifestation	SJS	TEN
Mucous membrane	>90%	>90%
BSA involvement	<10%	>30%
Erosions	Several sites	Several sites
Detachment of epidermis	Yes	Yes
Hyperkeratosis/desquamation	No	No
Neutropenia	No	30%
Eosinophilia	No	No
Atypical lymphocytes	No	No
Respiratory tract	Bronchial erosions/ARDS	Bronchial erosions/ARDS
Liver	Hepatitis 10%	Hepatitis 10%
Heart	No	No
Lymph node enlarged	No	No
Mortality rate	5%	30%

ARDS: adult respiratory distress syndrome; BSA: body surface area; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

DHS

The clinical syndrome includes severe eruption, fever, lymphadenopathy, hepatitis, hematological abnormalities with eosinophilia and atypical lymphocytes. It can involve other organs as well. The syndrome develops within two months following introduction of the drug and frequently between two to six weeks afterwards or immediately after a re-administration. Fever (23%–100% of cases) and cutaneous eruption (73%–100% of cases) are the initial signs, especially when related to antiepileptics.^{2,24} Edema of the face with periorbital accentuation is an alert for the diagnosis and can be very intense. Atypical targets can appear and over time the eruption becomes purpuric, markedly so in the lower limbs, and desquamation occurs after resolution. It can also present as a picture of exfoliative dermatitis associated with mucous involvement, such as cheilitis, erosions, exanthematous pharynx and enlarged tonsils.

Lymphadenopathy is frequently generalized and painful and improves gradually after drug withdrawal. Two distinct types of lymph node involvement may be present;

a benign lymphoid or a pattern with a pseudolymphomatous aspect. Various hematological abnormalities are observed, consist of anemia, pronounced leukocytosis, eosinophil and atypical lymphocytes similar to mononucleosis. Eosinophils may determine the potentially fatal involvement of internal organs. Hepatic involvement constitutes the most common visceral manifestation and as the main cause of mortality.

In 2006 a Japanese consensus group established a set of diagnostic criteria for DHS (Table 3). Diagnosis is confirmed by the presence of seven criteria as typical DHS or by the first five as atypical DHS.³⁰

Table 3. Diagnostic criteria for DHS established by a Japanese consensus group

Maculopapular rash developing > 3 weeks after starting with a limited number of drugs
Prolonged clinical symptoms 2 weeks after discontinuation of the causing drug
Fever (38°C)
Liver abnormalities (ALT>100 U/L)
Leukocyte abnormalities (at least one present)
Leucocytosis (>11×10 ⁹ /L)
Atypical lymphocytosis (>5%)
Eosinophilia (>1.5×10 ⁹ /L)
Lymphadenopathy
Human herpes virus 6 reactivation

ED

An inflammatory skin disease with erythema and scaling that affects nearly the entire cutaneous surface. It may follow exanthematous eruptions or may develop as erythema and exudation in the flexures. The process usually begins on the face and upper trunk with progression to other skin surfaces and spreads rapidly. Unlike SJS and TEN, the mucosa in ED patient is spared.^{5,28}

A study by Sabrina et al⁵ found that itching was the most common complaint, recorded in 69% of cases. Other symptoms including chills and photosensitivity recorded in 64.4% of cases. It takes 4 to 6 weeks to subside even after withdrawal of drugs and initiation of treatment. ED due to the dapsone/antileprosy drug may often mimic cutaneous T-cell lymphoma and it resolves after the offending drugs are withdrawn.⁸

Excessive heat loss and hypothermia can complicate ED. Widespread cutaneous vasodilatation may result in high-output congestive heart failure. Continuing exfoliation can result in significant protein loss and negative nitrogen balance.

CAUSATIVE AGENTS OF SCADR

The most common medicines that implicate SCADR in the literature, under the form of case reports or studies on series of patients, include anticonvulsants (phenytoin, valproic acid, phenobarbital, and carbamazepine), antibiotics (sulfonamides and aminopenicillins), NSAIDs

(oxicam derivatives), and chlormezanone and allopurinol.

A recent case reports from China showed that the most common drugs that cause SCADR were antibiotic drugs, NSAIDs, anticonvulsant, antirheumatic drugs. Also found were several cases of Traditional Chinese medicine induced SCADR (Table 4). A study conducted by Li et al⁹ found that antibiotics were the most common offending drugs of SCADR, followed by anticonvulsants and traditional Chinese medicines.

Table 4. Comparison of the causative agents of SCADR found in observed previous studies in China

Clinical type	Xiong ¹⁴	Ly ¹⁶	Li ¹⁷
Antibiotic agents	25%	25%	12.50%
Antipyretic/anti-inflammatory agents	21.90%	21.43%	8.33%
Drugs acting on the central nervous	12.50%	21.43%	54.16%
Antirheumatic agent	12.50%	17.86%	8.33%
Traditional Chinese medicine	-	3.57%	-
Others	17.20%	10.71%	16.67%
Unknown	7.80%	-	-

Causative agents of SJS and TEN

Different patterns were observed for drugs that cause SJS and TEN (Table 5). A 7 years retrospective study conducted by Devi et al in India implicated that the most common drugs that cause SJS and TEN were anticonvulsant, NSAIDs, antibiotic and Ayurvedic medication. Anticonvulsants account for 55% of the total cases, and Carbamazepine for 44% of the total cases caused by anticonvulsants.³¹ Another study in India also found that anticonvulsants were the most common drugs that induced SJS and TEN.¹⁰

Table 5. SJS and TEN causative drugs at several countries

Countries	Drugs
India ³¹	<i>anticonvulsant</i> , NSAIDs, antibiotic, ayurvedic medication
Malaysia ²⁷	<i>anticonvulsant</i> , antibiotics, analgesic and NSAIDs
Thailand ^{11,25}	<i>antibiotics</i> , anticonvulsant, anti tuberculosis, analgesics, anti-rheumatic drugs
Italy ⁴	<i>NSAIDs</i> , <i>rheumatic drugs</i> , antibiotic, anticonvulsant
China ⁹	<i>antibiotics</i> , anticonvulsant, TCM, analgesics, anti-rheumatic drugs

The more commonly implicated drugs are listed in italic.

In Malaysia, anticonvulsants (carbamazepine and phenytoin), antibiotics (sulfonamide and penicillin), analgesic and NSAIDs²⁷ were the order of drugs responsible for SJS and TEN. A retrospective study from Thailand reported that antibiotics, as a group, were the most common cause of SJS and TEN and accounted for 53% of cases, especially penicillin (31%) and sulfonamides (15%), followed by anticonvulsants, anti tuberculosis drugs, analgesics and anti rheumatic drugs.^{11,25}

A study by Luigi Naldi et al in four Italian regions found NSAIDs were the most common drugs that induced SJS, followed by antibiotic and anticonvulsant. They also found that rheumatic drugs, allopurinol and sulphasalazine, were followed by antibiotics and anticonvulsants as the most common drugs that induced TEN. A report from

Nigeria showed that antibiotics were the common drugs that induce SJS.³³

In China, a study by Li et al⁹ found that antibiotics were the most common drug that induced SJS and TEN. They also found that Traditional Chinese Medicines account for about 9% of SJS and 50% of TEN cases. A study by Lin et al³⁴ in Taiwan indicated that carbamazepine, phenytoin and allopurinol were associated with a significantly increased risk of SJS and TEN in oriental peoples.

Though it is rare, there was a report about ranitidine, corticosteroid and metronidazole inducing SJS.^{28,35,36} Thyroid drugs were also reported to induce SJS and TEN.¹⁷

Causative agents of DHS

The most common precipitants are the aromatic anticonvulsants. Faulty metabolism of these drugs is thought to precipitate the disease process, which has also been associated with the initiation or reactivation of infection with human herpes virus type 6.^{32,35} There is a 75% incidence of cross-reactivity between these anticonvulsants. Other medications known to cause DHS include dapsone, sulfonamides, allopurinol, minocycline^{28,37} and diaminodiphenylsulfone.³²

Study by Li et al in Peking, found that the most common causative drugs were anticonvulsants followed by antibiotics, NSAIDs, anti rheumatic drugs and Traditional Chinese medicines.⁹ However, a study by Wan et al in Guangzhou, found allopurinol was the most common causative drugs followed by anticonvulsants (carbamazepine), dapsone and NSAIDs.¹²

Causative agents of ED

Antiepileptics, cimetidine, lithium, gold, allopurinol, quinidine and calcium channel blockers are the common causes of ED, although, theoretically, any drugs may cause ED, including anesthetics, antihistamines, antivirals and herbal drugs.²

A study by Sabrina Pal et al in Pakistan found that drugs that caused ED were heavy metals (arsenic and mercury), isoniazid and penicillin.⁵ Virendra et al³⁸ in India found that the most common causative drugs in children were sulfonamide, isoniazid, streptomycin, NSAIDs and antiepileptic drugs. Another study conducted by Noel et al¹⁰ in India shown that phenytoin was the most common drug that caused ED on adult patients.

Luigi et al⁴ found an antibiotic, amoxycillin, was the most common cause of ED followed by the anticonvulsant, carbamazepine, in four Italian regions.

Studies by Qi Bao-quan et al²² found that NSAIDs was the most common cause of ED followed by antibiotics. Another study, also conducted in China by Li et al,¹⁷ found that anticonvulsants were the most common inducer of ED followed by NSAIDs and antibiotics.

RISK FACTORS AND PATHOGENESIS OF SCADRS

General consideration

In the last decade numerous discoveries and breakthroughs in biological molecular techniques, proteomics and pharmacogenetics have dramatically shifted our understanding of SCADRs. Many intensive studies on SCADRs have been conducted abroad or in the country that resulted in numerous new discoveries, including the concept of SCADRs pathophysiology.

It is now believed that many SCADRs are caused by the formation of reactive oxidative metabolites, and, perhaps, the formation of antibodies to drug-protein complexes and skin proteins that includes cytochrome P-450 enzymes or both.

Risk factors

Genetic polymorphisms that alter drug metabolism or immune responses in some individuals increase susceptibility to certain drugs or to certain SCADRs.³⁹ The incidence of higher HLA-B*1502 in the Han Chinese compared to other races make them more susceptible to SJS induced by carbamazepine. It has been suggested that the HLA-B allele may illicit an immune response by presenting peptides bound to the drugs or their metabolites to specific T cells.^{26,39-41} The HLB*5801 allele in the Han Chinese was an important genetic factor for allopurinol-induced SJS and TEN.^{39,42} Another study also found that the English population, with high incidences of HSP70 gene variants, are prone to carbamazepine induced SJS and TEN.³⁹

Viral infections may play a concomitant pathologic role in SCADRs.^{2,13,43} A study by Conilleau et al^{13,32} showed a significant increased in HHV6 antibody titers in DHS patients.

PATHOGENESIS OF SCADRS

Reactive metabolites

This hypothesis postulate that patients suffering from severe drug reactions were exposed to increased amounts of reactive (oxidative) metabolites. The increases of these metabolites are cause by: 1) decreased production of normal soluble a-toxic metabolites, 2) decreased ability to detoxify reactive metabolites.

A study by Spielberg et al found that DHS induced by anti epileptic drugs imparted by loss of detoxification capacity resulted in an accumulation of anti epileptic drugs or their metabolites. The study showed that lymphocytes cultured from patients with prior DHS have increased rates of necrosis when the putative anti epileptic drugs were added as compared with lymphocytes taken from unexposed control patients exposed to anti epileptic drugs. The study found that lymphocyte toxicity due to aromatic amines depends on

oxidation by cytochrome P-450 isoenzymes into reactive arene oxide metabolites. Lymphocyte toxicity was increased when epoxide hydrolase, the detoxifying enzymes that remove the reactive metabolites, was inhibited or defective.⁴⁰

Low constitutive N-acetylating capacity, an important function in the metabolism of certain drugs, was associated with increased risk of development SCADRs. A study by Dietrich et al found that patients with SJS or TEN have a low N-acetylating capacity, especially in Caucasian patients.⁴⁴ Genetic polymorphism in the N-acetylating phenotype has important clinical relevance in terms of drug metabolism.^{44,45}

Alteration of Glutathione and its associated enzymes that are essential in detoxification of carbamazepine metabolites, was associated with carbamazepine induced DHS.⁴⁶ HIV is the most common cause of the significant reductions of glutathione peroxidase and glutathione transferase.¹³

IMMUNOLOGY OF SCADRS

SJS and TEN

The immunopathogenesis of SJS and TEN is viewed as a cytotoxic immune reaction involving a massive apoptosis of epidermal keratinocytes that lead to the detachment of large sheets of epidermis. This is triggered by Fas and Fas ligand, TNF- α , TNF- α related apoptosis-inducing ligand (TRAIL), and granzyme B. Several studies showed that patients with SJS and TEN had increased serum soluble Fas ligand concentrations, perforin and TNF- α were also present when compared to healthy control.^{42,47} Other studies have shown the association of high TNF- α with the severity of the reaction.^{45,48} A study by Caproni et al found significantly increased Th1-related cytokines (IFN- γ , IL-2) and Th2-related cytokines (IL-5, IL-13). These cytokines were completely negative in healthy control specimens.⁴⁸

DHS

The exact immunopathology is still unknown but it has been postulated that this mechanism would combine pharmacogenetic dispositions with immunogenetic aspects. DHS is associated with an inherited deficiency of epoxide hydrolase, an enzyme required for metabolism of a toxic intermediate arene oxide formed during metabolism of phenytoin by the cytochrome P450 system. Uncontrolled activation of CD8⁺ cytotoxic T lymphocytes in response to HHV-6 infection may mediate epidermal cell injury in DHS.⁴⁹ The production of IL-5 and the chemokine eotaxin, a small protein synthesized by a number of different cell types and stimulated by interleukin-4 and interleukin-13 produced by Th-2 lymphocytes, are reported as the main determinants of eosinophilia in DHS.⁴⁷

ED

It is believed that ED is secondary to a complicated

interaction of cytokines and cellular adhesion molecules which include interleukins-1, interleukins-2, interleukins-8, intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor (TNF). These interactions result in a dramatic increase in the epidermal turnover rate, a higher than normal mitotic rate and an increase in the absolute number of germinative skin cells, whereas the transit time of keratinocytes through the epidermis decreases.^{2,8,38} The epidermis produces significantly elevated amounts of circulating vascular permeability factor or vascular endothelial growth factor in erythrodermic skin, resulting in dermal vascular proliferation and increased vascular permeability.⁸

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