ABSTRACT
Cutaneous adverse drug reaction is one of the most common manifestations of drug allergy. As the knowledge of the morphology of drug induced cutaneous lesions helps in the early identification of even a serious drug reaction, it is mandatory for the treating physician to pick up early signs of these reactions followed by a prompt withdrawal of the suspected drug. The paper discusses the clinical presentation and management of these including severe cutaneous adverse drug reactions. It emphasizes on need of a great amount of skill for its identification and management.

Keywords: Adverse drug reaction, Hypersensitivity reaction, Exanthema, Erythroderma.

INTRODUCTION
Cutaneous adverse drug reaction is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.1

Adverse drug reactions (ADRs) are responsible for about 3% of all hospital admissions and between 10 and 20% of hospital inpatients develop ADRs.2 The ready visibility of skin signs makes it easy to detect a drug reaction earlier so as to discontinue the drug in question. Skin manifestation is also the commonest presentation of drug allergy3,4 emphasizing the importance of recognition and withdrawal of the causative drug which at times may be life saving.

The presentation varies from mild in the form of a skin rash alone to severe having multisystem involvement in addition. It poses diagnostic difficulties because of its varied clinical presentation and also because of the need to find out the causative drug out of the many taken by the patient.

Women are more likely than men to develop ADRs.5 Patients with acquired immunodeficiency syndrome have an increased risk of developing drug reactions. The reasons may be multifactorial which include changes in the drug metabolism, oxidative stress, cytokine profiles and immune hyperactivation.6 The risk increases as they also receive multiple drugs for various associated ailments.

Rougeau proposed criteria7 which help to diagnose cutaneous adverse drug reactions:

a. Other causes for the eruption as viral exanthema should be excluded.
b. A temporal relationship between the drug and onset of rash should exist.
c. Improvement should be noted following drug cessation.
d. Reactivation upon challenge should be noted.
e. Cutaneous reaction is known to be associated with the drug.

MECHANISM OF DRUG ALLERGY
Drug reactions are of two types—Allergic and more commonly nonallergic.

Nonallergic Reactions
Nonallergic reactions are usually dose dependent and predictable and normally result from the known pharmacological actions of the drug. Rarely they can be unpredictable in the form of idiosyncratic or hypersensitive reactions which are dose independent and are unrelated to the pharmacological actions of the drug. This may also have a genetic basis though not all of them have a genetic influence. Genetic factors are known to affect the pharmacokinetics and pharmacodynamics of the drug. The metabolic pathways most subject to genetic influence include oxidation, hydrolysis and acetylation.8 Thus, genetic variations in all these areas may underlie intolerance and idiosyncrasy.9-11

Drug reactions are also known to occur more commonly with certain HLA types emphasizing the importance of genetic factors in the pathogenesis of drug reactions.

Allergic Reactions
On the other hand, allergic reactions require a prior immune stimulation by the drug in question. They can be divided into four types (Coombs and Gell).
Hypersensitivity Reactions

**Type 1:** This is an IgE dependent reaction wherein the drug or its reactive metabolite binds to IgE present on the surface of basophils or mast cells and cause degradation of these cells with the resultant release of vasoactive mediators like histamine, prostaglandin D2, leukotriene C4, eosinophil and neutrophil chemotactic factors, platelet activating factor and bradykinin which clinically results in urticaria, angioedema or systemic anaphylactic reactions.

The most common causes of IgE–mediated drug-induced hypersensitivity are antibiotics (especially the penicillins) and anesthetic related drugs, particularly muscle relaxants.

**Type 2:** Here there is a complement mediated cytolysis leading to cell damage after the antibody binds to the surface of the cell. An example is the thrombocytopenic purpura that may result from antibodies to quinidine-platelet conjugates.

The other examples of this type of reaction are drug induced pemphigus, bullous pemphigoid and linear IgA disease. Drug induced pemphigus is divided into the following two types:

1. Drug dependent pemphigus wherein exogenous factors such as thiol (-SH) containing drugs (e.g. D-penicillamine, captoprill) cause pemphigus by binding with the plakoglobin and thus altering the immunogenicity. Thiols can also alter the immune system directly by its action on the T cells.

2. True (drug-triggered) pemphigus wherein in a genetically predisposed individual, nonthiol group drugs (e.g. penicillin, cephalosporins) trigger pemphigus by the virtue of amide group present.

**Type 3:** Serum sickness is the prototype of this kind of reaction wherein there is formation of antigen-antibody complexes and subsequent activation of complement cascade and inflammatory response. Here the antigen antibody complexes are present in the circulation with antigen excess. The immune complexes get deposited in the skin, gastrointestinal tract and kidneys. It can manifest in various forms like urticaria and anaphylaxis or vasculitis both as a result of anaphylotoxins C3a and C5a generated during the process of complement cascade activation. Another example of this type of hypersensitivity reaction is Arthus reaction which is a localised form occurring at the injection site.

**Type 4:** In recent years increasing evidence indicates that drug specific T cells play a cent role in the pathogenesis of these exanthema. T cells (both CD4 and CD8) produce various cytokines which are responsible for the various manifestations. Earlier for the delayed hypersensitivity reactions, a hapten-prohapten model was believed to be the only mechanism involved wherein a chemically reactive small molecule (hapten) required binding with a larger molecule to be able to be recognized by the immune system or a chemically inactive molecule (prohapten) after metabolism becoming active and then being recognized by the immune system. Lately, it was also demonstrated that the inert drug itself and not a metabolite was recognized by T cells.

There is also an upregulation of major histocompatibility complex (MHC) class II expression on keratinocytes.

**CLINICAL PRESENTATION AND DIAGNOSIS OF VARIOUS DRUG REACTIONS**

As the clinical patterns of drug reactions are very variable, it is a great task for the clinicians to diagnose and manage these reactions. It is also mandatory to differentiate mild from a severe reaction thus requiring an astute clinical awareness of the various clinical patterns. The common clinical manifestations include maculopapular rash, purpura, bullous lesions, erythema multiforme, fixed drug eruptions, and more serious forms like exfoliative dermatitis, acute generalized exanthematous pustulosis, toxic epidermal necrolysis and Steven Johnson’s syndrome (SJS). Chronic onset drug-induced disorders include pigmentary changes, drug-induced

<table>
<thead>
<tr>
<th>Lesion(s)</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td>Aspirin; NSAIDs; angiotensin-converting enzyme inhibitors; penicillin;</td>
</tr>
<tr>
<td></td>
<td>cephalosporins; opiates; peptide hormones; radiocontrast dyes; vaccines</td>
</tr>
<tr>
<td>Maculopapular eruptions</td>
<td>Aspirin; NSAIDs; ampicillin; anticonvulsants; barbiturates; isoniazid;</td>
</tr>
<tr>
<td></td>
<td>phenothiazines; quinolones; sulfonamides; thiazides; co-trimoxazole</td>
</tr>
<tr>
<td>Vesiculobullous eruptions</td>
<td>Aspirin; NSAIDs; barbiturates; furosemide; griseofulvin; penicillamine;</td>
</tr>
<tr>
<td></td>
<td>penicillin; sulfonamides; thiazides</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>Penicillamine; gold; levodopa; heroin; penicillin; rifampin; phenylbutazone</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Amiodarone; chlorpromazine; furosemide; quinolones; sulfonamides;</td>
</tr>
<tr>
<td></td>
<td>tetracycline; thiazides</td>
</tr>
<tr>
<td>Fixed drug eruptions</td>
<td>Acetaminophen; anticonvulsants; barbiturates; metronidazole; oral</td>
</tr>
<tr>
<td></td>
<td>contraceptives; penicillin</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Allopurinol; cimetidine; gold; phenytoin; quinolones; propylthiouracil;</td>
</tr>
<tr>
<td></td>
<td>thiazides; NSAIDs</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome;</td>
<td>Sulfonamides; co-trimoxazole; tetracyclines; barbiturates; thiacezeno;</td>
</tr>
<tr>
<td>toxic epidermal necrolysis</td>
<td>phenytoin; carbamazepine; phenylbutazone</td>
</tr>
</tbody>
</table>

Table 1: Agents commonly implicated in drug induced skin lesions
autoimmune bullous diseases, pseudo lymphoma, lichenoid and acneiform eruptions.

A knowledge of the specific morphology of the skin rash associated with a particular drug helps in suspecting and timely withdrawal of the drug in question. Table 1 shows drugs commonly implicated in skin lesions.24

Drug Induced Urticaria and Angioedema

Urticarial reaction which consists of pruritic erythematous edematous usually evanescent and sometimes persistent wheals (Fig. 1) may also be drug induced apart from other causes, is classical of IgE mediated type 1 hypersensitivity reaction. It may also occur as a ‘pseudoallergic’ reaction due to direct release of inflammatory mediators because of the direct binding of the drug to mast cell or basophils. Angioedema, caused by the same pathogenic mechanism involves deep dermis and subcutaneous tissue. It presents mainly as asymptomatic or painful swelling which are less or nonitchy (Fig. 2). In the most severe form it may present with laryngeal edema, hypotension or bronchospasam. Penicillin is one of the most common causes for this kind of reaction the others being nonsteroidal anti-inflammatory drugs and sulphamides. Along with these, radiocontrast media, animal sera, blood products can also cause both reactions.

Skin prick tests, enzyme linked immunosorbent assay (ELISA) and the radiosorbent test (RAST) may be useful in the diagnosis.

Histopathological examination of urticaria shows a normal epidermis with venular dilatation with edema in the dermis and superficial and deep dermal mononuclear infiltrate admixed with eosinophils and neutrophils. In angioedema, the infiltrate and edema extend to the subcutis.

Exanthematous Eruption

Exanthematous eruptions, sometimes referred to as morbilliform or maculopapular, are the most common form of drug eruptions, accounting for approximately 95% of skin reactions.25 This manifests usually as symmetrical blanching, erythematous, papular eruption of sudden appearance with or without systemic features (Fig. 3). Mucous membrane involvement is rare. Systemic manifestations when present may include lymphadenopathy, fever, eosinophilia and organ dysfunction. Penicillins, sulphonamides, phenylbutazone, phenytoin, carbamazepine and gentamicin are the common causative drugs. In patients with concomitant infectious mononucleosis, the risk of developing an exanthematous eruption while being treated with an aminopenicillin (e.g.: ampicillin) increases from 3 to 7% to 60 to 100%.26 Histopathology shows sparse perivascular infiltrate of lymphocytes with or without eosinophils.

The main differential diagnosis is viral exanthems. Viral exanthems are commonly accompanied by fever, lymphadenopathy and the rash usually starts on the face and later progresses to involve the trunk. Continuation of the drug may lead to erythroderma. The rash usually fades with desquamation or hyperpigmentation.

Fixed Drug Eruptions

Fixed drug eruptions (FDE) commonly present as erythematous or dusky red macules progressing to edematous plaques occurring anywhere on the body with or without constitutional symptoms (Fig. 4). Genitals, hands and feet are the favored sites. Local burning or stinging sensation may be present. It can develop from few minutes to few hours after the drug intake. Widespread and bullous lesions are known to occur when severe. A peculiar feature of this is the residual slate gray hyperpigmentation which on rechallenge become active with or without the development of new lesions.

Histopathology shows necrotic keratinocytes, superficial and deep dermal perivascular infiltrate of lymphocytes, eosinophils and occasional neutrophils. Melanophages when present give a clue to the diagnosis.
Sulphonamides, tetracyclines, barbiturates, carbamazepine, phenolphthalein and NSAIDs are the common culprit drugs.

**Drug Induced Lichenoid Eruptions**

Though clinically resemble classical lichen planus with violaceous pruritic papules and plaques on the trunk and extremities, drug induced lesions are more eczematous and may be extensive (Fig. 5). There may also be sparing of mucous membranes.

Histologically lichenoid drug eruption may have focal parakeratosis, cytoid bodies in the stratum corneum and granulosum along with the presence of eosinophils and plasma cells in the inflammatory infiltrate and perivascular inflammatory infiltrate in the deep dermis apart from the classical features of lichen planus.

The drugs implicated are penicillamine, beta blockers, captopril, antimalarials, phenothiazines, NSAIDs, sulfonylureas and antitubercular drugs among the common ones.

**Drug Induced Photosensitivity Reactions**

It is defined as a reaction on the photoexposed areas often sparing upper eyelids, retroauricular and submental areas following drug intake (Fig. 6).

It can be divided into phototoxic and photoallergic reaction. The differences are listed in Table 2. Photoallergic reaction represent a T-cell mediated reaction in which ultraviolet light alters either the hapten or the avidity with which the hapten combines with the carrier protein to form a complete photoantigen.

**Drug Induced Vasculitis**

Classically affecting small vessels, it presents clinically with palpable purpura commonly on the lower extremities. Other manifestations include nodules, ulcers, urticarial lesions and hemorrhagic bullae. Systemic involvement is common with involvement of liver, kidney, gut and central nervous system and can be life-threatening.

Drugs that are associated with vasculitis include propylthiouracil, hydralazine, granulocyte-macrophage colony-stimulating factor, allopurinol, cefaclor, minocycline, penicillamine, phenytoin, isotretinoin and anti-TNF agents.

Other causes of vasculitis have to be ruled out. Tissue eosinophilia and positive perinuclear staining ANCA against myeloperoxidase may point to the diagnosis.

Withdrawal of the drug and systemic corticosteroids are the mainstay of treatment.

**Drug Induced Pseudolymphoma**

Named so because of its resemblance to lymphoma clinically presenting as red papules, plaques or nodules which may be solitary or multiple with or without lymphadenopathy developing months to years after the administration of the
Fig. 6: Photoallergic reaction to thiazide diuretics

Table 2: Differences between phototoxic and photoallergic reaction

<table>
<thead>
<tr>
<th>Phototoxic reaction</th>
<th>Photoallergic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictable</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Occurs with the first exposure to a certain amount of the</td>
<td>Occurs after a sensitization phase and is a type 4</td>
</tr>
<tr>
<td>drug with the required intensity of sunlight</td>
<td>hypersensitivity reaction</td>
</tr>
<tr>
<td>Clinical manifestations is an exaggerated sunburn (Fig. 6)</td>
<td>It is an allergic reaction which is eczematous and pruritic</td>
</tr>
<tr>
<td>Usually confined to the sunexposed area</td>
<td>Lesions can be seen beyond the sunexposed parts</td>
</tr>
<tr>
<td>Causative drugs are commonly tetracyclines, quinolones,</td>
<td>Causative drugs are sulphonamides, thiazide diuretics,</td>
</tr>
<tr>
<td>amidodarone, psoralens, methotrexate, voriconazole and</td>
<td>NSAIDs, phenothiazine, antimalarials, calcium channel</td>
</tr>
<tr>
<td>furosemide (frusemide), coal tar</td>
<td>blockers</td>
</tr>
<tr>
<td></td>
<td>Topical photoallergens include topical anesthetic drugs,</td>
</tr>
<tr>
<td></td>
<td>antihistamines, PABA containing sunscreens</td>
</tr>
<tr>
<td>Histopathology is that of a sunburn reaction</td>
<td>Histopathology is like an allergic contact dermatitis</td>
</tr>
</tbody>
</table>

Drug induced Acneiform Eruptions

Papulopustular acne like eruptions with same sites of involvement as acne but absent comedones is the hallmark of this condition (Fig. 7). Lesions are usually monomorphic Common drugs implicated in the causation are corticosteroids, iodides, bromides, oral contraceptives, isoniazid. Epidermal growth factor receptor antagonists used in oncology are also responsible for acneiform eruptions. Folliculitis occurs in 43 to 85% of patients who take these drugs; this applies to all epidermal growth factor receptor antagonists. Withdrawal of the drug with antiacne treatment results in gradual disappearance of lesions.

Drug Induced Lupus

Drug induced lupus commonly presents with absent skin lesions, but there are other systemic features of lupus like fever, weight loss, arthralgia and respiratory manifestations. Renal involvement seems to be rarer compared to classical SLE. The common drugs associated with lupus are beta blockers, anticonvulsants, procainamide, hydralazine, lithium, isoniazid, minocycline.

Immunological abnormalities commonly present are positive ANA with homogenous pattern, antihistone antibodies and anti single stranded DNA antibodies.

A genetic basis has been described as demonstrated by HLA DR4 association in 73% of hydralazine induced lupus and 70% of patients with minocycline induced lupus.

Acute Generalized Exanthematous Pustulosis (AGEP)

It is a peculiar kind of drug eruption with the following proposed diagnostic criteria:  
a. An acute pustular eruption
b. Fever of >38°C
c. Neutrophilia with or without mild eosinophilia
d. Subcorneal or intraepidermal pustules on skin biopsy
e. Spontaneous resolution in <15 days.

AGEP is usually due to penicillins or macrolides, especially ampicillin/amoxicillin and clavulanic acid, pristinamycin, quinolones, (hydroxy) chloroquine, anti-infective sulphonamides, terbinafine, diltiazem, carbamazepine and spiramycin, metronidazole.\textsuperscript{37-41}

The pustules which are numerous, sterile and non follicular commonly appear with fever on the flexures, trunk and upper extremities appearing within a few hours of ingestion of the offending drug. Associated features may be fever, facial and hand edema, vesicles and EM like lesions (Fig. 8). Leukocytosis may also be noted.

Histopathological examination shows subcorneal and intraepidermal pustules, dermal edema and a perivascular lymphohistiocytic infiltrate.

The main differential diagnosis of a generalized pustular drug eruption is pustular psoriasis\textsuperscript{42} which may be difficult to differentiate with the help of histopathological examination alone.

**Exfoliative Dermatitis (Erythroderma)**

It is defined as an inflammatory skin reaction involving more than 90% of the body surface area. Apart from other causes, it may also occur secondary to drug intake.

Clinically it presents as redness and exfoliation generalizing rapidly to involve extensive areas of the body. Patient has systemic manifestations like fever with chills, lymphadenopathy and anorexia. The possible complications include hypoproteinemia, hypo or hyperthermia, fluid and electrolyte loss, high output cardiac failure and septicemia (Fig. 9).

The most common causes of erythroderma is a pre existing skin disease. Common drugs implicated in the causation are penicillins, sulphonamides, NSAIDs, chloroquine, phenytoin, isoniazid among others.

Skin biopsy often helps in differentiating drug induced from other causes of erythroderma showing the classical features of the pre-existent skin disease. Drug induced erythroderma may show nonspecific subacute or chronic spogiotic dermatitis.

**Erythema Multiforme, Toxic Epidermal Necrolysis (TEN) and Steven Johnson Syndrome (SJS)**

Erythema multiforme (EM) is caused mainly due to infections the commonest being herpes virus. Drugs which are implicated in the causation of both EM and SJS are beta lactam antibiotics, barbiturates, carbamazepine, sulphonamides, lamotrigine, leflunamide, macrolides, NSAIDs, phenothiazines, etc.
With a prodrome of fever and flu-like symptoms it presents with classical target lesions comprising of three zones of central purpura or dusky red erythema, a middle zone of edema and an outer zone of erythema mainly distributed on the extremities more than the trunk (Fig. 10). Sometimes only two zones can be appreciated. As the name suggests it may also have different morphology of lesions including papules and vesicles.

In a typical target lesion, the histological changes include vacuolar degeneration of the lower epidermis and individual necrotic keratinocytes with perivascular lymphohistiocytic infiltrate and dermal edema. Epidermal changes may be very subtle to severe necrosis in bullous lesions.

There may also be involvement of mucous membranes and when extensive, the condition may be named Erythema multiforme major or Steven Johnson syndrome (SJS).

Steven Johnson syndrome is commonly associated with fever, myalgia, arthralgia with more extensive mucosal (oral, genital, conjunctival, nasal cavity, urethral) and facial lesions (Fig. 11). Involvement of trunk also is present with target like lesions. Skin involvement is limited to 10% of the body surface area. Though this syndrome is distinct from toxic epidermal necrolysis (TEN), there is an overlap in a considerable number of patients when skin involvement ranges between 10 and 30% of the total body surface area. When it exceeds 30% it is termed TEN (Fig. 12).

Steven Johnson syndrome and TEN are mainly the result of drugs in contrast to EM. The common culprit drugs include sulfonamides, penicillins, cephalosporins, isoniazid, NSAIDs, anticonvulsants, antiretroviral drugs like abacavir and nevirapine, antifungals like terbinafine and griseofulvin.

Toxic epidermal necrolysis is a medical emergency with a high mortality rate with full thickness skin necrosis along with severe involvement of mucous membranes (oropharynx, eyes and genitals). The estimated incidence ranges from 0.4 to 1.2 per million population per year.43

Patients with HIV infection, systemic lupus erythematosus and bone marrow transplant recipients seem to be predisposed to this disorder.44,45

Toxic epidermal necrolysis presents with a prodrome of fever, nausea, vomiting, sore throat, chest pain, arthralgia, myalgia and burning sensation in the skin followed by dusky red ill defined erythema, areas of target like lesions progressing to form denuded areas. The progression may take few hours to 3 to 4 days. Nikolsky sign is positive. The simultaneous involvement of multiple mucosae like conjunctivae, nasopharynx, esophagus and anus increases the morbidity and mortality.

The acute complications of this condition include dehydration, electrolyte loss and septicemia along with or without multisystem involvement in the form of pneumonia, nephritis, hepatic and myocardial damage. The chronic complications of SJS and TEN include fibrosis and strictures.

Identification of the causative drug is often difficult. In general, most drugs causing TEN have been given in the previous 1 to 3 weeks. Drugs started less than 7 days or more than 2 months before the onset of the reaction are unlikely to be responsible.46
Histopathological examination of skin sections show epidermal spongiosis and exocytosis with perivascular mononuclear infiltrate in early lesions to complete epidermal atrophy in a case of established TEN.

The pathophysiology of these reactions is not fully understood yet. Various theories have implicated the involvement of immunological mechanisms in particular those mediated by memory cytotoxic T cells. Although it was originally classified as a type IV delayed hypersensitivity reaction, it now appears that the immunological mechanisms governing the SJS reaction are initiated by the Fas antigen, a cell surface molecule that can mediate apoptosis leading to widespread keratinocyte apoptosis and subsequent epidermal necrosis. Perforin released from natural killer T cells is also believed to initiate keratinolysis.

Clinicians use the SCORTEN score (TEN specific severity of illness score) to determine the severity of the illness where important indicators like heart rate, renal function and age are taken into account.

Management requires multidisciplinary skilled approach like in case of burns with a specialist team. Maintaining the fluid and electrolyte balance, nutritional support, close monitoring to identify and treat sepsis, taking care of the denuded areas are to be given utmost importance. The role of systemic corticosteroids in the management has always been controversial. Intravenous Ig has been shown to be beneficial.

### Bullous Drug Eruptions

Blistering drug eruptions consist of drug-induced pemphigus and pemphigoid, linear IgA bullous dermatosis and pseudoporphyria cutanea tarda.

Some causes of blistering drug eruptions are given in Table 4.

In pseudoporphyria, porphyria like bullous eruptions are seen on the extremities following the causative drug intake. These patients do not have derangement in porphyrin metabolism unlike in patients with porphyria cutanea tarda.

In drug-induced bullous pemphigoid, tense bullae similar to bullous pemphigoid in a younger age group with usually absent anti BMZ antibodies with a history of a known drug causing BP like eruptions help in pinpointing the diagnosis (Fig. 13).

The commonest type of presentation of drug-induced pemphigus is like pemphigus foliaceus and erythematous with superficial blisters. Most patients have circulating autoantibodies with the same antigenic specificities as in other forms of pemphigus. Patients of pemphigus with drugs containing thiol group have a good prognosis on withdrawal of the drug compared to those with nonthiol group induced pemphigus.

Histopathological examination cannot distinguish drug induced from nondrug induced pemphigus.

### Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

In its complete form, DRESS also known as drug-induced hypersensitivity syndrome (DIHS) is typically characterized by a severe skin eruption, lymphadenopathy, fever, hepatitis,

<table>
<thead>
<tr>
<th>Type of eruption</th>
<th>Causative drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus</td>
<td>Captopril, cephalosporins, penicillin, penicillamine, piroxicam, gold/sodium aurothiomalate</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Furosemide, ACE inhibitors (captopril, enalapril), penicillin, penicillamine, chloroquine, sulfasalazine</td>
</tr>
<tr>
<td>IgA bullous dermatosis</td>
<td>Captopril, ceftriaxone, co-trimoxazole, furosemide, G-CSF, interleukin-2, lithium, NSAIDs, penicillin, rifampicin, vancomycin</td>
</tr>
<tr>
<td>Pseudoporphyria cutanea tarda</td>
<td>NSAIDs, tetracycline, thiazides, furosemide</td>
</tr>
</tbody>
</table>

### Table 3: SCORTEN score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1 point awarded for each parameter; SCORTEN derived by totalling scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
<td></td>
</tr>
<tr>
<td>Presence of a malignancy</td>
<td></td>
</tr>
<tr>
<td>Epidermal detachment &gt;30%</td>
<td></td>
</tr>
<tr>
<td>Heart rate &gt;120/min</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate &gt;20 mmol/l</td>
<td></td>
</tr>
<tr>
<td>Urea &gt;10 mmol/l</td>
<td></td>
</tr>
<tr>
<td>Glycemia &gt;14 mmol/l</td>
<td></td>
</tr>
<tr>
<td>SCORTEN</td>
<td>Probability of death (%)</td>
</tr>
<tr>
<td>0-1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
</tr>
<tr>
<td>More than 5</td>
<td>90</td>
</tr>
</tbody>
</table>

**Fig. 13:** Drug induced bullous pemphigoid secondary to carbamazepine
arthralgias, pulmonary infiltrates, interstitial nephritis and hematological abnormalities.\textsuperscript{7,9,58} The incidence of DRESS is estimated at between 1 in 1000 and 1 in 10 000 exposures to antiepileptic drugs.\textsuperscript{59} The other drugs which may cause this pattern of reaction include sulphonamides, minocycline, dapsone, carbamazepine and allopurinol.

The pathomechanism of the condition is not well understood and seems to be multifactorial. Clinically a generalized erythematous exanthematous rash appears 2 to 6 weeks after the drug intake and is usually associated with fever. Infiltrated papules coalescing to form erythroderma along with vesicles and pustules may also occur. Edema of the face is characteristic (Fig. 14). Lymphadenopathy, interstitial nephritis and hepatitis are the common associations. Patients with DRESS may develop a worsening of the clinical picture once the initial reaction starts subsiding. This is due to reactivation of members of the herpes virus family, HHV6 and HHV7 in particular, but EBV and/or CMV as well.\textsuperscript{60,61} Eosinophilia which is an essential criterion is often associated with atypical lymphocytosis. Liver function tests may be deranged in a considerable number of individuals.

RegiSCAR group has given the diagnostic criteria for the diagnosis\textsuperscript{62} (Table 5).

Early withdrawal of the drug is mandatory. Systemic corticosteroids are given when there is a visceral involvement.

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS (SCAR)

Certain life-threatening drug reactions like SJS, TEN, drug hypersensitivity reactions (DHR), DRESS and AGEP are classified as SCAR as they are: (a) severe, (b) unpredictable and (c) drug induced.\textsuperscript{63}

MANAGEMENT OF CUTANEOUS DRUG REACTIONS

- Withdrawal of the offending drug is the single most important and effective measure to be done immediately.
- Notification of the reaction to the concerned regulatory authority is a mandatory measure.
- Substitute of the essential drug of a different group to be introduced with careful observation. Take utmost care not to give a drug with a potential to cross-react with the offending drug.
- Before considering on intradermal, patch or prick tests, the risk assessment has to be done as it may prove fatal as the patient is re-exposed to the drug. They can develop a generalized rash or even anaphylaxis. At the same time it is necessary to find out the culprit drug out of the many and also to find out the safe alternative which can be given to the given condition. Appropriate controls are necessary to avoid false positive results.
- Blood drug levels may be measured when over dosage is suspected or when the patient is comatose to arrive at the diagnosis.
- The knowledge of the known side effects of the drug helps in the identification of the drug wherever possible.
- Most of the reactions subside with withdrawal of the causative drug and symptomatic treatment with antihistaminic (H1 receptor blocker) drugs and topical calamine lotion. Topical corticosteroids may sometimes be necessary.
- Subcutaneous injection of adrenaline and systemic corticosteroids in case of severe angioedema and anaphylaxis.
- In case of photosensitivity reactions, additional sunprotection, use of broad spectrum sunscreens, topical corticosteroids and systemic antipruritic drugs are given.

Table 5: Regi-SCAR group criteria for diagnosis of DRESS\textsuperscript{63}

<table>
<thead>
<tr>
<th>Features</th>
<th>No</th>
<th>Yes</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;35.50°C</td>
<td>–1</td>
<td>0</td>
<td>–1</td>
</tr>
<tr>
<td>Enlarged lymph glands (&gt;2 sites, &gt;1 cm)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>700-1499 or 10-19.9%</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>&gt;1500 or &gt;20</td>
<td>–</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Skin rash</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Extent &gt;50%</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>At least 2 of purpura, edema, purpura, scaling</td>
<td>–1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Biopsy suggesting DRESS</td>
<td>–1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Internal organ involvement</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>One</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>2 or more</td>
<td>–</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Resolution in more than 15 days</td>
<td>–1</td>
<td>0</td>
<td>–1</td>
</tr>
<tr>
<td>At least 3 biological inv done and negative to exclude alternative diagnosis</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Final score:<2 = no case, 2-3 = possible case, 4-5 = probable case, >5 = definite case
• Severe drug reactions require hospital admission.
• In severe reactions systemic corticosteroids may be life saving.

CONCLUSION

Identification and management of cutaneous drug reactions need a great amount of skill. The enormous number of new drugs released into the market along with multiple drugs taken by the patient for various ailments requires the clinician to have a thorough knowledge regarding the possible side effects of the drug and the cross reactions which may occur.

REFERENCES


