“CLINICO PATHOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS ”

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BRANCH XX

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CERTIFICATE

This is to certify that the dissertation titled **"CLINICO PATHOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS"** is a bonafide work done by **Dr.Balamurugan. L,** Post graduate student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 3, during the academic year 2015 – 2018. This work has not previously formed the basis for the award of any degree.

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DECLARATION

The dissertation entitled **"CLINICO PATHOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS"** is a bonafide work done by **Dr. BALAMURUGAN L,** Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 3, during the academic year 2015-2018 under the guidance of **Prof. DR. V. SAMPATH M.D., DERMATOLOGY,** Professor, Department of Dermatology, Madras Medical College, Chennai -3.

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DECLARATION

I, **Dr.Balamurugan L,** solemnly declare that this dissertation titled **"CLINICO PATHOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS"** is a bonafide work done by me at Madras Medical College during 2015 - 2018 under the guidance and supervision of **Prof. U. R. DHANALAKSHMI, M.D., D.D., D.N.B.,** Professor and Head of the Department, Department of Dermatology, Madras Medical College, Chennai-600003.

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CONTENTS

Introduction

INTRODUCTION

In modern day clinical practice most of the physicians encounter adverse drug reactions in many forms. Nearly quarter of hospitalized patients suffer from an adverse drug reaction. Though such reactions are common, comprehensive information regarding various parameters assoiated with such drug reactions are not available as many cases are either misdiagnosed or underdiagnosed. With a wide range of newer drugs entering the market each day, the possibility of newer drug reactions or commoner drug reactions presenting in a different form should be considered.

Most of the times drug reactions are trivial and benign. But it is absolutely essential to diagnose the condition and to find out the offending drug to avoid a life threatening reaction in the future. Adverse drug reactions are not confined to the skin but can involve multiple organ systems. Adverse cutaneous drug reactions range from the trivial maculopapular rash to the potentially fatal toxic epidermal necrolysis. There are also no specific laboratory investigation or confirmatory drug testing available to find the offending drug and the diagnosis in most instances is purely by clinical judgement.

Hence all the physicians should have a detailed knowledge of such drug reactions, the common offending drugs and prognostic indicators to handle such reactions appropriately.

Aims & Objectives

AIM OF THE STUDY

To assess the following parameters

1. The epidemiology of adverse cutaneous drug reactions in our set up.
2. Drugs commonly involved in adverse cutaneous drug reactions.
3. Various clinical presentations of adverse cutaneous drug reactions.
4. To correlate the clinical, histological and biochemical investigations in adverse cutaneous drug reactions.

Review of Literature

REVIEW OF LITERATURE

A drug is defined as a chemical substance, or combination of substances, which is administered for investigation, prevention or treatment of symptoms or diseases[1].

An adverse drug reaction (ADR) is an undesirable clinical manifestation resulting from administration of a particular drug[1].

WHO defines adverse drug reaction as " a response to a drug that is noxious, unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function"[2].

Serious adverse drug reaction is defined as " any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, resulting in persistent or significant disability / incapacity, or is life threatening"[3].

Adverse drug reactions (ADR) are considered a major health problem to the individual as well as for the society[4]. ADRs are under reported and are an under estimated cause of morbidity and mortality. ADRs are estimated to represent the sixth leading cause of death [1]. The cost of managing ADRs can be high, whether they occur in the inpatient or in the outpatient setting. ADRs cause patients to lose confidence in treating physicians or have negative emotions towards them. Patients seek self treatment options, which further precipitate

additional ADRs. Hence ADRs should be quickly diagnosed and managed to limit the detrimental effects on the patients.

Risk factors for developing an adverse drug reaction[5] include

- an older age
- female gender
- number of drugs taken by the patient and
- associated renal or hepatic impairment[6].
- the incidence of most drug eruptions is increased in the setting of immunosuppression; e.g. in patients with AIDS (CD4+ <200/ mm3), the risk of developing an exanthematous eruption to sulfamethoxazole is 10 to 50 fold greater than in the general population[7]. This is a paradox as most drug reaction are immunologically mediated.

General incidence of ADRs:

The incidence of ADRs varies from 6% to 30%[8,9]. Percentage of patients developing an ADR during hospitalization varies in different studies, ranging from 1.4 to 44%, although the incidence ranges between 10–20% in most of the studies[10 - 12]. Adverse drug reactions constitute 3–8% of admissions in a hospital setting[13 - 15]. In patients with an adverse drug event the average extra length of hospital stay was 1.9 days, and the average extra cost of hospitalization was $1939, observed in one study in the USA[16]. It is estimated that about 1 in 40 consultations in general practice are because of ADRs[17]. The percentage of consultations for ADRs increased from 0.6% in patients aged 0 –20 years to 2.7%

in patients aged more than 50 years[18]. Antibiotics, antiepileptics, non steroidal anti inflammatory drugs (NSAIDs), antitumour agents and anticoagulants were the most frequently implicated classes of drugs involved in ADRs[19]. The incidence of fatality due to drug reactions among patients is estimated to be 0.1 to 0.3% [20,21]. Fatality due to allergy occurs at a rate of 0.09 per 1000 cases[22]. The actual incidence of ADRs may be even greater, as some ADRs mimic natural disease states and thus go undetected and / or unreported.

Classification of Adverse Drug Reactions:

Adverse reactions can be classified in two broad groups. First type is due to exaggeration of an intended pharmacologic action of the drug. eg, increased bleeding with anticoagulants or bone marrow suppression with antineoplastics. The second type occurs from toxic effects unrelated to the intended pharmacologic actions. The latter effects are frequently severe, often unanticipated (especially with new drugs) and may result from recognized, and also from previously undescribed mechanisms[23].

Table 3.1 : Classification of adverse drug reactions

Type of Reaction	Features	Examples
A: Dose related (Augmented)	Common. Related to the pharmacologic action of the drug – exaggerated pharmacologic response. Predictable. Low mortality.	Dry mouth with tricyclic antidepressants, respiratory depression with opioids, bleeding with warfarin, digoxin toxicity
B: Non - dose related (Bizarre)	Uncommon. Not related to the pharmacologic action of the drug. Unpredictable. High mortality.	**Immunologic reactions:** anaphylaxis to penicillin **Idiosyncratic reactions:** malignant hyperthermia with general anesthetics
C: Dose related and time related (Chronic)	Uncommon. Related to the cumulative dose.	Hypothalamic - pituitary - adrenal axis suppression by corticosteroids, osteonecrosis of the jaw with bisphosphonates
D: Time related (Delayed)	Uncommon. Usually dose related. Occurs or becomes apparent sometime after use of the drug.	Carcinogenesis Tardive dyskinesia Teratogenesis Leucopenia with Lomustine
E: Withdrawal (End of use)	Uncommon. Occurs soon after withdrawal of the drug.	Withdrawal syndrome with opiates or benzodiazepines (e.g., insomnia, anxiety)
F: Unexpected failure of therapy (Failure)	Common. Dose related. Often caused by drug interactions	Inadequate dosage of an oral contraceptive when used with an enzyme inducer. Resistance to antimicrobial agents

Adverse drug reactions can be labelled under one of the following six categories: (WHO 2014)[24,25]

- certain
- probable / likely
- possible (unlikely)

- conditional
- unclassified, and
- unassessable / unclassifiable.

Determining the cause of a suspected ADR is a complex process. Many patients take more than one drug, and it is difficult to distinguish which agent would have caused the ADR. An important step to identify an ADR and determining causality is by obtaining an accurate history of patient's drug list.

It is important to assess

- the interval between administration of the drug and onset of drug reaction
- worsening of reaction with repeated or increased dosing (Rechallenge)
- decrease in the intensity of reaction by reducing the dose of drug or discontinuing the drug (Dechallenge)
- previous similar reactions on exposure to the suspected drug
- reaction known to occur with long term use of the medication
- symptoms appearing or worsening when a drug was discontinued Answering such questions can help the physician to determine causality.

Several algorithms and probability scales have been developed to assist with causality determination. Among those published are

- the Jones algorithm,
- the Yale algorithm,

- the Karch algorithm,
- the Begaud algorithm, and a
- quantitative approach algorithm (Srinivasan 2011).

Two of the most commonly used are the Naranjo ADR Probability Scale and Liverpool ADR causality assessment tool, because of their simplicity and time efficiency. In the Naranjo ADR Probability Scale, the ADR probability classification can be determined by answering 10 questions about the ADR and assigning a numeric score to each answer.

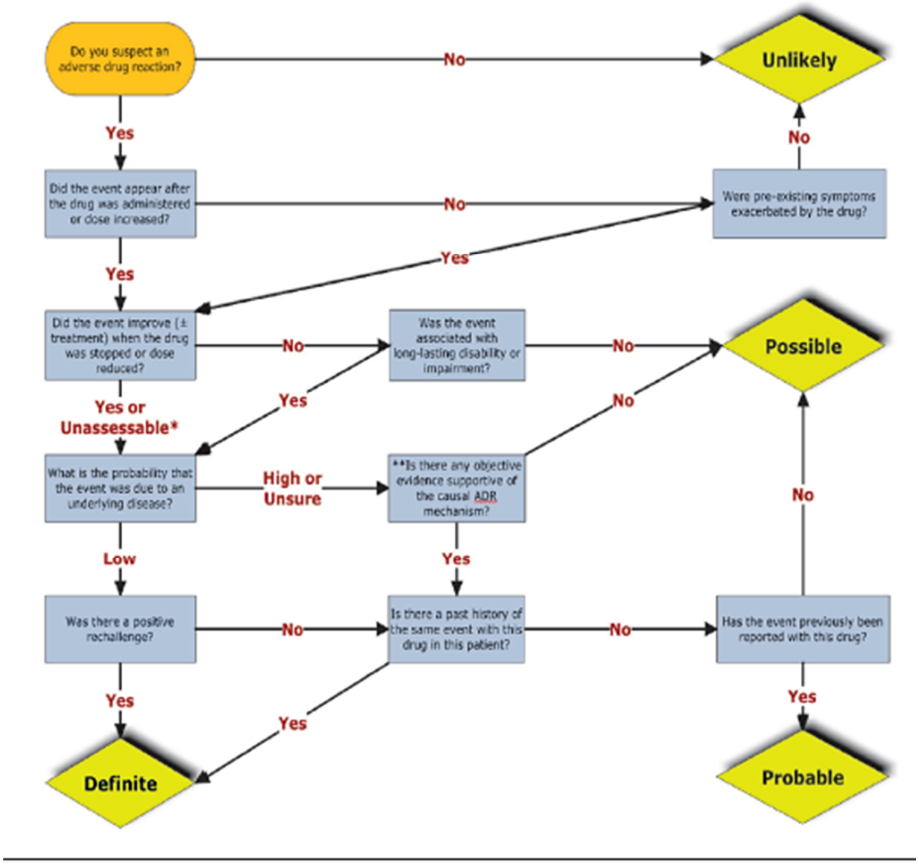
Image 3.1: Naranjo ADR Probability Scale[26]

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event appear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that, on their own, could have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Total Score	ADR Probability Classification
9	Highly Probable
5–8	Probable
1-4	Possible
0	Doubtful

Liverpool ADR causality assessment tool[27], another commonly used method to assist with causality determination is shown below.

Image 3.2: Liverpool ADR casualty assessment tool



Adverse Drug Reactions should be monitored and reported regularly which helps in preserving the safety and quality of life for the patient. It also aids in cost saving to the patient and the health care institution. By reporting known or suspected ADRs, pharmacists, other health care practitioners, and patients can assist in identifying patterns and trends, which may lead to increased regulatory scrutiny or even the withdrawal of drugs that do not have a favorable risk benefit ratio. There are various reporting agencies throughout the world engaged in monitoring ADRs.

Table 3.2: Various ADR reporting agencies

United States	Premarketing Clinical Trials Postmarketing Surveillance The FDA Adverse Event Reporting System The Institute for Safe Medication Practices The Joint Commission MEDMARX
Canada	The Canada Vigilance Program Canadian Adverse Reaction Newsletter (CARN)
UK	Yellow Card Scheme Drug Safety Update
India	Pharmacovigilance programme(PvPI)
Global ADR Reporting(WHO)	Uppsala Monitoring Centre in Sweden, through a database called "VigiBase"

Pharmacovigilance programme (PvPI):

Pharmacovigilance involves the study of drug related injuries and making recommendations for warning or withdrawal of pharmaceutical agents. This encompasses the understanding , detection, assessment, and prevention of ADRs. Pharmacists play a vital role in every step of the pharmacovigilance process, by which patients are prevented from undergoing unnecessary procedures or taking unwarranted drugs.

Indian pharmacopoeia commission (IPC), Ghaziabad functions as National Co ordination Centre (NCC) for pharmacovigilance programme in India. In various medical institutions in India about 250 ADR monitoring centres (AMC)

were established to monitor and collect reports about ADRs, under NCC - PvPI[28].

Suspected ADR reporting forms are available in the website of IPC in 10 vernacular languages. ADRs can also be reported via PvPI helpline number, 18001803024 on weekdays from 9 am to 5.30 pm[28].

Adverse cutaneous drug reactions:

Definition:

An adverse cutaneous drug reaction (ACDR), also called as "Drug eruption", is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompass all adverse events related to drug eruption, regardless of the etiology[29].

Adverse cutaneous drug reactions (ACDRs) are the most frequent manifestation of all adverse drug reactions accounting for about 24% in one study and 29% in another study[30,31]. The incidence of drug eruptions in most estimates are inaccurate, as many mild and transitory eruptions are not recorded, and skin disorders are sometimes falsely attributed to drugs. The incidence of ACDR in developed countries range from 1 to 3% among in patients[32,33], whereas in developing countries such as India, some studies peg it to 2 - 5% of the inpatients[34 - 37]. According to World Health Organization (WHO) approximately 2% of all ACDRs are considered "serious" and only very few are fatal [5,38]. Relative incidence rate of ACDR among new patients attending dermatology OPD were found to be 2.05 per 1000 in a study by Abanti S et al[39].

ACDRs can be classified based on

1. Pathomechanism and
2. Clinical severity.

Based on pathomechanisms ACDRs can be classified into non immunologic (75 - 80%) and immunologic (5 - 10%). The remaining 20 - 25% of adverse drug events are caused by unpredictable effects that may or may not be immune - mediated (Table 3).

Table 3.3 : Classification of ACDRs based on pathomechanism

<table>
<tr><th colspan="2">Non immunological</th><th>Immunological (unpredictable)</th></tr>
<tr><td>Predictable</td><td>Unpredictable</td><td rowspan="2">• IgE dependent drug reactions
• Immune complex dependent drug reactions
• Cytotoxic drug induced reactions
• Cell mediated reactions</td></tr>
<tr><td>• Overdosage
• Side effects
• Cumulation
• Delayed toxicity
• Facultative effects
• Drug interactions
• Metabolic alterations
• Teratogenicity
• Non immunological activation of effector pathways
• Exacerbation of disease
• Drug induced chromosomal damage</td><td>• Intolerance
• Idiosyncrasy</td></tr>
<tr><td colspan="2"></td><td>Miscellaneous</td></tr>
<tr><td colspan="2"></td><td>• Jarisch Herxheimer reactions
• Infectious mononucleosis - ampicillin reaction</td></tr>
</table>

Pathogenesis of adverse cutaneous drug reactions:

Non immunologic mechanisms:

Overdose:

- Predictable clinical manifestations
- Exaggeration of the drug's pharmacologic actions.
- Due to prescribing error or deliberate excess by the patient.
- Can be observed in patients with usual doses if they have differing rates of absorption, metabolism or excretion.
- Example - methotrexate toxicity in elderly patients with reduced renal function.

Pharmacologic side effects:

- Undesirable or toxic effects
- Cannot be separated from the desired pharmacologic actions .
- Example - chemotherapeutic agents targeting rapidly dividing cells causing alopecia, mucositis and pancytopenia.

Cumulative toxicity:

- Prolonged exposure to a medication.
- Example - Accumulation of silver, minocycline and amiodarone within the skin leading to distinctive discoloration of the skin.

Delayed toxicity:

- Toxic, dose dependent effect
- Occurs months to years after the discontinuation of a medication.
- Examples - arsenic and the development of squamous cell carcinomas

Drug – drug interactions:

- Interactions between two or more drugs administered simultaneously
- Occurs at several different steps:

(1) intestinal drug interactions - tetracycline and calcium

(2) displacement from binding proteins or receptor sites - methotrexate and sulfonamides

(3) enzyme stimulation or inhibition - cyclosporine and azoles

(4) altered drug excretion - methotrexate and probenecid

Alterations in metabolism:

- Induce cutaneous changes by their effects on the nutritional or metabolic status of the patient.
- eg - Bexarotene may induce severe hypertriglyceridemia and eruptive xanthomas, while isoniazid may be associated with pellagra like changes.

Exacerbation of disease:

- Exacerbation of pre existing dermatologic disease.
- Example - Androgens in patients with acne vulgaris, lithium and interferon in patients with psoriasis.

Facultative effects:

- Drug induced alterations in skin or mucous membrane flora.
- Example - Antibiotics that destroy Gram positive bacteria, allow the multiplication of resistant Gram negative species.
- Pseudomembranous enterocolitis after clindamycin

Teratogenicity and other effects on the fetus:

- Drug induced developmental malformations during the period of organogenesis
- Example - thalidomide , retinoids , cytotoxic drugs
- Fetal damage in later pregnancy . Eg - warfarin, phenytoin, steroids , diethylstilbesterol

Non immunological activation of effector pathways:

(anaphylactoid reactions)

- Release mast cell mediators directly and produce urticaria or angio oedema, Eg - opiates, codeine
- Activate complement by an antibody independent mechanism – radio contrast media
- Amplified mast cell degranulation and enhanced biosynthesis of lipoxygenase products eg.NSAIDS
- May potentiate bradykinin activity , Eg.ACE inhibitors

Immunological mechanisms:

IgE dependent (type I) drug reactions:

Urticaria and Anaphylaxis:[40]

Polyvalent drug protein conjugates $\Longrightarrow$ specific IgE molecules on sensitized tissue mast cells/circulating basophil leukocytes $\Longrightarrow$ release of chemical mediators (histamine, eosinophil chemotactic factor of anaphylaxis, leukotriene C4/prostaglandin D2, pro inflammatory cytokines)[41]

⟹ effects on target tissues (skin, respiratory, gastrointestinal and/or cardiovascular systems)

Interleukin -5 (IL-5) and eotaxin ⟹ activation and recruitment of eosinophils drug-induced cutaneous eruptions[42].

Eosinophil degranulation ⟹ release of pro inflammatory mediators[43] dilatation ⟹ and increased permeability of small blood vessels ⟹ oedema and hypotension, bronchiolar smooth muscle contraction, excessive mucus secretion, and chemotaxis of inflammatory cells (polymorphs/ eosinophils).

Clinically presents as pruritus, urticaria, laryngeal oedema, bronchospasm and anaphylactic shock with hypotension and possibly death in severe cases. Immediate reactions occurs within minutes of drug administration. Accelerated reactions occurs within hours or days, and are generally urticarial but may present with laryngeal oedema. Penicillins are the commonest cause of IgE dependent drug eruptions.

Antibody-mediated (type II) drug reactions

Binding of antibody to cells → complement mediated cytolysis → cell damage .

Classical examples of immune complex formation:

1. Drug (apronalide) as hapten → bound to the surface of a cell (platelets) with IgG class antibody → subsequent complement fixation → purpura

2. Antibodies to quinidine - platelet conjugates[44,45] → thrombocytopenic purpura.

Immune complex dependent (type III) drug reactions:

***Urticaria and anaphylaxis*:**

Immune complexes → activation of complement cascade → formation of anaphylatoxins (C3a and C5a) → triggers release of mediators from mast cells and basophils → urticaria or anaphylaxis.

Serum sickness:

Persistence of a drug antigen in the circulation for long duration → synthesis of IgG or IgM class antibodies → circulating antibody antigen immune complexes.

Serum sickness occurs when there is slow removal of persistent immune complexes by the mononuclear phagocyte system. Symptoms and signs develop about 6 days or more after drug administration. Clinically manifest as fever, arthritis, oedema, nephritis, neuritis, and an urticarial or papular rash.

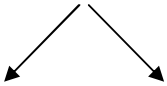
Usually seen in

1. serum therapy -- large doses of heterologous antibody(horse antiserum for the treatment of diphtheria).
2. antilymphocyte globulin therapy [46].

Vasculitis[47 - 49]:

Drug induced immune complexes play a part in the pathogenesis of cutaneous necrotizing vasculitis.

Immune complexes



Deposition on vascular endothelium interaction with platelets via Fc receptor

⇩ ⇩

Activation of the complement cascade platelet aggregation

⇩ ⇩

Generation of anaphylatoxins C3a and C5a microthrombus formation

⇩

chemotactic for basophils and mast cells.

⇩

vasoactive amines and pro inflammatory cytokines release

⇩

increased vascular permeability and neutrophil chemotaxis

⇩

release of lysosomal enzymes by neutrophils

⇩

Local inflammation.

These events lead to the histological appearance of leukocytoclastic vasculitis. Direct immunofluorescence (DIF) staining of skin biopsies shows deposition of immunoglobulins and complement in and around blood vessel walls. Examples include LE syndrome caused by

1. Hydralazine
2. Hydroxylamine metabolite of procainamide

Arthus reaction:

The Arthus reaction is a localized form of immune complex vasculitis.

Sensitized individual with circulating precipitating antibodies(IgG1 class)

⇩

ID or SC injection of antigen(vaccine)

⇩

Local immune complex formation

⇩

Cascade of events locally (as in vasculitis described above)

⇩

Erythema, oedema, haemorrhage and occasionally necrosis at the injection site

(peak at 4–10 hrs, then gradually wanes)

Cell mediated (type IV) reactions

`The role of delayed type cell mediated immune reactions in variety of cutaneous drug allergy has recently been elucidated[50 - 55]. These include morbilliform rashes, fixed drug reactions, lichenoid reactions, LE-like reactions, DRESS syndrome, Erythema multiforme and SJS/TEN.

Involvement of immune system of skin in cell mediated drug eruptions have been reviewed[50]. Drug specific activated CD4+ or CD8+ T cells are seen in circulation in patients with acute allergy to allopurinol, carbamazepine, paracetamol, phenytoin & sulfamethoxazole[56].

Predominant CD8+ T cell activation and predominant activation of CD4+ cells are associated with more severe (bullous) skin lesions / liver involvement and maculopapular reactions respectively[57,58]. In drug induced exanthems drug specific T - cell clones contained heterogeneous T - cell subsets with distinct phenotypes (CD4+ > CD8+ ,perforin and granzyme B +) and cell functions (IL 5 production, interferon - γ (IFN - γ) production and cytotoxic potential)[59,60].

In drug induced maculopapular and bullous eruptions and patch test reactions to betalactam antibiotics, CD8+ T cells predominates in the epidermis [61]. These T cells displaying a Th1 like cytokine pattern, are cytotoxic to epidermal keratinocytes in lectin induced cytotoxicity assays and proliferated in an antigen and MHC specific manner. In contrast, in patients with penicillin induced urticarial exanthems , T - cell lines are predominantly CD4+CD8−, with a Th2 cytokine pattern[62]. It has been proposed that T cells producing IL-5 might contribute to eosinophilia, whereas cytotoxic CD4+ T cells account for the tissue damage. Drug specific T cells , by secreting the IL - 8, contribute to the neutrophil infiltration in drug-induced AGEP [63]. In bullous drug eruptions target keratinocytes expresses ICAM -1 which plays an important role in the cytotoxicity of epidermal T cells[64].

Drugs are recognized by drug specific CD4+ and CD8+ T cells through T - cell receptors (TCRs) in MHC dependent manner. The role of HLA genes in severe drug reactions could be explained by this MHC restriction. Distinct T cell functions leading to different clinical phenotypes could be revealed by immunohistochemical and functional studies of drug reactive T cells .

Based on the above mechanisms , delayed type hypersensitivity reactions have been re classified into four main subtypes[52,65]:

A. IVa (Th1/monocyte directed)

B. IVb (Th2/eosinophil directed)

C. IVc (CD8+/Fas/perforin/granzyme B directed) and

D. IVd (IL-8/GM-CSF/neutrophil directed).

Influence of human leukocyte antigen (HLA) types:

Susceptibility to drug eruptions and association between HLA types has been extensively studied [65]. The genetic associations can be drug specific.

1. Reactions to gold associated with HLADRw3, HLA- DR5 and HLA -B8 [50-55].
2. Penicillamine toxicity associated with HLA phenotypes were as follows[50]

   a.HLA - DR3 and HLA - B8 with renal toxicity;

   b.HLA - DR3, HLA - B7 and HLA - DR2 with haematological toxicity; c.HLA - A1 and HLA - DR4 with thrombocytopenia, and

   d.HLA - DRw6 with cutaneous adverse reactions.
3. Intolerance to tiopronin given for rheumatoid arthritis seen in DR1 / DR4 heterozygosity, or the DR5 subtypes DRB1*1102 or DRB1*1201[66].

4. Chinese patients with drug eruptions after allopurinol
    a. positive association with HLA - Aw33 and HLA - B17/Bw58
    b. negative association with the HLA - A2 haplotype[66].
5. HLA - B*5701 has been linked with abacavir hypersensitivity[56 - 58].
6. Caucasian Australians with HLA - DRB1*0101 and high CD4+ T-cell counts, Sardinians and Japanese with HLA - Cw8 were predisposed to nevirapine hypersensitivity [58].
7. Carbamazepine induced Stevens Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) shows HLA - B*1502 positivity , but not carbamazepine induced maculopapular eruption or carbamazepine hypersensitivity syndrome[57].
8. Aspirin sensitive asthma - HLA - DQw2 [57].
9. Hydralazine induced LE - common in females with the HLA-DRw4 haplotype [62,64].
10. Fixed drug eruptions to febrazone and trimethoprim –sulfamethoxazole were linked to HLA - B22 and HLA - A30 B13 Cw6 respectively[64].

Genetic association can also be ethnicity specific – carbamazepine induced SJS/TEN associated with B*1502 is seen in Han Chinese from Taiwan and other Asian countries but not in whites, due to different allele frequencies [58,59]. These studies provide a basis for developing tests to identify individuals at risk for drug hypersensitivity[58]. As with HLA - B*5701 genotyping to prevent abacavir hypersensitivity, HLA-B*1502 genotyping in patients from Southeast Asian

countries before prescribing carbamazepine could be valuable in preventing carbamazepine induced SJS/TEN.

Adverse cutaneous drug reactions based on clinical presentation:

Based on clinical presentation, involvement of mucous membrane, severity and systemic involvement adverse cutaneous drug reactions can be classified into

a. Benign cutaneous adverse drug reactions (constitute the majority) and
b. Severe cutaneous drug reactions (constitutes 2%)

Benign cutaneous adverse drug reactions:

Drug induced exanthema:

Most common adverse cutaneous drug reaction

Synonym:

Morbilliform drug eruption, Maculopapular drug eruption

Commonest drugs causing maculopapular eruptions:

Ampicillin and penicillin, carbamazepine, sulphonamides, phenytoin, non steroidal anti inflammatory drugs (NSAIDs), allopurinol.

Pathogenesis:

Drug specific T cell mediated cytotoxicity

Histopathology[67]

- Non specific changes seen. Few specific changes are

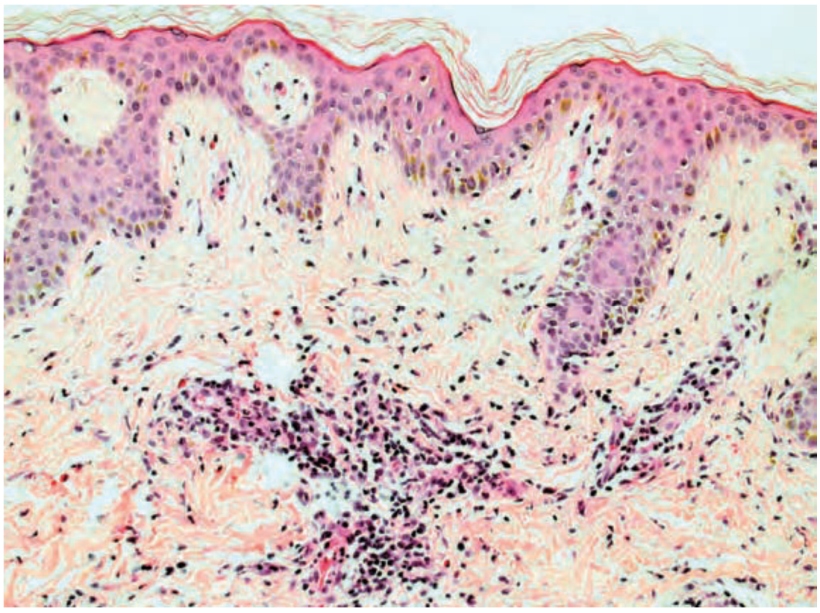
  a.Apoptotic keratinocytes

b.Eosinophils within inflammatory infiltrate

c.Papillary edema

d.Vascular changes

Image 3.3 – Histopathology of drug induced maculopapular rash



Clinical features:

Latency period is 7-10 days but vary between 5-21 days after ingestion of offending drug. There is profuse eruption of small pink papules (morbilliform, scarlatiniform or rubelliform rash) predominantly over trunk and flexural areas with relative sparing of face and pressure areas. Palms and soles can be involved.Sometimes the rash can be generalized. Purpuric spots and erosive stomatitis may occur.

Differential diagnosis:[68] Viral exanthema, DRESS

Disease course and prognosis:

Erythroderma can occur if the offending drug is continued. Spontaneous resolution seen in few cases even if offending drug is continued. Rash recurs on rechallenge with the drug.

Investigations:

- To rule out organ involvement as in DRESS syndrome
- Viral serology/PCR done to rule out viral infections

Management:

Offending drug should be stopped. Rashses resolve with desquamation , sometimes with post inflammatory hyper pigmentation. Emollients is all that needed in most of the cases. Mid potency topical steroids may be useful to reduce pruritis associated with rash.

Fixed drug eruptions:

First described by 'Bourns' in 1889.

Definition:

It is a adverse cutaneous drug reaction characterized by well defined lesions occurring on the same sites every time the offending drug is taken[69,70].

Most common drugs associated:[71].

NSAIDs (25%), paracetamol(24%), co-trimoxazole (5%) and tetracycline (5%).

Pathogenesis:[69 - 73]

FDE is an example of classical delayed type hypersensitivity reaction and key mediators are the skin resident T cells.

Effector / memory CD8+ T cells at the dermo epidermal junction
in resting FDE lesions

⇩

Rechallenge with the drug

⇩

Activation and expansion of resting CD8 + T cells

⇩

Release of interferon (IFN) γ and cytotoxic granules

⇩

Keratinocyte apoptosis

⇩

Regulatory T cells (FOX P3+ T Reg cells) are recruited and inhibit further activation of CD8+ T cells by apoptosis of activated T cells

⇩

Small population of CD8+ T cells escape apoptosis by the action of
IL 15 secreted by keratinocytes

⇩

Remain as resident cells until further activation

Genetics[74,75]:

Drug specific HLA associations was seen in few drugs. These include cotrimoxazole with HLA - A30 and febrazone induced FDE with HLA - B22

Histopathology[69,76]:

Early lesions -

a. interface dermatitis reaction pattern

b. vacuolar degeneration of basal keratinocytes,

c. dermal oedema

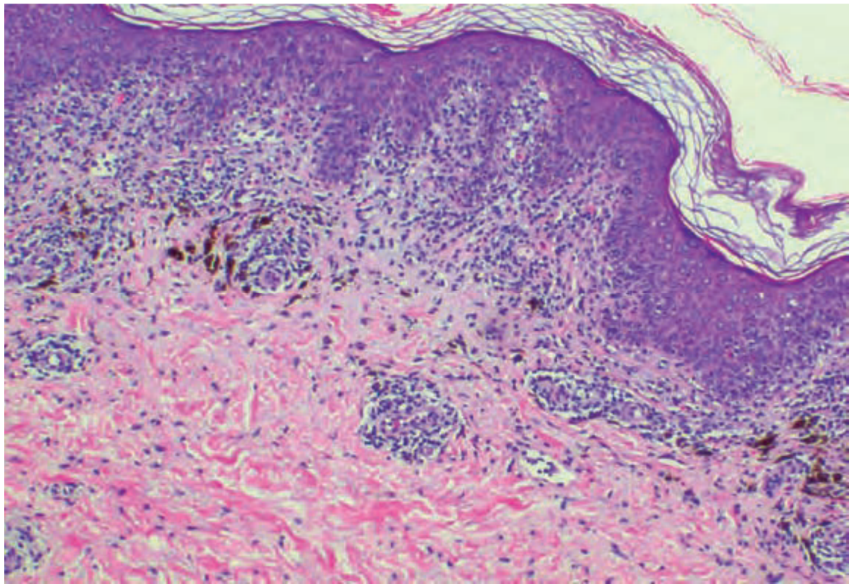
d. perivascular lymphocytic infiltrate of the upper dermis.

e. eosinophils may be present.

Resolved or healing lesion –

pigment-laden macrophages in the upper dermis

Image 3.4: Histopathology of fixed drug eruption



Clinical features:

Skin lesions with offending drugs can occur in all ages but most commonly in 40 - 80 years old age group with slight female preponderance. Symptoms start within 8 hours of exposure to offending drug for the first time, but

as early as 30 minutes on further exposures. Present as well defined round or oval erythematous and edematous patch or plaque. Later it becomes dusky, violaceous and sometimes vesicular or bullous. Usually seen as solitary lesions but sometimes as multiple lesions. Lips, genitals, palms and soles are the commonly affected sites. Isolated mucosal FDE is seen in 5% of patients. Lesions resolve with post inflammatory hyperpigmentation which usually persists for a very long time.

Clinical pattern of FDE:

FDE of Genitals and lips –NSAIDs

FDE of Genitals – tetracycline and cotrimoxazole

FDE of trunk and extremities – metamizole

FDE of face – carbocystiene

Linear FDE - Cotrimoxazole

Non pigmented FDE(Shelley & Shelley in 1987) – Pseudoephedrine, piroxicam, paracetamol, thiopental, sorafenib

FDE with systemic manifestations – Levamisole

Generalized bullous FDE (GBFDE):

This is a form of extensive FDE misdiagnosed as toxic epidermal necrolysis (TEN)[69,77]. Differentiating features are

- prior history of similar episodes
- mucosal surfaces are relatively uninvolved
- presence of large blisters with intact intervening skin and

- absence of multiple purpuric or target lesions.

Disease course and prognosis:

FDE is self limiting with an excellent prognosis. Post inflammatory hyperpigmentation persist for several months. The mortality rate in GBFDE is approximately 20%. Patients with GBFDE require the same level of treatment and care as for SJS and TEN.

Investigations:

1.Oral provocation tests – gold standard

2.Patch tests – reagents should be placed over sites of previous skin lesions rather than upper back. Positive in 50 % patients [78].

Management:

Offending drug should be stopped. Topical steroids for one to few skin lesions. For patients with multiple skin lesions systemic steroids can be given. Patients with GBFDE should be managed in ICU as patients with SJS/TEN.

Drug induced urticaria:

Second common cause of adverse cutaneous drug reactions.

Drug induced urticaria, anaphylaxis and angioedema can be "anaphylactoid" or "pseudoallergic" if they are non immune mediated and "allergic" if IgE mediated.

Most common drugs implicated[79,80]:

Aspirin, NSAIDs, ACE inhibitors, radio contrast media, local anaesthetics, dextran and recently infliximab. Many other drugs are implicated in causing urticaria, anaphylaxis and angioedema.

Pathogenesis:

Mediated by the presence of drug specific IgE antibodies.

On exposure to drug, IgE present on mast cell surface cross links

⇩

Release of mast cell mediators (histamine)

⇩

Vasodilatation, neuronal activation, smooth muscle contraction

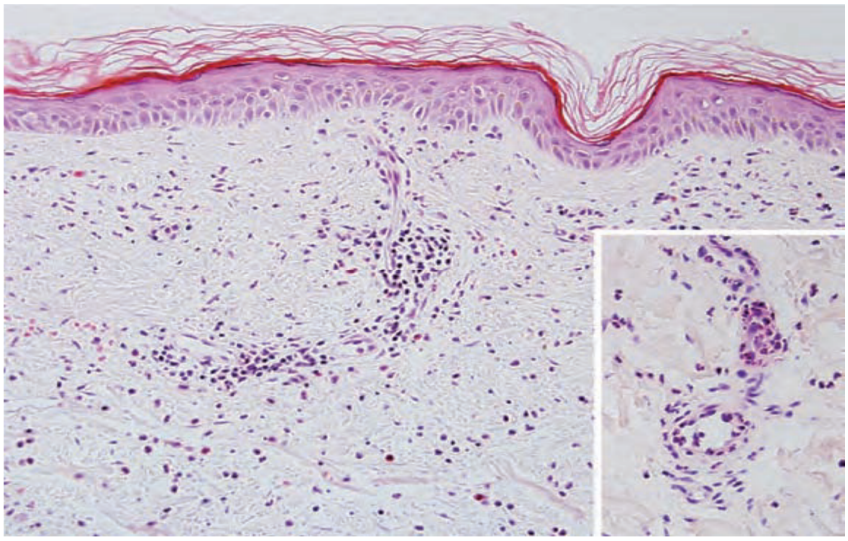
⇩

Wheal,flare, angioedema, bronchospasm and hypotension

Histopathology:

- Non specific
- Vascular and lymphatic dilatation
- Dermal oedema and
- Variable perivascular infiltrate consisting of lymphocytes, neutrophils and eosinophils

Image 3.5: Histopathology of drug induced urticaria



Clinical features

On the first occasion symptoms arise within 24–36 hours of drug ingestion.Lesions may develop within minutes of rechallenge. Urticaria occurring alone is more common than urticaria with angio oedema. Anaphylaxis usually develops on second exposure to a drug and within minutes to hours of drug administration and are often associated with skin or mucosal changes in less severe cases.There may be dizziness, skin tingling and redness of the bulbar conjunctiva, followed by urticaria, abdominal pain, angio oedema, bronchospasm, and vasomotor collapse in severe cases. More severe reactions and rapid progression within minutes to cardiac arrest is seen with intravenous administration. In patients with insect sting related and food induced anaphylaxis, slow evolution of symptoms are seen [81].

Complications and course of disease:

Symptoms resolve within days if offending drug is withdrawn immediately and treatment initiated early. Anaphylaxis if not managed properly can lead to death.

Investigations:

Careful history to identify the culprit drug , RAST(Radio Allergo Sorbent Assay) to identify drug specific IgE and patch testing.

Management:

Stop the offending drug. Oral or IV antihistaminics according to severity of symptoms. Oral or IV corticosteroids. SC or IM epinephrine in cases of anaphylaxis.

Drug induced serum sickness like reactions (SSLI):

Characterized by a clinical triad of fever, rash and arthralgias/arthritis.

Most common drugs implicated:

Cefaclor (Most common), penicillins and other β-lactams, minocycline, buproprion, infliximab, rituximab.

Pathogenesis:

Metabolism and biotransformation of the parent drug to reactive metabolites is essential. Inherited defects in the metabolism of these reactive intermediates may be a predisposing factor[82]. This is a type III hypersensitivity reaction.

Reactive drug metabolites (foreign antigen)

⇩

Antibodies bind to antigens

⇩

Immune complex formation

⇩

Deposition in small blood vessels of skin, joints and other organs

⇩

Clinical manifestations

Histopathology[83]:

- Dermal oedema
- Superficial and deep perivascular infiltrate of lymphocytes, neutrophils and eosinophils
- Vasculitis is usually absent

Clinical features:

More commonly reported in children with a median latency of 1-13 days. Initially manifests as migratory and pruritic urticarial wheals. Sometimes EMF like lesions, facial and periorbital edema also seen. Arthralgia, swelling and stiffness of small joints of hands and feet is seen. Mucosal and systemic involvement is rare in drug induced illness[84,85].

Disease course and prognosis:

Symptoms resolve quickly on drug withdrawal. Median duration of rash and joint symptoms are 5 and 3 days, respectively[86]. Drug induced SSLI is not associated with long term morbidity or sequelae.

Investigations:

Drug provocation testing is safe and reliable

Management:

- Withdrawal of culprit drug
- Symptomatic treatment – Antihistaminics, antipyretics and systemic steroids.

Drug induced lichenoid reactions:

Drug induced LP like lesions are clinically indistinguishable from classical LP but can be more severe. Milder form presents as LP like lesions an severe form as LE like lesions[87].

Most common implicated drugs:

For LP like lesions:

Antimalarials, ACE inhibitors, gold, β-blockers, mercury amalgam, lithium, non steroidal anti inflammatory drugs, methyldopa, pencillamine, quinidine, thiazide diuretics.

For LE like lesions:

ACE inhibitors (e.g. captopril), β-blockers (e.g. atenolol), calcium channel blockers (e.g. diltiazem), fluorouracil (systemic), hydralazine, clobazam, isoniazid, statins, sulfasalazine, procainamide, terbinafine, thiazide diuretics.

Pathogenesis:

Autoreactive T cells are directed against a drug - MHC antigen complex , followed by which the keratinocytes and Langerhans cells are viewed by the immune system as 'non - self', leading to apoptosis of keratinocytes.

Genetics:

73 % of patients with drug induced lupus (Hydralazine) have HLA - DR4[88] and with minocycline have HLA - DQB1.

Histopathology:

Hyperkeratosis, hypergranulosis, sawtooth acanthosis and band-like infiltrate in the superficial dermis.

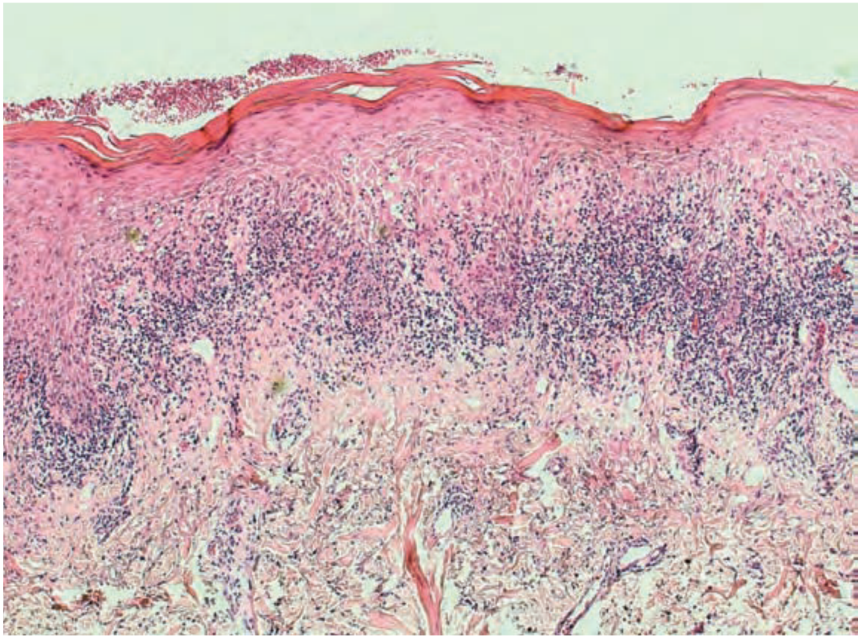
Histological features attributed to a drug trigger:

- Less dense but more pleomorphic infiltrate (including plasma cells and eosinophils)
- Cytoid bodies in the cornified and granular layers
- Presence of focal parakeratosis and
- Focal interruption of the granular layer[89]

Only distinguishing histological characteristics of drug induced LP:

- Higher frequency of necrotic keratinocytes (in clusters)
- Plasma cell and eosiniphilic infiltrate [90].

Image 3.6: Drug induced lichenoid reactions



Clinical features:

Latency period is months to even years after first time exposure to drugs. Clinical picture is similar to idiopathic LP with shiny papules and plaques with Wickham striae. Drug induced LE lesions are similar to idiopathic SLE with lesions in the photoexposed areas.

Disease course and prognosis:

Resolution of symptoms seen with withdrawal of drug in weeks to months.

Investigations:

- Skin biopsy to find lichenoid reaction pattern
- In drug induced LE – ANA positivity seen in 90% and Anti histone Ab seen in 75% of patients.

Management:

Withdrawal of culprit drug. High to very high potent steroids leads to resolution of symptoms. Systemic corticosteroids used in very severe disease .

Drug induced acneiform eruptions:

Constitutes 1% of all adverse cutaneous drug reactions

Most common drugs involved:

- Hormones - Corticosteroids, androgens and anabolic steroids, hormonal contraceptives, danazol
- Neuropsychiatric drugs - Tricyclic antidepressants, lithium , valproate, phenytoin, dantrolene
- Anti tuberculosis drugs - Isoniazid, rifampicin, ethionamide
- Halogens - Iodide, bromide, chlorine
- Vitamins - Vitamins B1, B6, B12
- Immunomodulators – Cyclosporin, sirolimus, azathioprine
- Others - Chemotherapeutic agents, epidermal growth factor receptors inhibitors, multikinase inhibitors, histone deacetylase inhibitors, granulocyte colony stimulating factor

Pathogenesis:

- Corticosteroids – Up regulation of TLR - 2 in involved keratinocytes leading to predominantly inflammatory lesions[91].
- Androgenic hormones - stimulates follicular keratinocyte proliferation, promote sebaceous gland hyperplasia and increases the sebum production[92,93].
- Sirolimus - direct toxicity, chemical modification of sebum and its effects on epidermal growth factor receptors (EGFR) and testosterone synthesis [94].

Clinical features:

Lesions occur after a mean latency period of 7-10 days, but may be longer with few drugs. Sudden onset of acneiform lesions without previous history of acne. Presence of monomorphic papules and pustules without comedones or cysts and predominantly in non seborrhoeic areas are characteristic features. But eruptions with EGFR inhibitors are seen in seborrhoeic areas.

Management:

Symptoms improves on withdrawal of offending drug. Systemic or topical treatment as for acne vulgaris may be helpful.

Symmetrical drug related intertriginous and flexural exanthema (SDRIFE):

Definition:

A self limiting and benign drug eruption, characterized by symmetrical involvement of the gluteal and intertriginous areas without systemic involvement.

Synonym:

Baboon syndrome

Most common implicated drugs:

Penicillins, cephalosporins, clindamycin, erythromycin, NSAIDs, pseudoephedrine, cimetidine, terbinafine

Pathogenesis:

Type IV delayed type hypersentivity reaction. A form of recall phenomenon with preferential trafficking of activated memory T cells to these sites, from previous physical/inflammatory insult.

Histopathology:

Superficial perivascular lymphocytic infiltrate which include neutrophils and eosinophils, spongiosis and vacuolar degeneration of the basal cells.

Clinical features:

Occurs in all age groups with male preponderance. Latency period ranges from hours to days after drug intake. Characterised by papules, pustules, vesicles

and sometimes bullae. Palms, soles and face are spared. Diagnosed on the basis of following criteria

- exposure to a systemically administered drug
- sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal area
- involvement of at least one other intertriginous/flexural location
- symmetry of the affected areas and
- absence of systemic symptoms and signs

Differential diagnosis :

AGEP, inverse psoriasis, intertrigo, Hailey Hailey disease, chemotherapy induced toxic erythema

Investigations:

Patch testing is positive in 50% of case and oral provocation test in 75% of patients.

Management:

Withdrawal of offending drug and supportive measures is all that needed. Rarely topical or systemic steroids are needed for symptom resolution.

Drug induced pruritus:

Pruritus can be localized or generalized and constitutes 13.1% of all adverse drug reactions.

Common drugs implicated[116]

Opioids, statins, paclitaxel, antimalarials, granulocyte - macrophage colony stimulating factor, interleukin - 2, matuzumab, ACE inhibitors, sulphonylurea derivates, NSAIDs.

Pathogenesis:

Primary (neuronal / central effects) and secondary (direct skin effects, alteration of biochemical profile and unexplained mechanisms)[96]

Clinical features:

Generalised itching with excoriation and lichenification with a latency period of few days. Dermographism is usually absent.

Management:

Withdrawal of offending drug. Cooling emollients like 0.5% menthol in aqueous solution will be of help in localized pruritus. Naltrexone, naloxone and nalbuphine can be tried in opioid induced pruritus. In severe pruritus , 5HT antagonists, serotonin receptor antagonists, D2 receptor antagonists, antihiatamines and gapapentin can be tried. In resistant drug induced pruritus phototherapy may be of use[97].

Drug induced Pityriasis rosea (PR):

It is an uncommon adverse cutaneous drug reaction but clinically resembles pityriasis rosea. Drugs commonly implicated are ACE inhibitors, NSAIDs, gold, omeprazole, metronidazole, terbinafine, rituximab and TNF α inhibitors. Clinically drug induced PR differs from classical PR by large lesions, absent herald patch, significant itching, oral lesions and persistence for a longer time. Only differentiating feature in histopathology to classical PR is presence of eosinophils. Remission seen within 1 - 2 weeks of withdrawal of offending drug. Topical steroids may be required in resistant cases.

Severe cutaneous adverse drug reactions (SCAR):

Constitute only 2% of all cutaneous drug reactions, but with very high mortality if not managed properly.

Acute generalized exanthematous pustulosis (AGEP):

Definition:

Acute generalized exanthematous pustulosis (AGEP) is characterized by the rapid appearance of sheets of sterile non follicular pustules, localized to the major flexures, in response to a drug. It is a self limiting and usually resolves without sequelae.

Synonyms :

- Exanthemic pustular psoriasis
- Toxic pustuloderma
- Pustular drug rash

Drugs implicated:

Pristinamycin, aminopenicillins. quinolones, chloroquine and hydroxychloroquine, sulphonamides, terbinafine, diltiazem

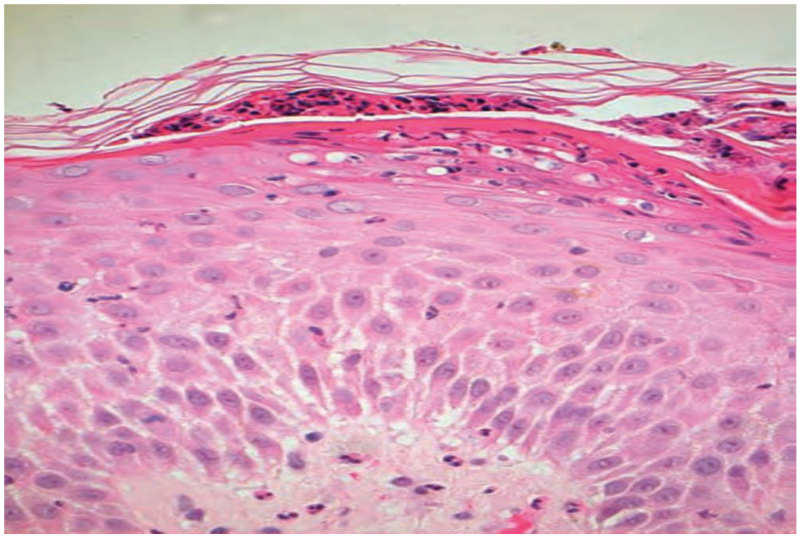
Pathogenesis:

Drug specific CD4+ and CD8+ T cells were demonstrated in patch test sites and in circulation. CXCL 8 and IL8 producing subsets of T cells have been demonstrated in circulation[98].Few subset of patients had IL 36 RN gene mutation which encodes for IL 36 Ra receptor antagonist similar to that seen in pustular psoriasis.

Histopathology:

Marked dermal and epidermal spongiosis, intraepidermal pustules and vesicles, neutrophilic perivascular infiltrate, occasional eosinophils may be present and infrequent necrotic keratinocytes seen.

Image 3.7: Histopathology of AGEP



Clinical features:

Occurs in adults with a mean age of 56 yrs and slight female preponderance[99]. 90 % are related to drugs and the remaining associated with infections like *Mycoplasma pneumoniae* [100], coxsackievirus [99], parvovirus B19 [101,102], cytomegalovirus (CMV) and mercury exposure [103] and spider bites.

Starts as sheets of sterile non-follicular pustules arising most commonly in the major flexures such as the neck, axillae and inframammary and inguinal folds typically in a background of edematous erythema. Less common features include atypical targets, purpura, blisters and vesicles. Mucous membrane involvement is rare.

Systemic manifestations include fever, leucocytosis with neutrophilia and eosinophilia, with liver , renal and pulmonary dysfunction in 18% of patients [104]. Rarely agranulocytosis is seen. Roujeau et al diagnostic criteria[105] for AGEP include

- Appearance of hundreds of sterile non follicular pustules at flexural sites.
- Histopathological changes of spongiosis and epidermal pustule
- Fever >38°C.
- Blood neutrophil count >7 × 109/L.
- Acute evolution.

Clinical variant :

ALEP (acute localized exanthematous pustulosis) - Characterized by similar lesions predominantly in a single area , most commonly the neck. First described in 2005[106].

Differential diagnosis:

Pustular psoriasis, sub corneal pustular dermatoses, DRESS, candidiasis

Disease course and prognosis:

Has a rapid onset and recovery. Prognosis is excellent with complete recovery with desquamation in few days

Investigations:

Complete hemogram, Biochemical profile, Acute phase reactants , Sepsis screening and skin biopsy

Management:

Corticosteroids based on severity of symptoms. Emollients. Empirical antibiotics for suspected infection. IV fluids and hemodynamic monitoring in cases with systemic involvement.

Drug reaction with eosinophilia and systemic symptoms (DRESS):

Definition:

Characterized by cutaneous features, a rash and systemic manifestation including haematological and solid organ disturbances [107].

Synonyms:

- Drug induced pseudo lymphoma
- Anticonvulsant hypersensitivity syndrome
- Drug induced hypersensitivity syndrome (DIHS)
- Drug induced delayed multiorgan hypersensitivity syndrome (DIDMOHS)
- DRESS was proposed by Bocquet *et al.* in 1996

Commonest drugs implicated:

Allopurinol, antiepileptics (carbamazepine, phenytoin, lamotrigine), antibiotics (vancomycin, amoxicillin, minocycline, piperacillin, tazobactam), sulpha drugs (sulphasalazine, dapsone, sulphadiazine), furosemide, omeprazole, ibuprofen

Pathogenesis:

Two theories has been put forward [108,109]

1.Drug specific T cell reaction

2.Viral reactivation

Drug specific T cell reaction:

Two concepts described were p - i concept and haptenisation theory.

Haptenisation theory: [110]

Immunologically neutral molecule(drug) → enzymatic degradation protein bound → rendered immunogenic → leading to T cell reaction

p-i concept(pharmacological interaction of drugs with immune receptor):[104]

Drug binds to protein attached to a MHC molecule or directly into a groove in MHC → presented to the T cell → cascade of action by stimulated T cells

Viral reactivation:

Herpesvirus reactivation has been demonstrated in DRESS [105,106]. The implicated viruses includes HHV 6, CMV, Epstein Barr Virus (EBV) and HHV-7 [108,111]. Virus reactivation occur in a sequential fashion, with HHV- 6 and EBV detected earlier in the course followed by HHV-7 and CMV [112]. Drug induced immunosuppressed state, characterized by hypogammaglobulinaemia facilitates reactivation of latent herpesvirus [113].

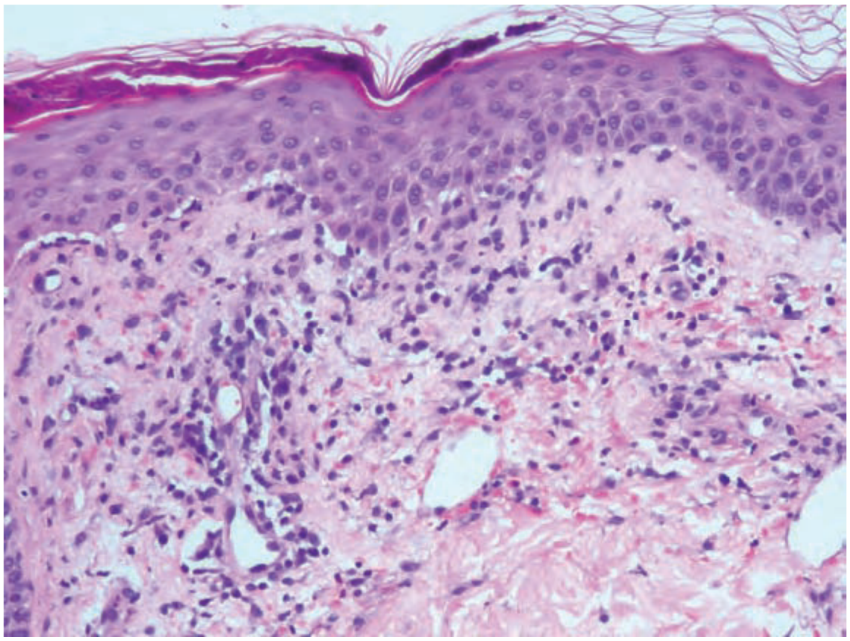
Genetic susceptibility:

- HLA B 5701 – Abacavir sensitivity
- HLA B 5801 – Allopurinol sensitivity
- HLA B 1502 - Carbamazepine sensitivity in South east asian population
- HLA B 3101 – Carbamazepine sensitivity in chinese and white population

Histopathology:[114]

Spongiosis, superficial perivascular lymphocytic infiltrate, an eosinophilic infiltrate in the dermis, basal cell vacuolar change with the prescence of necrotic keratinocytes. Changes resembling erythema multiforme correlates with more severe liver dysfunction, and may be predictive of a higher mortality .

Image 3.8: Histopathology of DRESS



Clinical features:

Typical latency period of 2 to 6 weeks between drug ingestion and onset of symptoms. Patient presents with prodromal phase characterized by asthenia, malaise and fatigue followed by rash with facial swelling .

Rash:

Most commonly an urticated papular exanthem accompanied by cutaneous edema. Other presentations include morbilliform eruption, erythroderma and

erythema multiforme like features. Characteristic finding in majority of patient is head and neck edema. Mucosal involvement is rare.

Lymphadenopathy:

Present in two or more sites in majority of patients.

Systemic involvement :

Hematological abnormalities:

Eosinophilia, pancytopenia (negative predictive factor)[115] , lymphocytosis with atypical lymphocytes. Leucopenia, lymphopenia and thrombocytopenia also noted.

Liver:

Seen in 70 to 90 percent of cases [100]. Severity varies from mild and transient hepatitis to fulminant hepatic failure . Patients with erythema multiforme like lesions and associated with minocycline have a higher risk of severe hepatic involvement .

Renal:

Seen in upto 10% of patients especially with allopurinol. Presents with proteinuria, and urinary eosinophils. Interstitial nephritis is seen histologically.

Heart - Pericarditis and myocarditis [116]

Lung - Pleural effusion, pleuritis and acute interstitial pneumonitis .

Central nervous system - Seizures, cranial nerve palsy, SIADH[117].

GIT - Diarrhoea, eosinophilic esophagitis and dysphagia .

Endocrine system - Hypothyroidism, hyperthyroidism, pancreatic insufficiency with type 1 diabetes[118].

Differential diagnosis:

Sepsis, AGEP, SJS, TEN, erythema multiforme, angioimmunoblastic lymphoma.

Disease course and prognosis :

Majority recover fully following drug withdrawal and management of acute episode. Mortality rate is 5 - 10 % with hepatic failure being the commonest cause. Organ specific chronic sequelae seen according to the organ involvement in acute episode.

Investigations:

To rule out organ involvement and to monitor systemic manifestations.

Management:

Withdrawal of offending drug, admission in a intensive care unit, IV fluids, thermoregulation, supplemental oxygen and topical emollients.

First line - oral prednisolone 1mg/kg/day tapered over 1 to 3 months .

- methyl prednisolone 1gm/day for three days [106].

Second line - Cyclosporine – 2 to 5 mg/kg/day [119]

- intravenous immunoglobulin 400mg/kg/day for 5 days[120].

Third line - ECMO, plasmapheresis, rituximab, valgancyclovir, N - acetyl cysteine [121].

Steven Johnson syndrome / Toxic epidermal necrolysis (SJS/TEN):

Synonym:

Lyell syndrome

History:

First described independently by Steven and Johnson in 1922[107]. Lyell coined the term Toxic epidermal necrolysis and described it in 1956[122].

Definition:

Severe mucocutaneous reactions characterized by blistering and epidermal sloughing

Most common implicated drugs

Allopurinol, Carbamazepine, Lamotrigine, Nevirapine, Oxicam NSAIDs, Phenobarbital, Phenytoin, Sulfamethoxazole and other sulfa antibiotics, Sulfasalazine

Pathogenesis[103]

MHC class I-restricted drug presentation

⇩

Drug-induced cytotoxic T lymphocytes

⇩

Cytokines and soluble factors

(tumour necrosis factor-α, interferon-γ, and inducible nitric oxide synthase

Fas ligand, perforin , granzyme and recently Granulysin)

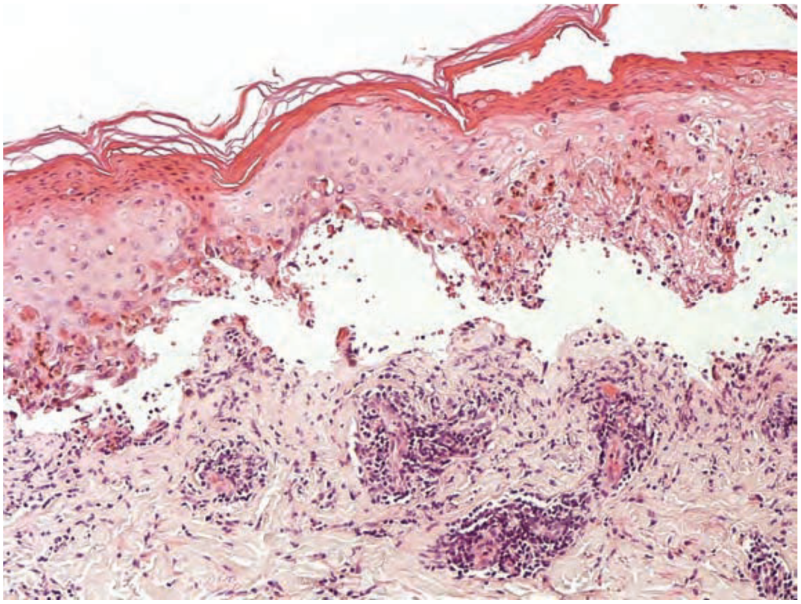
⇩

Apoptosis of keratinocytes

Histopathology

Ranges from individual cell apoptosis to confluent epidermal necrosis, basal cell vacuolar degeneration and subepidermal vesicle or bulla formation**,** mild perivascular infiltrate of lymphocytes and histiocytes and eosinophils occur in the minority of cases[108]

Image 3.9: Histopathology of SJS/TEN



Clinical features:

Occurs in all ages, but predominantly in children, infants and elderly with a female preponderance. Predominantly caused by drugs ,but a few cases especially in children caused by Mycoplasma pneumoniae[109]. Latency period is typically 7–10 days, but range from 5 to 28 days followed by a prodrome of malaise, fever and upper respiratory tract symptoms.

Earliest skin lesions are atypical targets and purpuric macules which commonly occur on the face, upper trunk and proximal limbs . Later spreads to involve entire body. Skin lesions increase over 5 - 7 days with development of vesicles and bullae. Nikolsky sign will be positive followed by epidermal detachment leading on to raw areas and secondary infection.

Erosive and haemorrhagic mucositis of eyes, mouth, nose and genitalia is an early feature. Oral mucosal involvement seen in 93%, eye involvement seen in 78% and genital mucosal involvement in 63% [133]. All three sites were involved in 66%. Ocular lesions include chemosis, conjunctivitis, pseudo membrane, corneal and conjunctival epithelial defects. Oral manifestations include painful mucosal erythema with subsequent blistering and ulceration. Haemorrhagic crusts over vermilion of lips seen. Involvement of mucosa of oropharynx, larynx, respiratory tract and oesophagus seen in severe cases. Urogenital tract involvement characterized by mucosal erythema, blistering and erosions.

Pulmonary manifestations include dyspnoea, increased respiratory rate and bronchial hypersecretion.

Severity of SJS/TEN[123]

- SJS : epidermal detachment less than 10% BSA + widespread purpuric macules /flat atypical targets.
- Overlap SJS -TEN: detachment of 10–30% BSA + widespread purpuric macules/flat atypical targets.

- TEN with spots: detachment more than 30% BSA + widespread purpuric macules/ flat atypical targets.
- TEN without spots: detachment more than 30% BSA + loss of large epidermal sheets without purpuric macules/ target lesions

Differential diagnosis:

Erythema multiforme major, pemphigus vulgaris, mucous membrane pemphigoid, bullous pemphigoid, paraneoplastic pemphigus, bullous lupus erythematosus, linear IgA bullous dermatosis, generalized bullous fixed drug eruption, acute bullous acute graft – versus host disease, staphylococcal scalded skin syndrome, acute generalized exanthematous pustulosis.

Complications:

Acute:

Hypothermia, transepidermal water loss, hyperglycaemia, hypoalbuminaemia, elevated liver enzymes, anaemia & neutropenia, acute kidney injury, hemoptysis, hypoxia, septiceamia (life threatening)

Chronic:

Skin - Post inflammatory dyspigmentation, scarring, telogen effluvium**,** eruptive melanocytic naevi, abnormal sweating, photosensitivity, heterotopic ossification

Ocular - corneal and conjunctival ulceration and scarring, dry eye, distichiasis, entropion, trichiasis, symblepharon or ankyloblepharon, ectropion and misdirected eyelashes.

Oral mucosa - Gingival synechiae and sjogren like syndrome[124]

Lung - bronchiolitis obliterans[125]

GIT - Eosophageal stricture, diarrhea, malabsorption and vanishing bile duct syndrome

Others - vaginal and introital adhesions, psychological sequelae, including post-traumatic stress disorder [126].

Disease course and prognosis:

Skin lesions increases over first 5- 7 days , followed by re -epithelialisation and complete healing in 2-3 weeks with treatment. The overall mortality in SJS/TEN is about 22%; in SJS less than 10%, while in TEN the mortality is approximately 30% [127].

Prognosis:

SCORTEN – (scores from 0-7)

- Age greater than 40 years
- Presence of malignancy
- Heart rate >120 beats/min
- Epidermal detachment >10% of BSA at admission
- Serum urea >10 mmol/L
- Serum glucose >14 mmol/L
- Bicarbonate level <20 mmol/L

Table 3.4 : Mortality rate of SJS/TEN according to SCORTEN

Number of parameters(%)	Predicted mortality
0	1.21
1	3.2
2	12.2
3	32.4
4	62.2
5	85.0
6	95.1
7	98.5

Investigations :

Needed to substantiate the diagnosis, exclude other blistering dermatoses and identify any systemic complications.

Management:

- Withdrawal of offending drug
- Admission in intensive care unit
- Temperature maintained at 25- 27 ^{0} C

Skin care:

Greasy emollients, bath in a weak solution of chlorhexidine (1/5000), topical antibiotic in sloughed or crusted areas, silicon dressings, biological dressings and skin grafts.

Care of mucosa:

Eyes - Ocular lubricant must be applied 2nd hourly, broad spectrum topical antibiotic for corneal ulceration**,** amniotic membrane transplantation (AMT) for loss of ocular epithelia

Oral mucosa - Apply WSP ointment frequently to the lip, anti inflammatory oral rinse containing benzydamine hydrochloride every 3 hours and topical corticosteroid four times per day

Urogenital mucosa - WSP ointment used as an emollient. Silicone sheet dressings for eroded areas in the vulva and vagina. Catheterisation to prevent urethral strictures

Fluid replacement and nutrition:

Crystalloid fluid at 2 mL/kg body weight / % of BSA epidermal detachment. During catabolic phase 20–25 kcal/kg/day and anabolic phase 25–30 kcal/kg/day is needed[45].

Active therapy:

- IVIG (0.5–1 g/kg daily for 3–4 consecutive days)
- Systemic corticosteroid (e.g. prednisolone 0.5–1 mg/kg daily for 10 days, and tapered; or IV methylprednisolone 500 mg on 3 consecutive days)
- Ciclosporin (3 or 4 mg/kg/day in divided doses for 10 days, and tapered)
- Plasmapheresis
- Single dose of TNF alpha inhibitor – Etanercept

Drug induced erythroderma:

Characterised by erythema and scaling involving 90 % of BSA. Accounts for 2 – 8 % of all adverse cutaneous drug reactions and 5 – 40 % of all erythroderma cases.

Synonym:

Drug induced exfoliative dermatitis

Commonly implicated drugs:

Antiepileptics, antibiotics, allopurinol, HAART, NSAIDs and complementary medicines.

Pathogenesis:

There is over expression of Th1 and Th2 type of cytokines and their ligands. Increased production of adhesion molecule CD61 by keratinocytes leads to hypersensitivity reaction by recruiting more epidermal T cells and Langerhan cells.

Clinical features:

Erythema, scaling and pruritis involving more than 90 % of BSA. Presence of constitutional symptoms such as fever and malaise along with lymphadenopathy, organomegaly and high output cardiac failure.

Complications:

Hypothermia, fluid and electrolyte imbalance, high output cardiac failure and sepsis.

Prognosis:

Drug induced erythroderma has the best prognosis among all erythroderma cases and resolves in 6 – 8 weeks on withdrawal of offending drug.

Treatment :

Withdrawal of offending drug followed by emollients, topical and systemic steroids.

Based on the above literature review, adverse cutaneous drug reactions are associated with significant morbidity and mortality especially in cases of SCAR. Among all the adverse cutaneous drug reactions, benign cutaneous drug reactions constitutes the majority (>90%) and severe cutaneous adverse drug reactions (SCAR) constitute only 2 – 8 %. There is a slight female preponderance and majority of the reactions are seen in the elderly age group.

Among the benign reactions maculopapular eruptions are the most common followed by urticaria, fixed drug eruptions, pruritis, acneiform eruptions with others constituting very less number of cases. Among the severe cutaneous drug reactions bullous lesions such as SJS/ TEN were the commonest, followed by erythroderma, DRESS and AGEP.

Among the drugs commonly implicated in benign reactions, antibiotics, NSAIDs and antiepileptics constitute the majority with others being less common. Antileptics, antibiotics and allopurinol were the commonest drugs implicated in SCAR, with DRESS having a slightly different etiological profile compared to others.

Presence of eosinophils was the consistent finding in HPE in majority of the cases, along with the findings in relation to the particular diagnosis.

Majority of the benign reactions can be managed on a OP basis by withdrawal of the offending drug and with antihistaminics, emollients, topical and systemic steroids. SCAR needs admission in a ICU, early and appropriate management of complications to decrease the morbidity and mortality associated with them when compared to benign cutaneous drug reactions.

Materials & Methods

MATERIALS AND METHODS

4.1 - Study design:

- Prospective observational study

4.2 - Study centre:

- Department of Dermatology, Rajiv Gandhi Government General Hospital & Madras Medical College, Chennai – 600 003.

4.3 - Study period:

- November 2016 to September 2017

4.4 - Study population:

- All patients who attended dermatology outpatient department with signs and symptoms of adverse cutaneous drug reactions are randomly selected for the study

4.5 - Inclusion criteria:

- All patients aged more than 12 years presenting with skin and mucosal lesions following exposure to a drug

4.6 - Exclusion criteria:

- Patients less than 12 years of age
- Patients who were not willing to be included in the study
- Patients who were not willing for follow up

4.7 - Sample size:

- All total of 36 patients who satisfied the above criteria were taken into the study.

4.8 - Study approval:

- Approval for the study was obtained from, Thesis & Ethical Committee of Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, prior to commencement of the study.

4.9 - Methodology:

A clinico pathological study of adverse cutaneous drug reactions was carried out during the period of November 2016 to September 2017.

Detailed case history was taken from each patient. Patients were enquired in reference to the duration and course of the disease, ailment for which the offending drug was taken, duration of treatment, route of administration, treatment taken for the present complaints, any previous history of similar complaints and any family history of cutaneous drug eruptions and were recorded.

In clinical examination, features like prodromal symptoms, site of involvement, morphology of lesions like presence of maculopapular rash, target lesions, widespread erythema, erosions, peeling of skin and mucosal lesions were noted and complete dermatological examination was carried out. Nikolosky sign was elicited and Tzanck smear was done in patients with vesiculobullous lesions. Associated systemic symptoms were noted.

Routine investigations of all patients were performed which included a complete hemogram ,renal and liver function tests, VCTC, VDRL. In relevant cases USG abdomen, pus culture and sensitivity and scraping to rule out fungal infections was done. Skin biopsy from lesional skin was subjected to histopathological examination.

All the parameters were recorded in a pretested proforma and were entered in a master chart, results were tabulated and analysed statistically.

4.10 - Follow up procedures:

Patients who were treated as out patients were asked to follow up after 4 days. Patients who had extensive skin involvement and other systemic abnormalities were admitted and followed up.The investigation reports were collected, recorded and classified. The diagnosis was confirmed on the basis of clinical, biochemical and histopathological features. Patients were treated according to their relevant diagnosis.

4.11- Ethical Issues

Participants were made aware about the nature and purpose of the study. It was also informed to all the participants that all data provided by the patients will be kept confidential and will be used only for the study purpose. Willingness and signature of the participants were taken on a previously designed consent form.

Written consents were obtained from all the subjects who participated in the study before data collection. Detailed description of the study and the aspects of patient confidentiality are explained to the subject and voluntary participation is sought. Institutional ethics committee of Madras medical college reviewed the study proposal for ethical consideration and approval.

Observations & Results

OBSERVATION AND RESULTS

Total number of patients who attended our OPD during the study period and satisfied the criteria for the study was 36. Total number of new cases in our OPD during the study period (November 2016 to September 2017) was 37948. Hence the incidence of adverse cutaneous drug reactions in our study population was 0.949 per 1000 person years (patients above 12 yrs of age).

Table 5.1 : Incidence rate of adverse cutaneous drug reactions in our OPD

No. of new cases (1 year) (above 12 yrs of age)	**No. of study patients** (above 12 yrs of age)	**Incidence** (above 12 yrs of age)
41398	**39.27** (calculated for 1 year with the incidence in previous 11 months)	**0.949** per 1000 person years

Table 5.2 shows the mean age group of our study population which was 39.33 (± 20.13, range 13 – 75 years). The lowest age in our study group was 13 years and the highest being 75 years.

Table 5.2: Age distribution

Age group(in years)	No. of patients	Percentage
12 - 20	8	22
21 -30	8	22
31 – 40	4	11
41 – 50	3	9
51 – 60	4	11
61 – 70	8	22
71 - 80	1	3

Chart 5.1: Graphical representation of age distribution

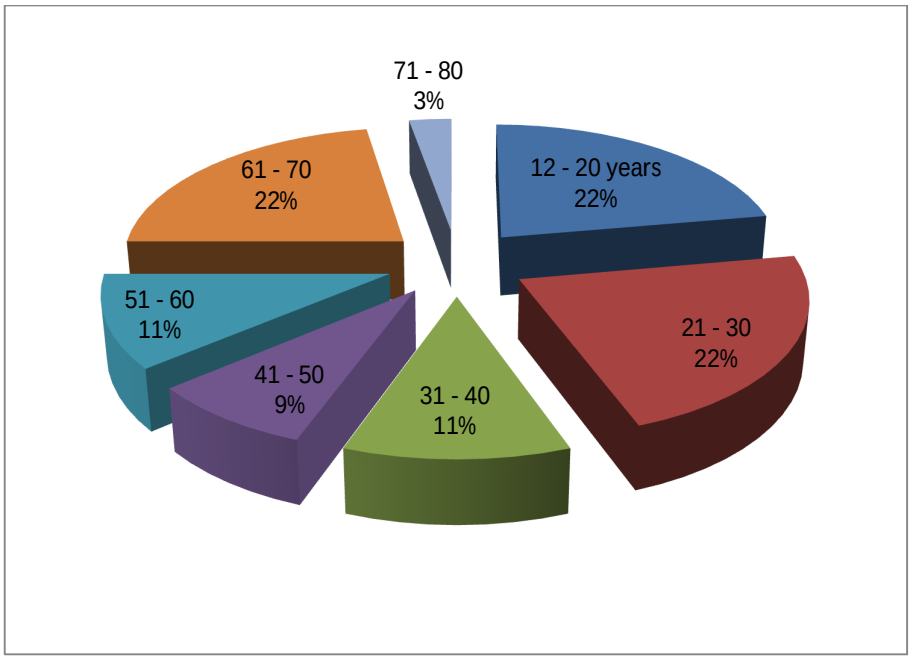
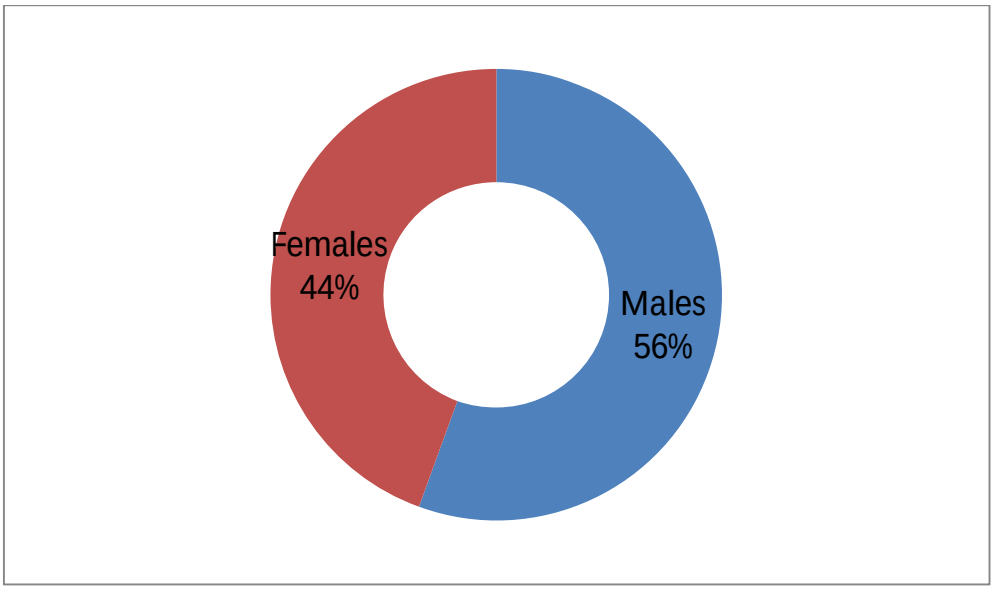


Table 5.3 shows the sex distribution among the study group, with 20 (56%) patients being males and 16 (44%) patients being females. Male to female ratio was 1.25: 1.

Table 5.3: Sex distribution

Sex	No. of patients	Percentage
Males	20	56
Females	16	44

Chart 5.2: Graphical representation of sex distribution



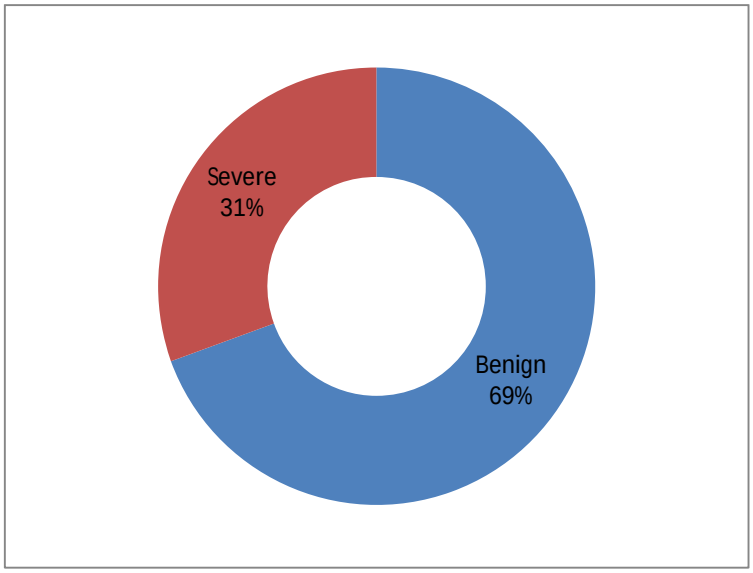
Out of the 36 patients in our study, one female who presented with generalized bullous FDE, had a family history of FDE (H/o of FDE in her father, but drug details were not available). None of the other study patients had any family history of drug hypersensitivity reactions.

Of the total 36 patients , 25 (69%) patients had benign cutaneous drug reactions and 11(31%) patients had severe cutaneous drug reactions, as shown in table 5.4

Table 5.4: Type of drug reactions

Type of reaction	No . of patients	Percentage
Benign	25	69
Severe	11	31

Chart 5.3: Graphical representation of type of drug reaction



Among the various clinical presentation, fixed drug eruption (FDE) was the commonest seen in 10 (28%) patients, followed by maculopapular rash (exanthem) in 8 (22%) of patients, SJS/ TEN in 7 (19%) patients, acneiform eruptions in 4 (11%), erythroderma in 2 (6%), EMF in 2 (5%), lichenoid reation,DRESS and SJS/DRESS overlap in 1 patient each, as shown in table 5.5.

Table 5.5: Clinical presentation

Diagnosis	No. Of Patients	Percentage
Acneiform eruptions	4	11
DRESS	1	3
EMF	2	5
Erythroderma	2	6
Exanthem	8	22
FDE	10	28
Lichenoid reaction	1	3
SJS/DRESS	1	3
SJS/TEN	7	19

Chart 5.4 – Graphical representation of various clinical presentation

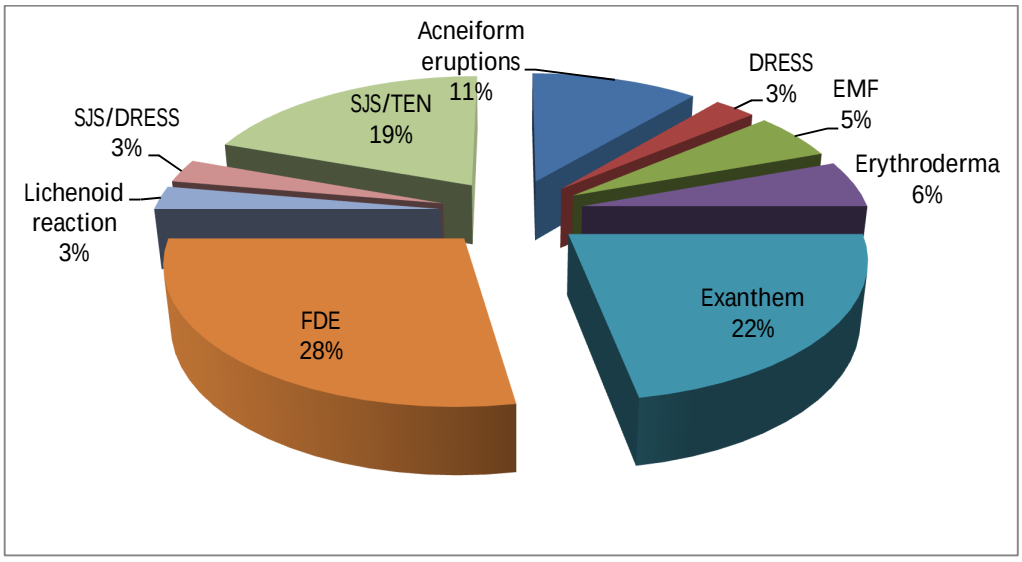
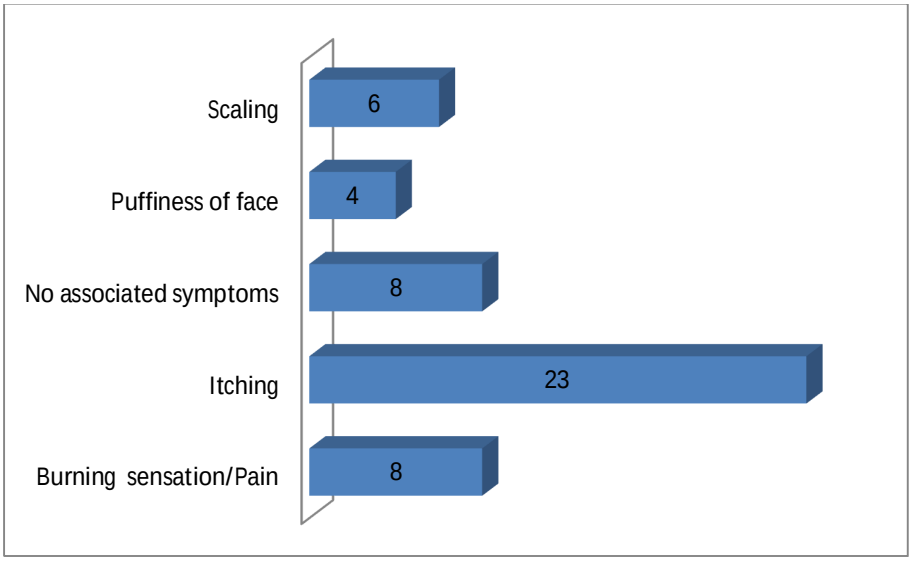


Table 5.6 shows the various symptoms associated with adverse cutaneous drug reactions, with itching being the most common, seen in 23(64%)patients, followed by burning sensation/ pain seen in 8(22%)patients, scaling in 6(17%) patients and facial puffiness in 4(11%) patient. 8 (22%) patients didn't have any associated symptoms.

Table 5.6 : Associated symptoms

Associated symptoms	No. of patients	Percentage
Burning sensation/Pain	8	22
Itching	23	64
No associated symptoms	8	22
Puffiness of face	4	11
Scaling	6	17

Chart 5.5: Graphical representation of associated symptoms

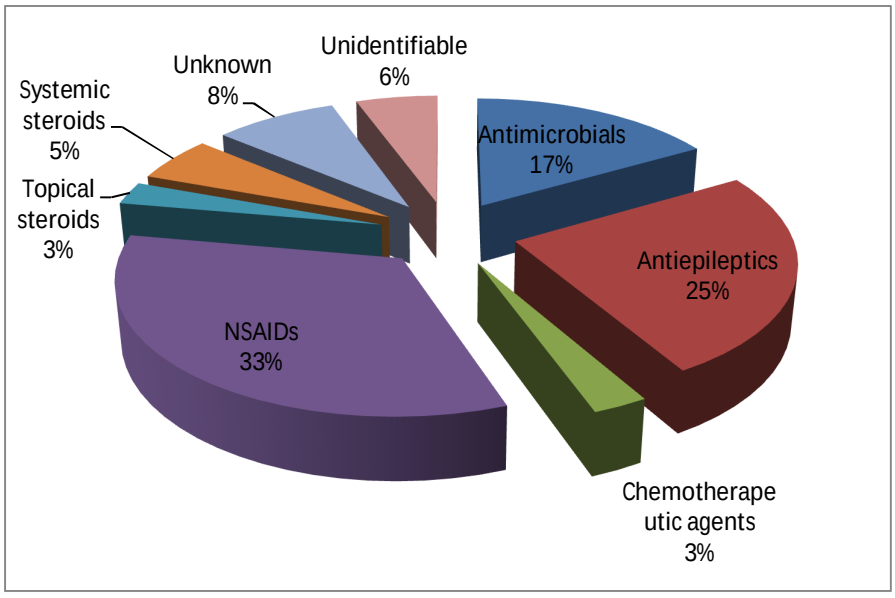


The most common offending drug in our study was NSAIDs (33%), followed by antiepileptics (25%), antibiotics (19%), systemic steroids (5%), chemotherapeutic agent (3%) and topical steroid (3%). The causative drug was unidentifiable in 2 (6%) patients as and was unknown in 3 (8%) patients. Details were shown in table 5.7

Table 5.7: Causative drug in adverse cutaneous drug reaction in our study

Offending Drug	No of Patients	Percentage
Antimicrobials	6	17
Antiepileptics	9	25
Chemotherapeutic agents	1	3
NSAIDs	12	33
Topical steroids	1	3
Systemic steroids	2	5
Unknown	3	8
Unidentifiable	2	6

Chart 5.6: Graphical representation of causative drug



Out of the 36 patients in our study, 29 patients had taken drugs prescribed by a physician and 7 patients had taken over the counter drugs, as shown in table 5.8

Table 5.8: Prescription status of causative drug

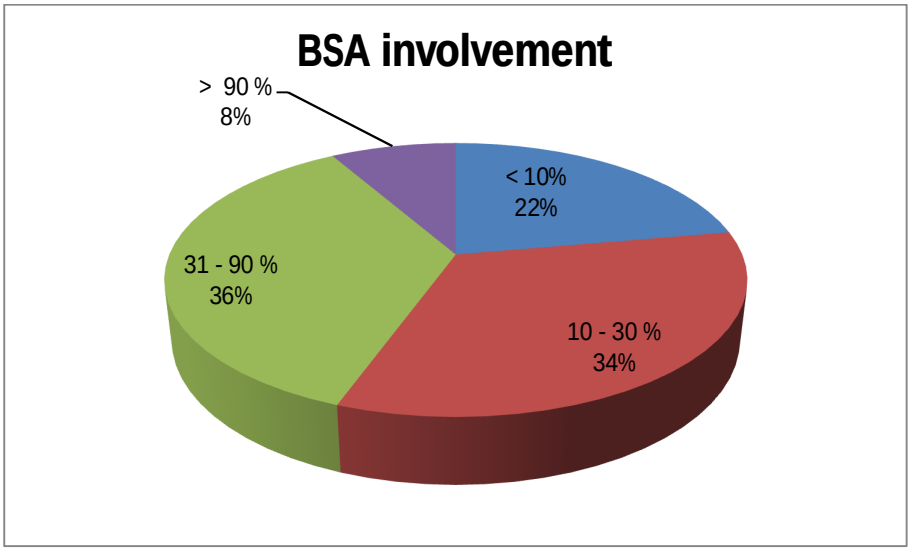
Prescription status	No. of patients	Percentage
Physician prescribed	29	81
Over the counter	7	19

Body surface area involvement (BSA) of skin lesions among our study patients is shown in table 5.9

Table 5.9 : Body surface area involvement

BSA	No. of patients	Percentage
< 10%	8	22
10 - 30 %	12	34
31 - 90 %	13	36
> 90 %	3	8

Chart 5.7 : Graphical representation of body surface area involvement

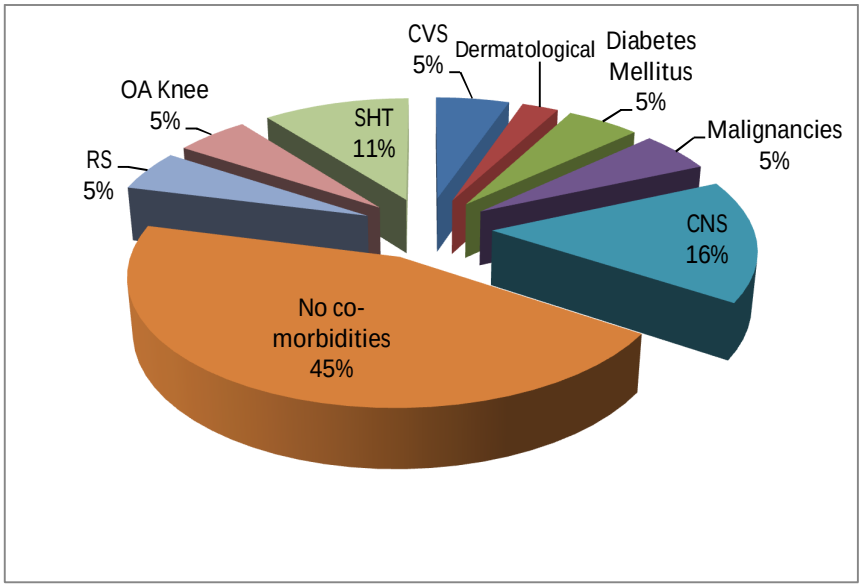


Comorbidities seen in patients with adverse cutaneous drug reactions in our study is shown in table 5.10

Table 5.10: Associated co morbidities

Co morbidities	No of Patients	Percentage
CVS	2	5
Dermatological	1	3
Diabetes Mellitus	2	5
Malignancies	2	5
CNS	6	16
No co-morbidities	17	45
RS	2	5
OA Knee	2	5
SHT	4	11

Chart 5.8: Graphical representation of associated co morbidities

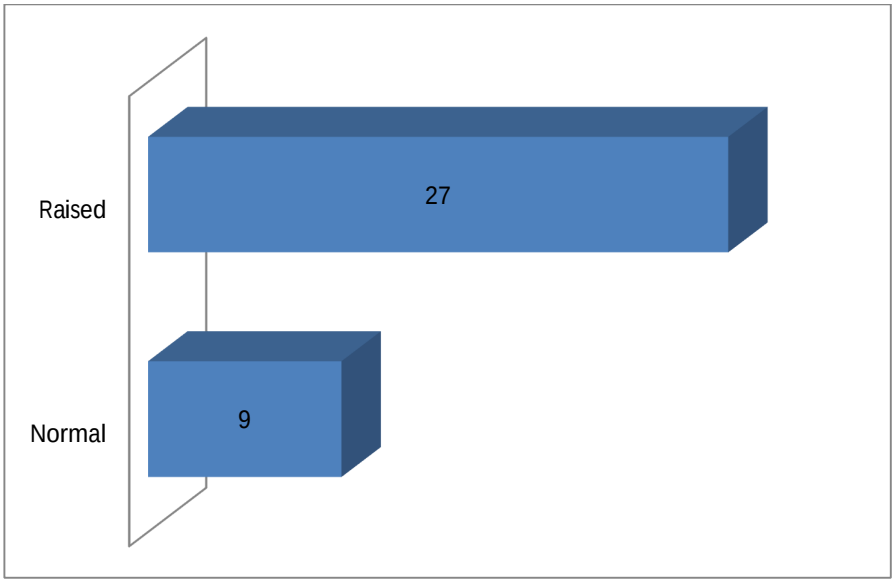


The erythrocyte sedimentation rate (ESR) values in our study patients is shown in table 5.11. 27 (75 %) patients had raised ESR.

Table 5.11: Erythrocyte sedimentation rate (ESR)

ESR	No.of patients	Percentage
Normal	9	25
Raised	27	75

Chart 5.9: Graphical representation of ESR

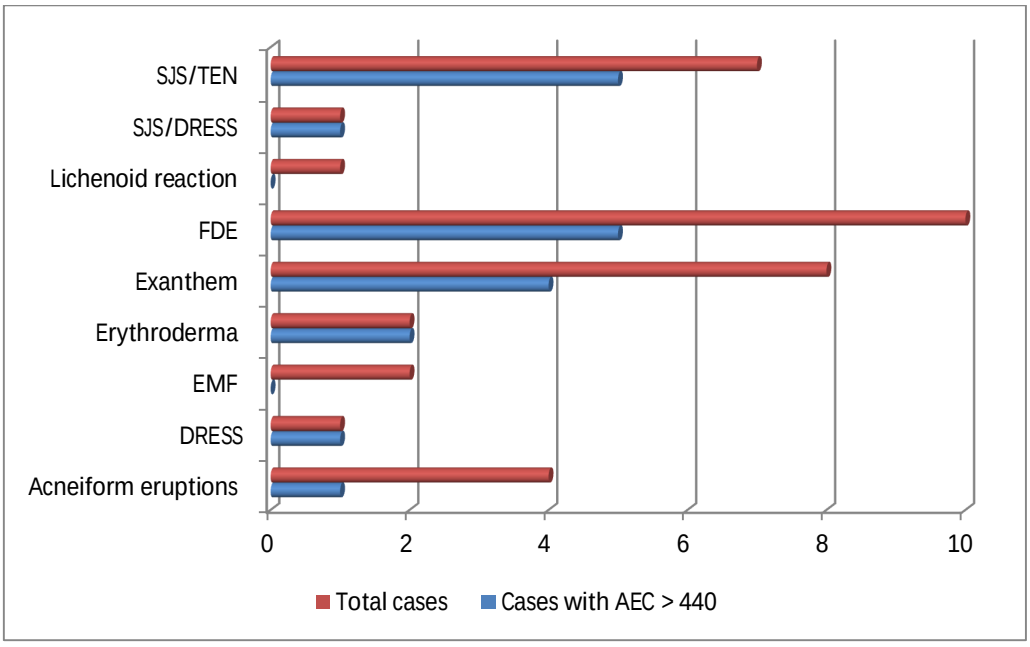


In our study population, 19 (53%) out of 36 patients had elevated absolute eosinophil count. 9 (82%) out of 11 patients with severe adverse cutaneous drug reactions and 10 (37%) out of 27 patients with benign cutaneous drug reactions had elevated eosinophil counts, which is shown in table 5.12.

Table 5.12: Absolute eosinophil count in our study patients

Clinical presentation	No. of patients with AEC > 440	Percentage
Acneiform eruptions (n=4)	1	25
DRESS (n=1)	1	100
EMF (n=2)	0	0
Erythroderma (n=2)	2	100
Exanthem (n=8)	4	50
FDE (n=10)	5	50
Lichenoid reaction (n=1)	0	0
SJS/DRESS (n=1)	1	100
SJS/TEN (n=7)	5	71

Chart 5.10 : Graphical representation of absolute eosinophil count in our study patients

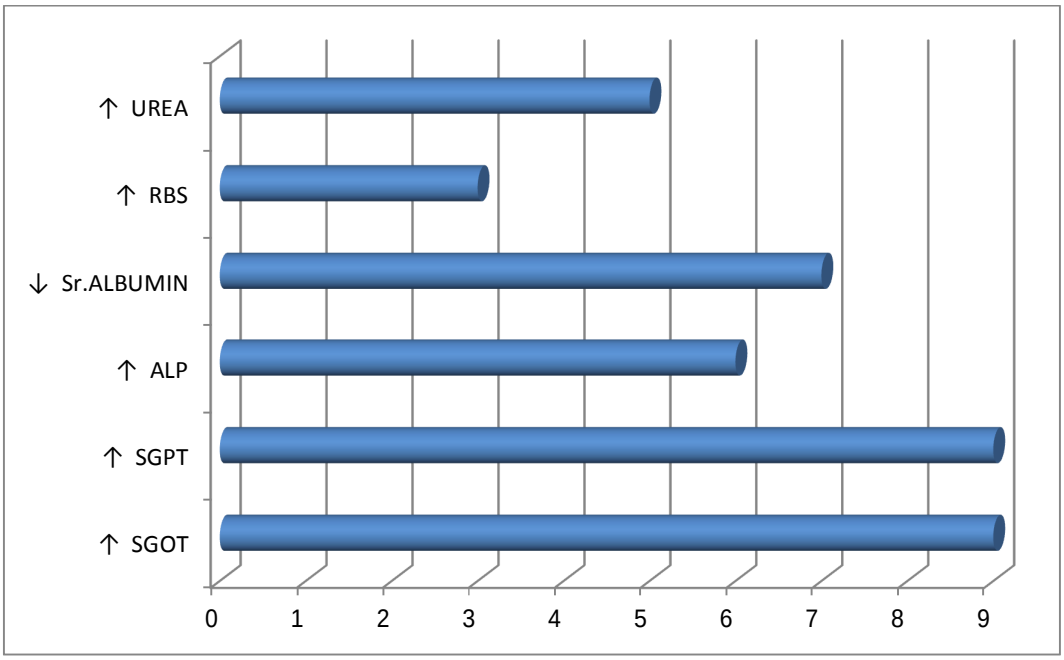


In our study population, only 11 patients had elevated biochemical parameters at the first visit for OP patients and at the time of admission for patients with SCAR. 6 (54%) out of 11 patients with SCAR had elevated biochemical parameters and only 5 (20%) patients out of 25 with benign adverse cutaneous drug reactions had elevated biochemical parameters. The details have been tabulated (Table 5.13)

Table 5.13: Biochemical parameters in our study patients

CLINICAL PRESENTATION	↑SGOT	↑SGPT	↑ALP	↓SERUM ALBUMIN	↑RBS	↑UREA
Acneiform eruptions (n=4)	0	0	0	1	1	0
DRESS (n=1)	1	1	1	1	0	1
EMF (n=2)	0	0	0	0	0	0
Erythroderma (n=2)	1	1	1	1	0	0
Exanthem (n=8)	1	0	0	0	1	0
FDE (n=10)	2	2	2	1	0	0
Lichenoid reaction (n=1)	0	1	0	0	0	1
SJS/DRESS (n=1)	0	0	0	0	0	0
SJS/TEN (n=7)	4	4	2	3	1	3

Chart 5.11 : Graphical representation of biochemical parameters in our study patients

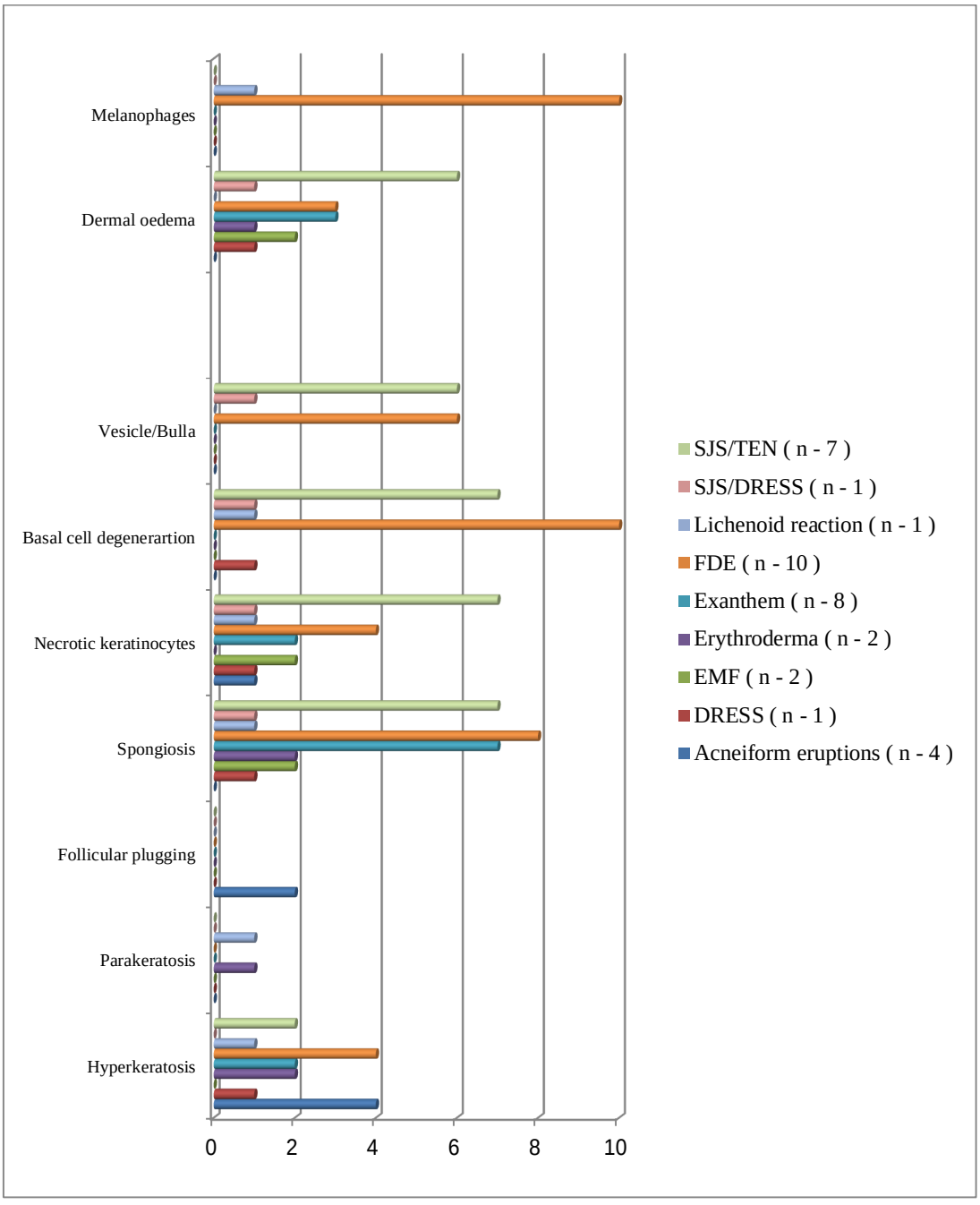


The histopathological features of various clinical presentation of adverse cutaneous drug reactions has been recorded and tabulated. The commonest presentation was the presence of dermal perivascular and interstitial lymphocytic infiltrate along with presence of eosinophils in most of the cases and neutrophils in few cases. Hyperkeratosis and follicular plugging was seen in acneiform eruptions. Spongiosis, basal cell degeneration and necrotic keratinocytes were commonly seen in FDE and SJS / TEN. Pigment incontinence and dermal melanophages were seen in cases of FDE. Subepidermal split and bullae were seen in SJS / TEN and bullous FDE cases. Band like upper dermal inflammatory infiltrate was seen in a case of lichenoid drug reaction. Various histopathological features are shown in table 5.13 and its graphical representation in chart 5.11.

Table 5.14 : Histopathological features in our study population

Clinical presentation	Hyperkeratosis	Parakeratosis	Follicular plugging	Spongiosis	Necrotic keratinocytes	Basal cell degenerartion	Vesicle / Bulla	Dermal oedema	Pigment incontinence	Melanophages
Acneiform eruptions (n - 4)	4	0	2	0	1	0	0	0	0	0
DRESS (n - 1)	1	0	0	1	1	1	0	1	0	0
EMF (n - 2)	0	0	0	2	2	0	0	2	0	0
Erythroderma (n - 2)	2	1	0	2	0	0	0	1	0	0
Exanthem (n - 8)	2	0	0	7	2	0	0	3	0	0
FDE (n - 10)	4	0	0	8	4	10	6	3	10	10
Lichenoid reaction (n - 1)	1	1	0	1	1	1	0	0	1	1
SJS/DRESS (n - 1)	0	0	0	1	1	1	1	1	0	0
SJS/TEN (n - 7)	2	0	0	7	7	7	6	6	1	0

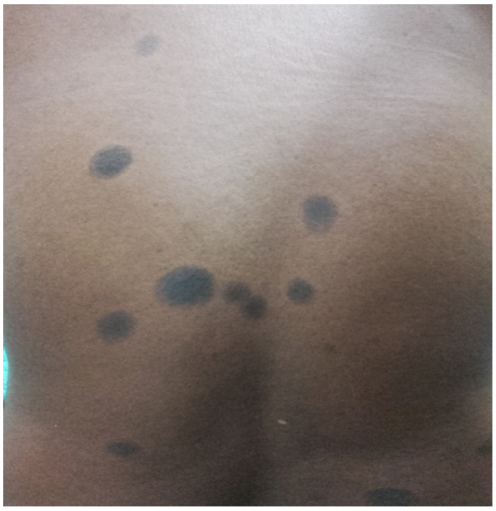
Chart 5.12 : Graphical representation of histopathological features in our study population

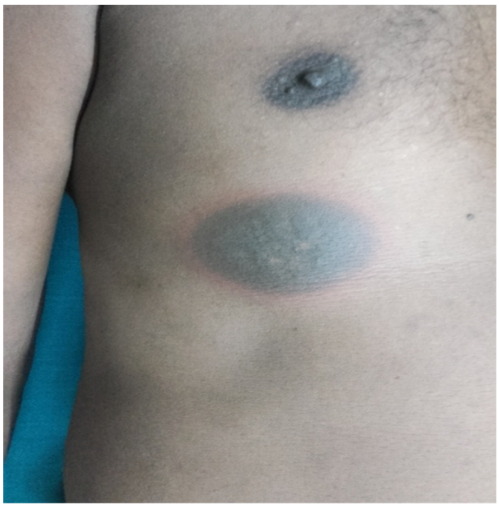


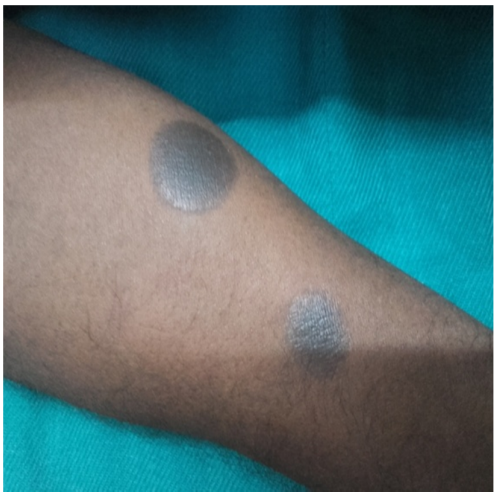
Clinical Images

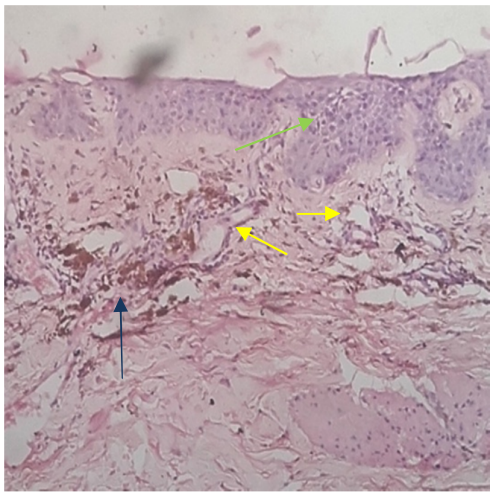
IMAGE 1

Fixed drug eruption (FDE)





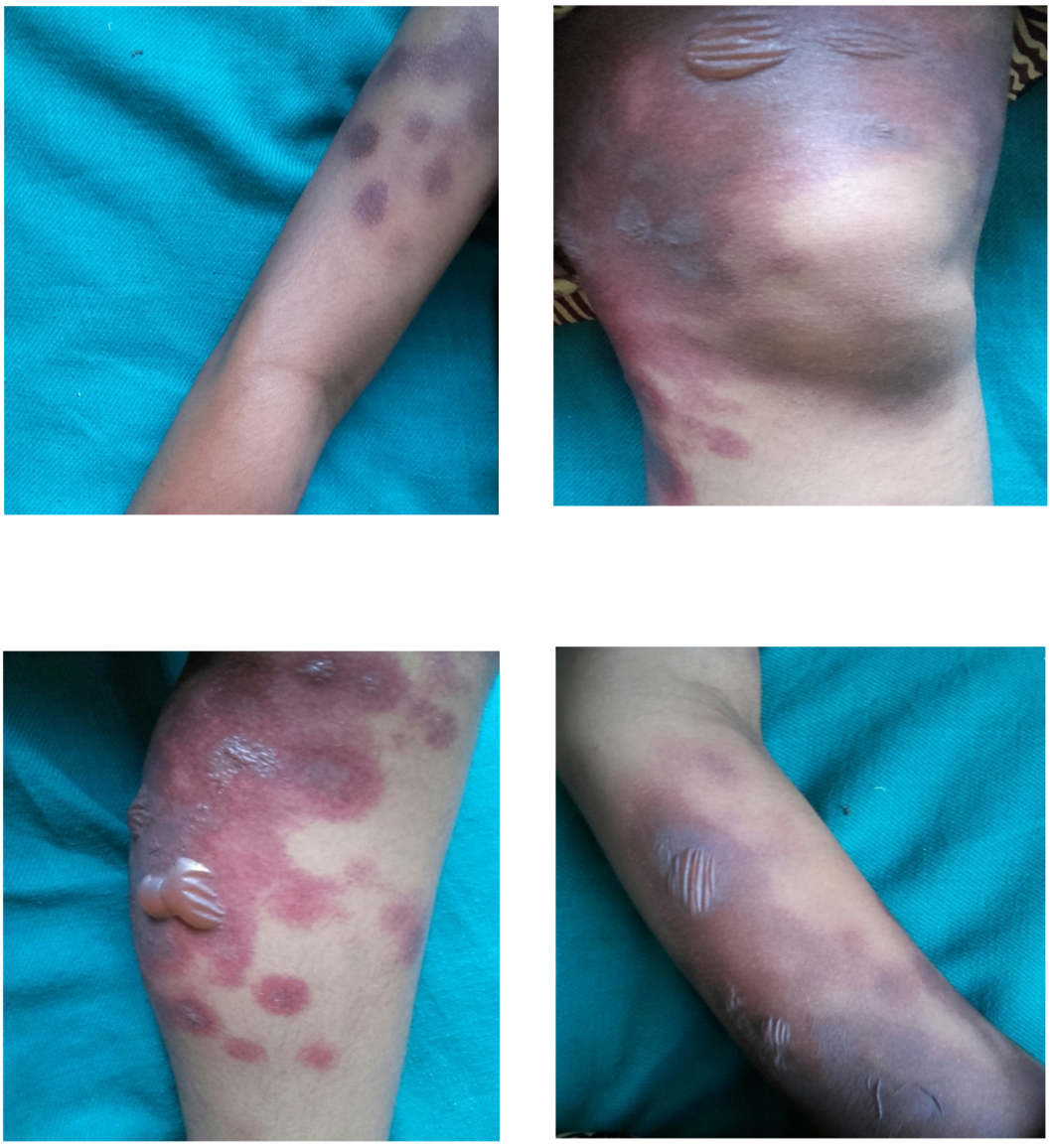




Histopathology of FDE shows spongiosis (green arrow), lymphocytic infiltrate (yellow arrows) and pigment incontinence and melanophages in dermis (blue arrow).

IMAGE 2

Generalised bullous fixed drug eruption (GBFDE)

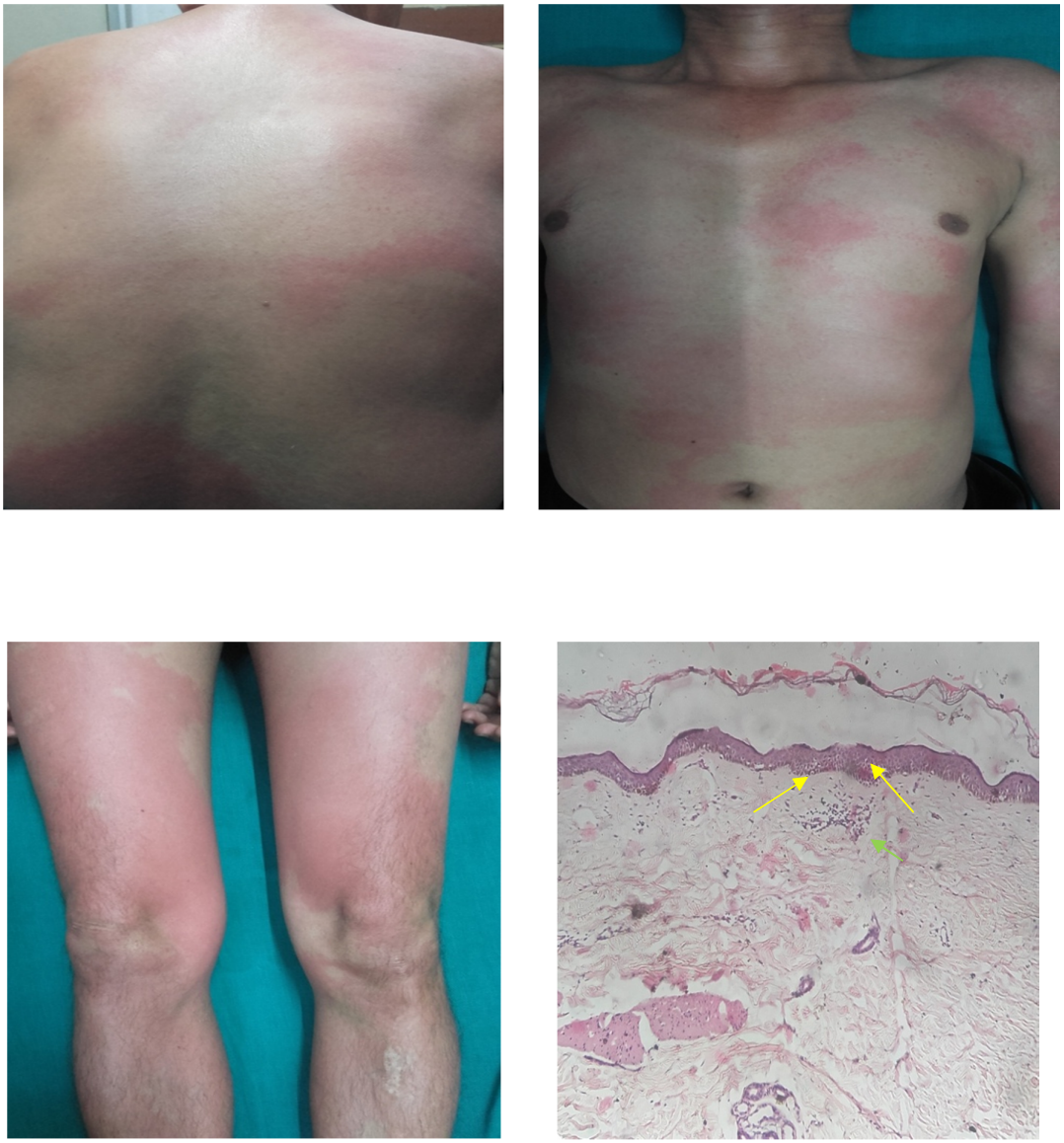


Multiple erythematous and hyperpigmented patches

and plaques with bullae

IMAGE 3

Drug induced exanthem

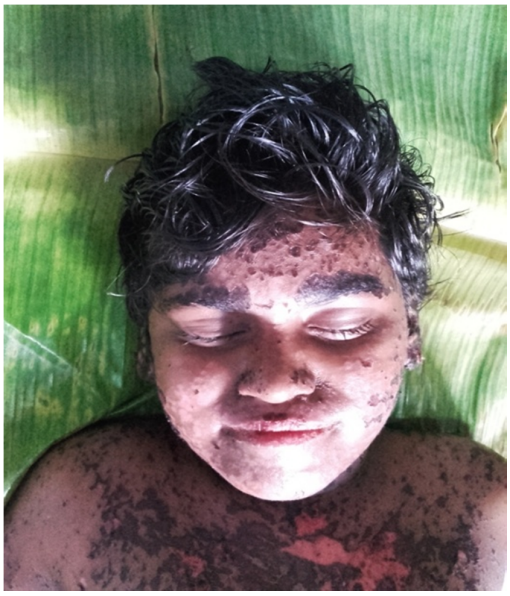


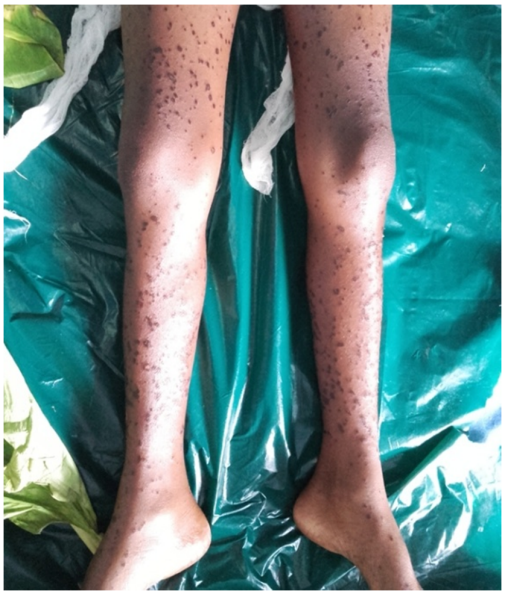
Histopathology of drug induced exanthem shows spongiosis (yellow arrow) and perivascular lymphocytic infiltrate (green arrow)

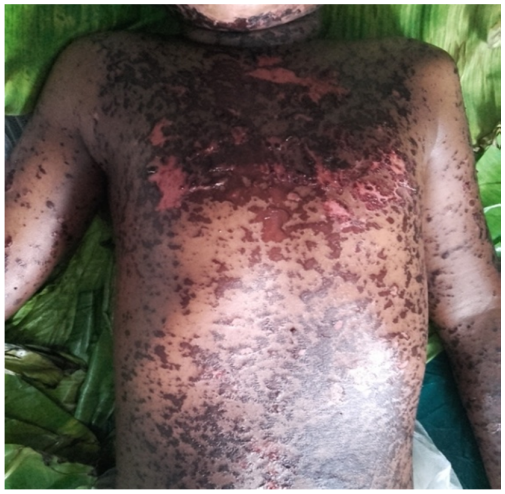
IMAGE 4

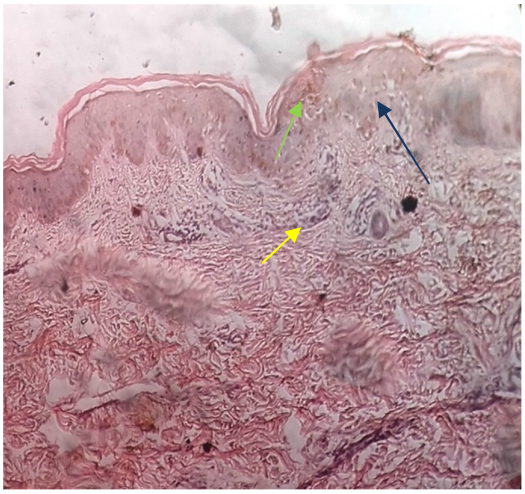
Steven Johnson syndrome

(Epidermal detachment <10% BSA)





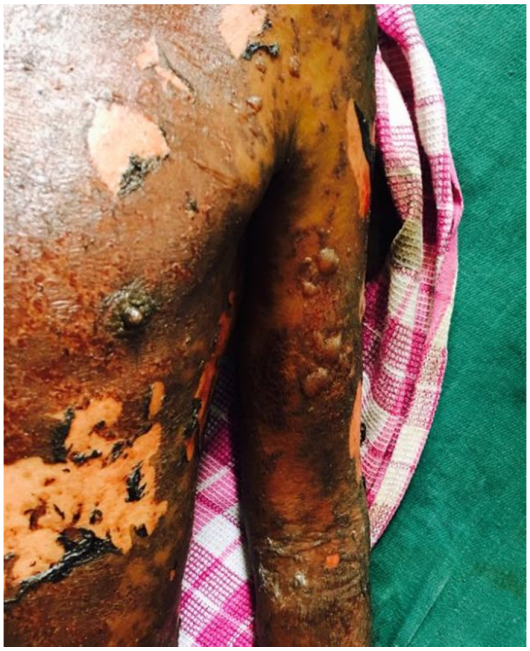


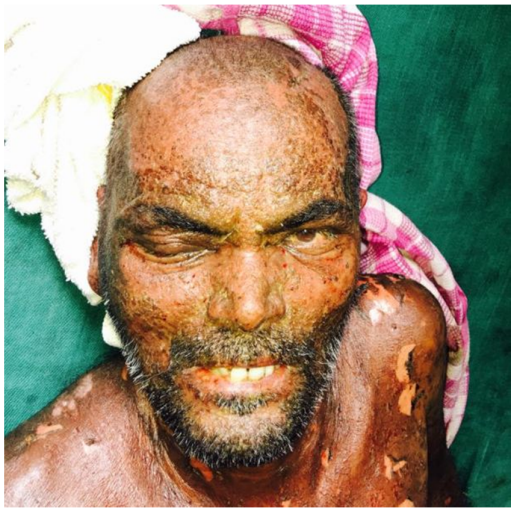


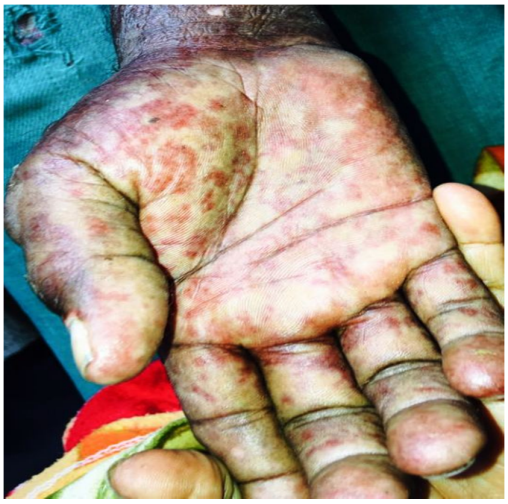
Histopathology of SJS shows - spongiosis & basal cell degeneration (blue arrow), necrotic keratinocytes (green arrow) and lymphocytic infiltrate (yellow arrow).

IMAGE 5

Toxic epidermal Necrolysis (TEN)



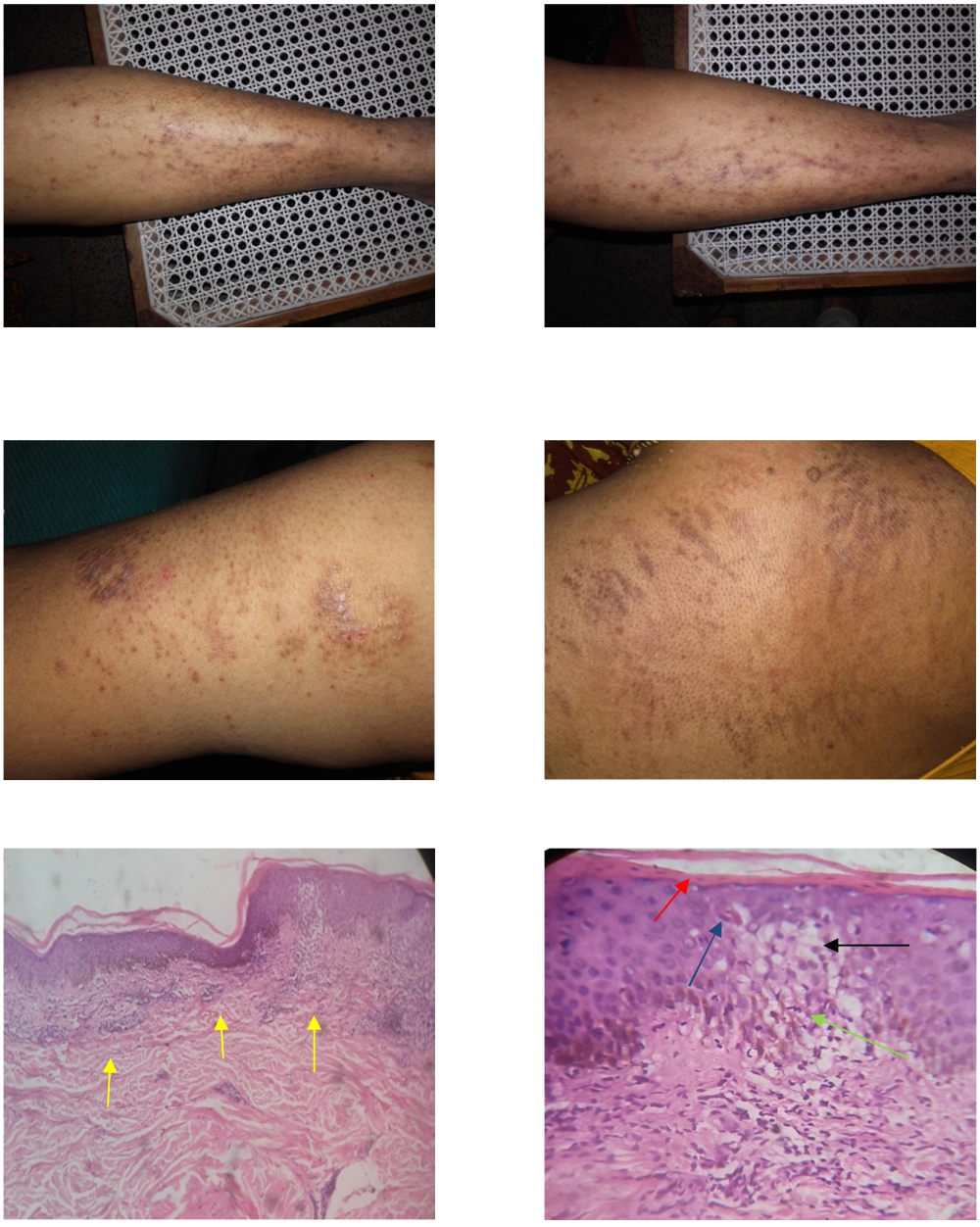




Epidermal detachment involving >30 % BSA & mucosal involvement

IMAGE 6

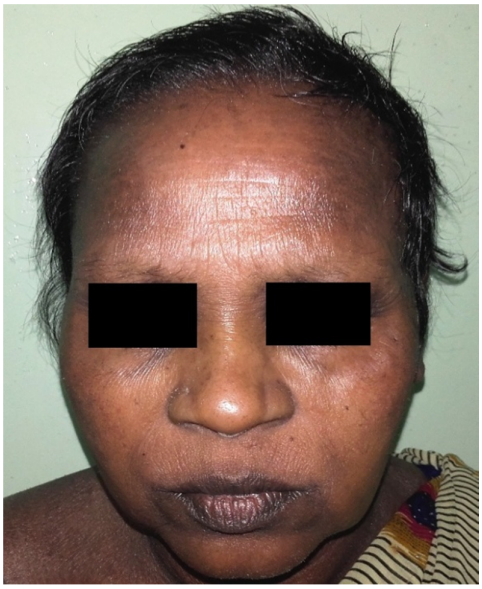
Drug induced lichenoid eruption

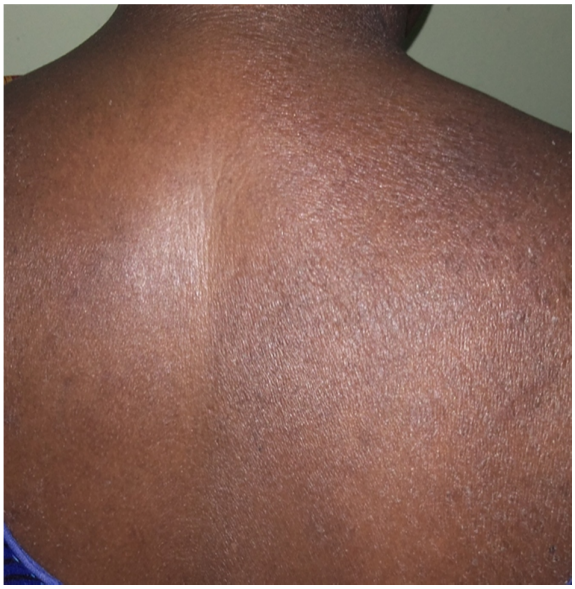


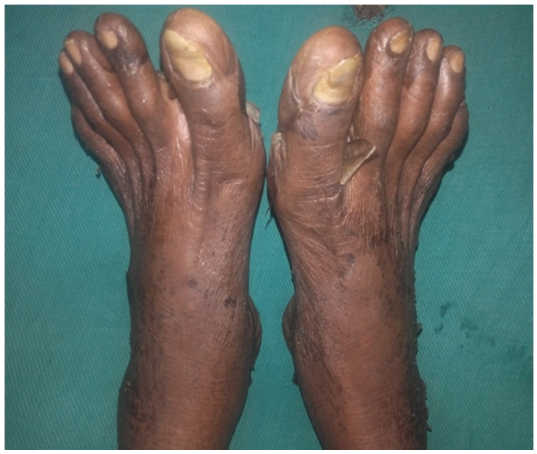
HPE of the lesions show – parakeratosis (orange arrow), spongiosis (black arrow), basal cell degeneration (green arrow), colloid bodies (blue arrow) & band like inflammatory infiltrate in the upper dermis (yellow arrows)

IMAGE 7

Erythroderma







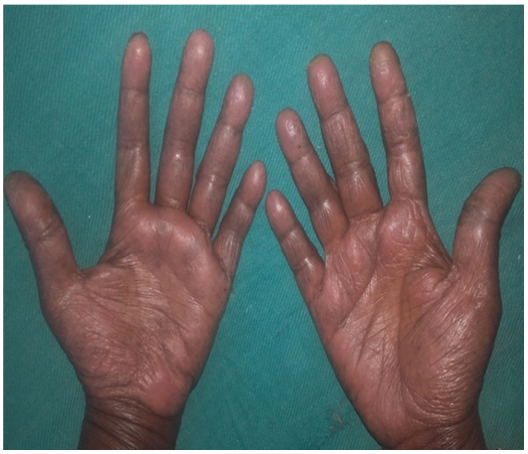
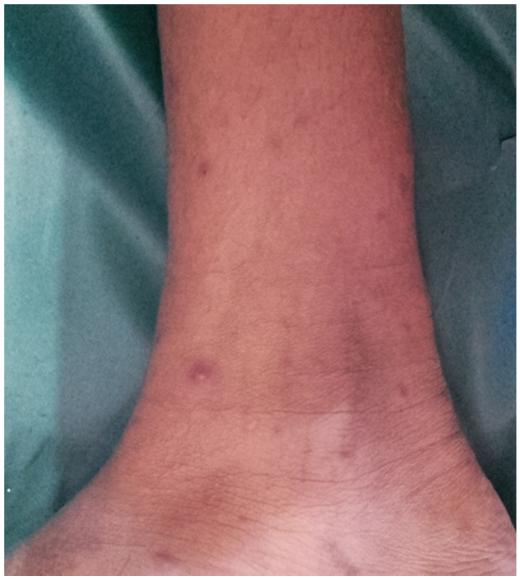
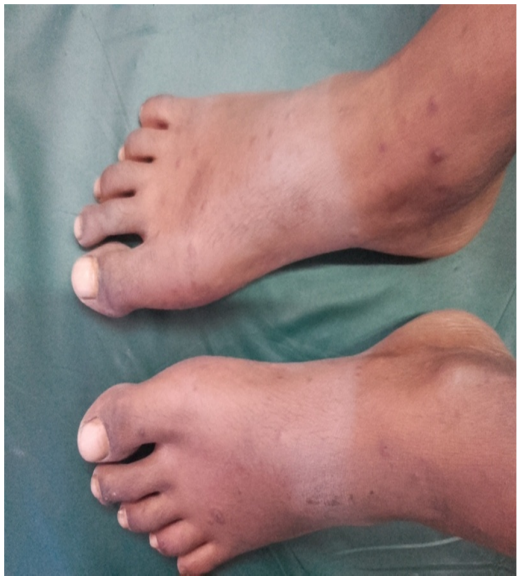
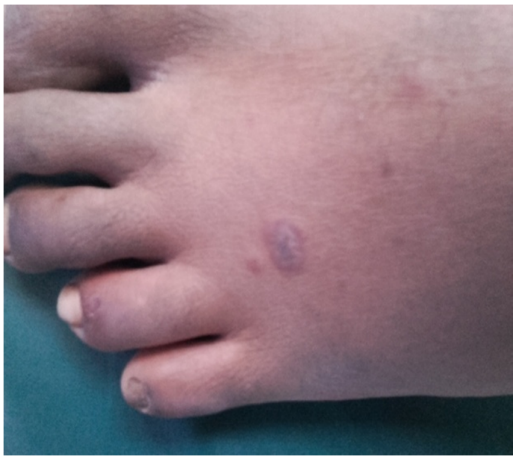


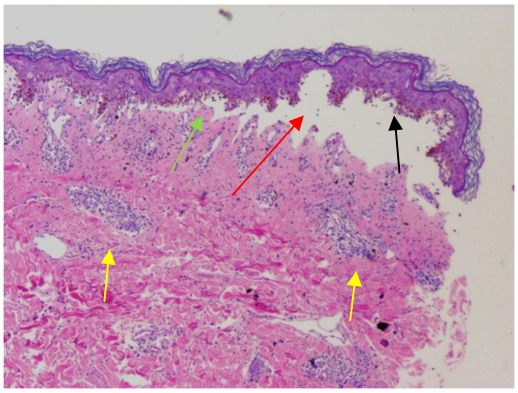
IMAGE 8

Erythema multiforme









HPE of the lesion shows – basal cell degeneration (green arrow), necrotic keratinocytes (black arrow), subepidermal split (red arrow) in cases of bullous emf & perivascular infiltrate (yellow arrows).

Discussion

DISCUSSION

Adverse cutaneous drug reactions (ACDR) are one of the underestimated causes of significant morbidity in both hospitalized and outpatients. In patients with severe cutaneous adverse drug reactions , the mortality is high if not diagnosed early and managed appropriately. Various studies had been conducted over the years to assess the incidence, various clinical presentations and common offending drugs.

The incidence of adverse cutaneous drug reactions in our study population was 0.949 per 1000 person years in patients above 12 years of age. In a study conducted by Chatterjee et al , the incidence of adverse cutaneous drug reactions was found to be 2.6 per 1000 in a dermatology outpatient clinic[128]. In another study conducted by Abanti S et al , the primary incidence of ACDR in a dermatology outpatient setting was found to be 2.05 per 1000[39]. The decreased incidence seen in our study can be attributed to the fact that most of the patients with milder forms of drug reactions do not report to us, and are treated in private clinics around our study centre.

The mean age of our study population was 39.33(± 20.33, 13 – 75 years). This is in concordance with the studies conducted by Pudukadan et al and Abanti S et al , where the mean age has been 37.06 (± 30.12, 9 – 75 years) and 33.8 (± 17.19, 4 – 82 years) respectively[37,39] . 55 % of our patients were in the age group of 12 – 40 years, which was in concordance to the studies conducted by Pudukadan et al , Abanti S et al and Patel Raksha M et al where 47 / 90 patients

were in the age group of 20 – 39 years, 52.80% of patients in the 16 – 35 years age group and 52% in the 11 – 40 years group respectively[37,39,129].

Among our study population, 20 were males and 16 were females with a ratio of 1.25 : 1. According to Pudukadan et al the male to female was 0.87 : 1 and it was 1.04 : 1 in a study conducted by Anjaneyan G et al[129,130]. In the studies conducted by Abanti S et al and Patel Raksha M et al, the male to female ratio had been 0.95 : 1 and 1.27 : 1 respectively. The male to female ratio in our study is in concordance with the study conducted by Patel Raksha M et al but the slight difference from other studies can be attributed to the geographical variations in the study population.

Table 7.1 : Male to female ratio in adverse cutaneous drug reaction

Study	**Male to female ratio**
Pudukadan et al (2001 – 03)	0.87 : 1
Patel Raksha M et al (1997 – 2006)	1.27 : 1
Abanti S et al (2008 – 09)	0.95 : 1
Anjaneyan G et al (2010 – 11)	1.04 : 1
Our study	**1.25 : 1**

The commonest clinical presentation in our study was fixed drug eruption (FDE) seen in 10/36 patients, followed by maculopapular rash in 8/36, SJS/TEN in 7/36, acneiform eruptions in 4/36, erythema multiforme & erythroderma in 2 patints each and lichenoid drug eruption, DRESS and SJS/DRESS overlap in 1 patient each. The percentage of various drug eruptions in studies conducted by Pudukadan et al, Abanti S et al, Anjaneyan et al, Patel Raksha M et al and

Luciane et al has been compared in table 6.2[131]. The various clinical presentation of adverse cutaneous drug reactions in our study is in concordance with the study conducted by Pudukadan et al and Abanti S et al.

Table 7.2 : Percentage of various drug eruptions in other studies

Studies	FDE	Maculopapular rash	SJS/TEN	EMF	Acneiform eruption	Erythroderma	Lichenoid eruption	DRESS
Pudukadan et al	31.1	12.2	18.8	6.7	3.3	3.3	4.4	-
Abanti S et al	24.5	30.18	24.5	-	-	7.54	-	-
Anjaneyan G et al	23	25	4	1	10	-	-	2
Patel raksha M et al	30.5	18	4	1	2.5	2.5	-	-
Luciane F F Botelho et al	-	37.6	12.8	-	-	-	-	14.5
Our study	28	22	19	6	11	6	3	3

One patient out of the 36, presented with generalized bullous FDE, and gave history of drug hypersensitivity reaction in the family. Her father had FDE but details were not available regarding the offending drug . There was no such report of occurrence of same type of drug eruption in the family on reviewing the previous studies.

In our study the commonest drugs causing adverse cutaneous reactions were NSAIDs (33%) followed by anticonvulsants (25%) and antibiotics (19%). The causative agent was unidentifiable in 5% of patients as they were under multiple medications and unknown in 9% of patients, as they have had over the counter medications and were unaware of the drug details. In Pudukadan et al study cotrimoxazole (22.2%) was the commonest offending drug, followed by dapsone (17.8%), anticonvulsants (14.5%) and NSAIDs (12.1%). In the study by Abanti S et al antibiotics constituted 50.9% , followed by anticonvulsants and NSAIDs each constituting 11.3 % [37,39]. In the study conducted by Luciane F F Botelho et al, 23.9 % of the reactions were due to anticonvulsants, 22.2% due to antibiotics and 29 % patients were taking multiple medications[131].

Severe cutaneous drug reactions in our study were caused most commonly by antiepileptics (55%), followed by antibiotics and NSAIDs each constituting 18%. Antibiotics (59%) were the commonest cause, followed by anticonvulsants (26%) and NSAIDs (3.8%) for SCAR in Pudukadan et al study. The slight discordance in the causative agents between the studies can be attributed to the small sample size in our study.

Out of the 36 patients in our study, 29 (81%) patients had developed reactions to physician prescribed drugs and 7 (19%) patients due to over the counter (OTC) medications. This is in concordance with the study by Abanti S et al where physician prescribed drugs constituted 88.7 % and OTC drugs 11.3%.

Cutaneous drug reactions due to OTC drugs constitutes a significant proportion and steps should be taken to prevent patients going for OTC medications by proper counselling of patients and strict rules to be laid down for pharmacies regarding drug distribution.

Table 7.3 : Commonly incriminated drugs in drug eruptions

Study	Anticonvulsants	Antibiotics	NSAIDs	Multiple drugs
Pudukadan et al	14.5%	41%	12.1%	-
Abanti S et al	11.3%	50.9%	11.3%	-
Luciane F F Botelho et al	23.9%	22.2%	-	29%
Our study	***25%***	***19%***	***33%***	***5%***

Most common presenting symptom was itching (64%), followed by skin rashes (61%), burning sensation & pain in the skin (22.2%) and fluid filled lesions (16.7%). This is in concordance with the study conducted by Anjaneyan et al where itching (37%) was the commonest presentation, followed by rash (18%) and swelling (15%).

Mean latency period in our study population was 17.90 ± 46.06 days (range, 1 – 180 days), in which 2 patients with acneiform eruptions, 1 with exanthem and 1 patient with lichenoid eruption had a latency period ranging from 4 months to 6 months and patients with FDE had the shortest latency of 4 hours . This is in concordance with Pudukadan et al study in which the mean latency

period was 14.01 days (1 – 172 days), but with a slight difference from the study by Abanti S et al where the mean latency period was 6.2 days (1 – 43 days)[37,39].

Table 7.4 :Mean latency period between drug intake and onset of drug eruption

Study	Mean latency period (in days)	Range (in days)
Pudukadan et al	14.01	1 - 172
Abanti S et al	6.2	1 - 43
Our study	17.90	1 - 180

Among the co morbidities associated with drug reactions, CNS disorders (16.6) was the commonest, followed by SHT (11%), diabetes, CVS disorders, RS disorders, malignancies & OA knee each constituting 5%. No associated co morbidities was seen in 47% of the patients. This is concordance with the study conducted by Pudukadan et al where a previous systemic illness was present in 48.09% of patients.

Skin lesions were involving < 10% body surface area (BSA) in 22% , 10 – 30 % BSA in 34%, 31 – 90 % BSA in 36% and >90 % BSA in 8% of patients in our study. In Pudukadan et al study 46% , 16%, 34% and 4% patients have had < 10%, 10 – 30 %, 31- 90 % and > 90 % BSA involvement respectively. In Anjaneyan et al study 38 %, 44% and 18% of patients have had 0 -25%, 26 – 75 % and > 76 % BSA respectively . The results of BSA involvement of skin lesions in our study is in concordance with other studies.

Table 7.5 : Body surface area involvement (BSA)

Study	< 10 %	10– 30 %	31– 90 %	> 90%
Pudukadan et al	46%	16%	34%	4%
Our study	22%	34%	36%	8%

Regarding absolute eosinophil counts (AEC), among our study patients 19/36 (53%) patients had high AEC (>440 cells/cumm). 9/11 (82%) patients with SCAR had AEC > 440, which was statistically significant . 8/11 (73%) patients with SCAR had AEC > 1000, with highest AEC of 2960 was seen in a patient with DRESS. This is in concordance to Pudukadan et al study where 42.2 % of patients had AEC > 500, and the study by Anjaneyan et al in which 15 % of patients had high AEC and 3/7 patients with SCAR have had AEC > 500. According to American Academy of Dermatology, a high eosinophil count of more than 1000 cells / cumm indicates severe cutaneous drug reactions[132]. In a study by Ramagosa et al , high eosinophil counts was found to have little diagnostic value in adverse cutaneous drug reations[133]. Though high AEC is of little diagnostic value it might have a prognostic significance in SCAR and further studies are needed to validate it.

Table 7.6 : Absolute eosinophil count (AEC)

Study	AEC > 440 in total study patients	In Benign reactions	In Severe reactions
Pudukadan et al	42.2%	-	-
Anjaneyan et al	15%	-	43%
Our study	53%	40%	82%

Elevated liver parameters like raised SGOT, SGPT and ALP was seen in 25 % of our study patients mostly in those with severe cutaneous drug reactions, and abnormalities in other biochemical parameters were seen in 19 % of patients. 23.3% of patients have had liver function abnormalities and 10 % have had other abnormal biochemical values in the study by Pudukadan et al. The results of our study is in concordance with the previous studies.

Table 7.7 : Abnormalities in biochemical parameters in study patients

Study	Elevated liver enzymes	Abnormality in other biochemical parameters
Pudukadan et al	23.3%	10%
Our study	25%	19%

By histopathological examination (HPE) the most common observed feature in our patients was dermal lymphoytic infiltrate, followed by spongiosis, necrotic keratinocytes, basal cell degeneration and dermal edema. Pigment incontinence and melanophages was predominantly seen in cases of FDE.

Eosinophils in the dermal infiltrate was seen in most of the cases except for cases of acneiform eruptions where neutrophils predominated along with lymphocytesand follicular plugging. Basal cell degeneration, necrotic keratinocytes, subepidermal bulla and lymphoytic infiltrate were the common HPE findings in cases of DRESS, SJS, TEN and bullous FDE. In a study by Weinborn M et al, spongiosis, dermal edema, basal cell degeneration, lymphocytic infiltrate and rare necrotic keratinocytes were seen in cases of DRESS and necrotic keratinocytes were absent in cases of maculopapular rash[134]. In our study necrotic keratinocytes were seen in 2 out of 8 cases of maculopapular rash and in all the cases of bullous FDE, SJS, TEN and DRESS. HPE is not a specific diagnostic modality in cases of drug reactions and there were not much studies conducted comparing the various histopathological featurs in drug reactions. But it would be helpful in cases where the diagnosis is in doubt, such as maculopapular rash and DRESS.

Table 7.8 : Histopathological features of various clinical presentation of ACDR in our study patients

Clinical presentation	Commonest HPE features seen in our study
Acneiform eruptions	Hyperkeratosis, follicular plugging, follicular & perifollicular lymphocytic and neutrophilic infiltrate
DRESS	Spongiosis, necrotic keratinocytes, basal cell degeneration, perivascular lymphocytic infiltrate
EMF	Spongiosis, necrotic keratinocytes, perivascular and interstitial eosinophilic & lymphocytic infiltrate
Erythroderma	Flaky hyperkeratosis, spongiosis, dermal edema, perivascular and interstitial neutrophilic & lymphocytic infiltrate
Exanthem	Hyperkeratosis, spongiosis, perivascular lymphocytic infiltrate with eosinophils & rarely necrotic keratinocytes
FDE	Spongiosis, necrotic keratinocytes, basal cell degeneration, perivascular and interstitial lymphocytic infiltrate, pigment incontinence and dermal melanophages
Lichenoid reaction	Hyperkeratosis, basal cell degeneration, few colloid bodies and eosinophils, band like upper dermal inflammatory infiltrate.
SJS/TEN	Spongiosis, necrotic keratinocytes, basal cell degeneration, sub epidermal bulla, perivascular and interstitial lymphocytic & eosinophilic infiltrate

Limitations of the Study

LIMITATIONS OF THE STUDY

1. Sample size in our study was small. Only 36 patients presented to our department during the study period.
2. Children less than 12 years present initially to Institute of child health (ICH), Egmore, Chennai. Patients are sent here for opinion, but further follow up is not available and hence we were not able to include them in the study.
3. Milder form of adverse cutaneous drug reactions mimics some of the common dermatoses and are misdiagnosed and treated as dermatological disorders in private clinics and those patients don't present to us.
4. Specific investigations to diagnose the causative drug in cases where the patient is on polypharmacy are not available, apart from oral challenge test which pose a significant risk to the patients.
5. Histopathological examination of lesional skin which is diagnostic in most of the dermatological disorders doesn't have a high predictive value in cases of adverse cutaneous drug reactions.

Conclusion

CONCLUSION

In a clinico pathological study of adverse cutaneous drug reactions conducted in our Department of Dermatology, Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai during the period of November 2016 to September 2017, in a total of 36 patients,

1. Males were more commonly affected than females in a ratio of 1.25:1.
2. Mean age group of the study population was 39.33 years, with majority of patients in the 2^{nd}, 3^{rd} and 7^{th} decade.
3. Itching was the most common presenting complaint (64%), followed by burning sensation and scaling.
4. 69% of patients presented with benign drug eruptions and 31% of patients presented with severe cutaneous adverse reactions.
5. Fixed drug eruption (FDE) was the commonest benign cutaneous adverse reaction, seen in 28% of the patients.
6. Non steroidal anti inflammatory drugs (NSAIDs) (33%) were the most common offending drug followed by anticonvulsants (25%) and antibiotics (17%).
7. Steven Johnson syndrome / Toxic epidermal necrolysis (SJS/TEN) was the most common severe cutaneous adverse drug reaction (19%) and anticonvulsants were the commonest cause of severe cutaneous adverse drug reactions (63.5%).

8. Elevated absolute eosinophil count of more than 1000 cells / mm^3 was seen in 82% of patients with severe cutaneous drug reactions on admission.
9. Abnormalities in biochemical parameters were seen predominantly in patients with severe cutaneous adverse drug reactions (SCAR), with elevated liver enzymes (30.5%) being the most common abnormality.
10. On histopathological examination of skin lesions, spongiosis and presence of few necrotic keratinocytes were the commonest finding, with basal cell degeneration and extensive keratinocyte necrosis being seen mostly in patients with severe cutaneous adverse drug reactions.
11. One female patient in our study presented with history of similar drug reaction in her family.

Adverse cutaneous drug reactions are a cause of significant morbidity and mortality in cases of SCAR, in both outpatients and hospitalized patients. Anticonvulsants are the commonest offending drugs in severe cutaneous drug reactions. Hence the treating physician should obtain a detailed history regarding previous drug reactions, exercise caution in prescribing such medications and should have high index of suspicion to diagnose these cases early which may be life saving to the patient.

High absolute eosinophil count may have prognostic significance in cases of severe cutaneous drug reactions , though it not diagnostic of such an event. Significant number of patients with cutaneous drug reactions, especially those with severe reactions have elevated liver enzymes and abnormalities in other

biochemical parameters, the nature of which will be helpful in assessing the severity of the disease.

Histopathological examination of skin, though it doesn't show any specific feature pertaining to any of the drug reaction, will be helpful in differentiating cases of drug reaction from other dermatoses which has features similar to drug reaction, and are difficult to diagnose by clinical examination alone.

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Annexures

ABBREVIATIONS

ACDR	–	Adverse cutaneous drug reaction
ADR	–	Adverse drug reaction
AGEP	–	Acute generalized exanthematous pustulosis
AIDS	–	Aquired immune deficiency syndrome
ANA	–	Anti nuclear antibodies
DIF	–	Direct immunofluoroscence
DRESS	–	Drug reaction with eosinophilia and systemic symptoms
EGFR	–	Epidermal growth factor receptor
FDA	–	Food and drug administration
FDE	–	Fixed drug eruption
GBFDE	–	Generalised bullous fixed drug eruption
GMCSF	–	Granulocyte monocyte colony stimulating factor
HLA	–	Human leucocyte antigen
ICAM	–	Intercellular adhesion molecule
IPC	–	Indian pharmacopoeia commission
LE	–	Lupus erythematosus
MHC	–	Major histocompatibility complex
NCC	–	National co ordination centre
NSAIDS	–	Non steroidal anti inflammatory drugs
PCR	–	Polymerase chain reaction
PvPI	–	Pharmaco vigilance programme of India
RAST	–	Radio allergosorbent assay
SDRIFE	–	Symmetrical drug related intertriginous and flexural exanthem
SJS/TEN	–	Steven Johnson syndrome / Toxic epidermal necrolysis
SSLI	–	Serum sickness like illness
TCR	–	T cell receptor
TLR	–	Toll like receptor

Master Chart

	History														Past history											General examination										Dermatological examination														Hematological parameters								Diagnosis	Offending Drug
	Patient	Age (in years)	Sex	Rashes	Annular lesions	Fluid filled lesions	Itching	Scaling	Puffiness of face	Pain over the lesions	Treatment	Native drug	Latency (in days)	Systemic Hypertension	Diabetes mellitus	Coronary artery disease	Seizures	Bronchial asthma	Malignancy	Others	Recent drug change	Previous Drug reaction	Addiction	Drug reaction in family	Pallor	Clubbing	Cyanosis	Lymphadenopathy	Jaundice	pedal edema	PR (per minute)	BP (mm Hg)	Temp (℉ F)	Maculopapular rash	Annular lesions	Purpura	Target lesions	Vesicles/Bulla	% BSA involvement	Oral mucosa	Genital mucosa	Conjunctival	Scalp/Hair	Nails	Palms/Soles	Hemoglobin (in gm/dl)	WBC (* 1000 cells/cumm)	Differential count (Ne, L, E)	Platelets (*1,00,000 cells / cumm	ESR (mm in 1 hour)	AEC (cells / cumm)	RBC	WBC	PLT		
1	P1	55	F	Y	N	N	Y	Y	Y	N	N	N	7	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	90	136/80	n	Y	N	N	N	N	90	N	N	N	n	n	S	12.4	7.6	52,35,13	1.85	12	760	n	n	Ad	Exanthem	NSAID
2	P2	17	M	N	Y	N	Y	N	N	N	N	N	11	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	90	100/70	n	Y	N	N	Y	N	<10	N	N	N	n	n	n	12.9	6.9	70,21,9	2.74	50	421	n	n	Ad	EMF	Phenytoin
3	P3	29	F	Y	N	N	N	N	N	N	N	N	180	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	70	100/60	n	Y	N	N	N	N	20	N	N	N	n	n	n	8.8	5.4	72,24,4	2.11	48	356	Mi,H	n	Ad	Acne . Erup	OCP
4	P4	50	F	Y	N	N	Y	N	N	N	N	N	120	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	90	146/100	n	Y	N	N	N	N	30	N	N	N	n	n	n	11.4	9.1	70,26,4	1.64	10	350	n	n	Ad	Liche. Derm	Thiazides
5	P5	40	M	Y	N	N	Y	N	N	N	N	N	150	N	N	N	N	N	Y	N	N	N	Y	N	Y	N	N	N	N	N	80	100/60	100	Y	N	N	N	N	80	Y	N	N	n	n	n	11.2	4.7	57,37,6	1.3	10	256	Mi,H	D	Ad	Exanthem	CTP drug/Phenytoin
6	P6	65	M	N	Y	N	N	N	N	N	N	N	0.5	Y	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	80	130/90	n	N	Y	N	N	Y	10	N	N	N	n	n	n	13.5	7.1	52,35,13	2.72	14	379	n	n	Ad	Bullous FDE	NSAID
7	P7	21	M	Y	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N	Y	100	110/76	101	Y	N	N	N	N	<10	Y	Y	N	n	n	n	12	10	50,12,38	3.51	38	2790	n	Eo	Ad	DRESS/SJS	NSAID
8	P8	14	F	N	Y	Y	N	N	N	N	Y	N	0.5	N	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	100	100/60	n	Y	Y	N	N	Y	50	N	N	N	n	n	n	10.4	12	56,31,13	1.71	40	740	Mi,H	Eo	Ad	GBFDE	NSAID
9	P9	18	F	Y	N	N	Y	N	N	N	N	N	20	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	100	100/70	n	Y	N	Y	Y	N	<10	Y	Y	N	n	n	TL	10.9	8.8	64,20,16	1.83	20	1084	Mi,H	n	Ad	SJS	Carbamazepine
10	P1	61	F	Y	N	N	Y	Y	Y	N	N	N	5	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	96	130/86	100	Y	N	N	N	N	100	N	N	N	n	n	S	12.7	12	63,24,13	3.72	72	1160	n	n	Ad	Erythroderma	Cephalosporin/NSAID
11	P11	70	M	Y	N	Y	N	N	N	N	N	N	17	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	86	120/70	n	N	Y	N	N	Y	30	Y	Y	N	n	n	n	13.5	7.3	46,28,26	1	60	971	n	Eo	Ad	Bullous FDE	NSAID
12	P12	22	M	Y	N	N	Y	N	N	N	N	N	60	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	68	100/70	n	Y	N	N	N	N	10	N	N	N	n	n	n	14.1	8.3	60,34,6	4.07	30	270	n	n	Ad	Acne . Erup	Topical steroids
13	P13	22	F	N	Y	N	N	N	N	N	N	N	0.5	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	76	120/84	n	N	Y	N	N	N	<10	N	N	N	n	n	n	10.9	9.1	71,22,7	2.4	17	240	n	n	Ad	FDE	Paracetamol
14	P14	52	M	Y	N	N	Y	Y	N	N	N	N	4	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	100	120/76	n	Y	N	N	N	N	80	N	N	N	n	n	S	14.4	5.4	60,27,13	1.42	44	420	n	n	Ad	Exanthem	Unknown
15	P15	35	M	Y	N	N	Y	N	N	N	N	N	60	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	90	150/100	n	Y	N	N	N	N	15	N	N	N	n	n	n	13.7	6.8	60,34,4	3.4	10	172	n	n	Ad	Acne . Erup	Systemic Steroids
16	P16	40	F	Y	N	N	Y	N	N	Y	N	N	25	N	N	N	Y	N	N	N	Y	N	Y	N	Y	N	N	N	N	Y	90	140/70	n	Y	N	Y	N	N	10	Y	Y	Y	n	n	P	14	16	75,15,10	0.79	80	1170	n	I,Eo	D	SJS	Carbamazepine
17	P17	75	M	N	Y	Y	Y	N	N	N	N	N	0.3	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y	76	100/60	n	N	Y	N	N	Y	<10	N	N	N	n	n	n	9.4	11	75,10,15	1.47	26	1500	Mi,H	Eo	Ad	Bullous FDE	Ciprofloxacin
18	P18	55	F	N	N	Y	N	N	N	Y	N	N	12	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	N	100	100/60	100	N	Y	N	Y	Y	<10	Y	N	Y	n	n	P	9.6	2.8	61,22,17	1.93	41	597	Mi,H	D	D	SJS	NSAID
19	P19	62	M	N	Y	N	Y	N	N	N	N	N	0.3	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	80	150/100	n	N	Y	N	N	N	<10	N	N	N	n	n	H A	14.4	7.4	70,23,7	4.14	15	410	n	n	Ad	FDE	NSAID
20	P20	28	M	Y	N	N	Y	N	N	N	Y	Y	14	N	N	N	Y	N	N	N	Y	N	Y	N	N	N	N	N	N	Y	100	110/80	101	Y	N	N	N	N	100	Y	N	N	S	BI	S	13.2	12	54,36,10	1.75	38	1100	n	n	Ad	Erythroderma	Carbamazepine
21	P21	45	M	N	Y	N	N	N	N	N	N	N	1	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	80	150/70	n	N	Y	N	N	N	10	N	N	N	n	n	n	14.2	8.4	70,22,8	4.22	24	350	n	n	Ad	FDE	Ciprofloxacin
22	P22	50	M	N	Y	N	N	N	N	N	N	N	0.5	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	N	86	116/86	n	N	Y	N	N	N	<10	N	N	N	n	n	H A	11.4	6.1	64,32,4	2.65	12	216	n	n	Ad	FDE	paracetamol

	History													Past history											General examination								Dermatological examination														Hematological parameters								Diagnosis	Offending Drug
	Patient	Age (in years)	Sex	Rashes	Annular lesions	Fluid filled lesions	Itching	Scaling	Puffiness of face	Pain over the lesions	Treatment	Native drug	Latency (in days)	Systemic Hypertension	Diabetes mellitus	Coronary artery disease	Seizures	Bronchial asthma	Malignancy	Others	Recent drug change	Previous Drug reaction	Addiction	Drug reaction in family	Pallor	Clubbing	Cyanosis	Lymphadenopathy	Jaundice	pedal edema	PR (per minute)	BP (mm Hg)	Temp (℉ F)	Maculopapular rash	Annular lesions	Purpura	Target lesions	Vesicles/Bulla	% BSA involvement	Oral mucosa	Genital mucosa	Conjunctival	Scalp/Hair	Nails	Palms/Soles	Hemoglobin (in gm/dl)	WBC (* 1000 cells/cumm)	Differential count (Ne, L, E)	Platelets (*1,00,000 cells / cumm	ESR (mm in 1 hour)	AEC (cells / cumm)	RBC	WBC	PLT		
23	P23	13	F	Y	N	N	Y	N	N	N	N	N	6	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	100	90/60	n	Y	N	N	N	N	100	N	N	N	n	n	S	12.1	9.8	60,27,13	2.71	40	980	n	n	Ad	Exanthem	Sodium valproate
24	P24	35	F	Y	N	N	N	N	N	Y	Y	N	3	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	110	100/60	101	N	N	Y	Y	Y	>50	Y	Y	Y	n	n	P	10.8	3.9	71,25,4	2.5	30	170	n	D	Ad	TEN	Unknown
25	P25	51	M	Y	N	N	Y	N	N	N	Y	N	3	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	80	116/74	n	Y	N	N	N	N	70-80	N	N	N	n	n	n	14	7.6	67,22,11	1.72	24	767	n	n	Ad	Exanthem	Ciprofloxacin
26	P26	20	F	Y	N	N	Y	N	N	N	N	N	30	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	76	90/60	n	Y	N	N	N	N	70-80	N	N	N	n	n	n	10.4	8.1	65,30,5	2.52	20	396	Mi,H	n	Ad	Exanthem	Phenytoin
27	P27	13	M	N	Y	N	Y	N	N	N	N	N	2	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	70	90/60	n	Y	N	N	Y	N	<10	N	N	N	n	n	n	10.8	8.8	67,30,3	2.42		272	Mi,H	n	Ad	EMF	NSAID
28	P28	16	F	Y	N	N	Y	N	N	N	Y	N	60	N	N	N	Y	N	N	N	Y	N	N	N	Y	N	N	Y	Y	Y	110	80/60	102	Y	N	N	N	N	90	Y	N	N	n	n	S	10	22	70,14,16	1	70	2960	Mi,H	I,Eo	D	DRESS	Phenytoin/Lamotrigine
29	P29	21	M	Y	N	N	Y	Y	Y	N	N	N	1	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	96	100/70	103	Y	N	N	N	N	80	N	N	N	n	n	S	11.1	41	89,11	1.1	65	110	n	Ne	Ad	Exanthem	Arterolane+Piperaquine
30	P30	27	M	Y	N	N	Y	N	N	Y	N	N	5	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	N	N	100	100/66	100	Y	N	Y	Y	Y	10	Y	N	Y	n	n	P	13.4	14	59,22,19	1.22	50	1420	n	n	Ad	SJS	Cotrimoxazole
31	P31	20	M	Y	N	N	N	Y	N	N	N	N	120	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	N	N	78	110/79	n	Y	N	N	N	N	20	N	N	N	n	n	n	10	5	69,16,15	1.9	24	760	Mi,H	n	Ad	Acne . Erup	CTP drug/Steroids
32	P32	66	F	N	Y	Y	N	N	N	N	N	N	0.5	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	89	146/96	100	Y	Y	N	N	Y	<10	Y	N	N	n	n	H A	9.2	9.3	85,7,8	0.84	36	550	Mi,H	n	D	Bullous FDE	Unknown
33	P33	61	M	Y	N	N	N	N	N	Y	Y	N	30	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N	Y	110	90/60	102	Y	N	Y	N	Y	50	Y	N	Y	n	n	P	8.8	18	74,18,8	2.47	48	1192	Mi,H	Eo	Ad	TEN	Phenytoin
34	P34	68	F	N	Y	Y	Y	N	N	N	N	N	0.3	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	85	136/70	n	N	Y	N	N	Y	10	N	N	N	n	n	n	13.4	11	62,30,8	4.75	42	879	n	n	Ad	Bullous FDE	NSAID
35	P35	65	F	Y	N	N	Y	Y	Y	N	N	N	2	N	N	N	N	N	N		N	N	N	N	Y	N	N	N	N	N	96	120/70	n	Y	N	N	N	N	90	N	N	N	n	n	S	8.3	13	66,26,8	3.67	31	1024	Mi,H	n	Ad	Exanthem	Paracetamol
36	P36	14	M	Y	N	N	Y	N	N	Y	Y	N	14	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	100	80/50	100	Y	N	Y	N	Y	20-30	Y	N	Y	n	n	P	8.8	5.5	70,26,4	3.56	30	310	Mi,H	n	Ad	SJS/TEN	Carbamazepine

				Biochemical parameters																Others			Histopathological examination												Diagnosis	Offending Drug
	Patient	Age (in years)	Sex	Urine albumin	Urin sugar	RBS (mg /dl)	Total bilirubin (mg /dl)	Direct bilirubin (mg/dl)	SGOT (IU / L)	SGPT (IU / L)	ALP (IU / L)	Total protein (gm /dl)	Albumin (gm / dl)	Blood Urea (mg / dl)	Serum Creatinine (mg / dl)	Na+ (mEq / L)	K+ (mEq / L)	Cl- (mEq / L)	HCO3- (mEq / L)	VCTC	VDRL	USG abd	Hyperkeratosis	Parakeratosis	Spongiosis	Acanthosis	Necrotic keratinoytes	Basal cell degeneration	Pattern of infiltrate	Inflammatory Cells	Vesicle / Bulla	Dermal Edema	Pigment incontinence	Melanophages		
1	P1	55	F	T	Nil	142	1	0.1	17	22	94	6.4	3.8	31	0.7	130	35			Ne	NR	n	N	N	Y	Y	N	N	PV,INT	L,E	N	N	N	N	Exanthem	NSAID
2	P2	17	M	Nil	Nil	74	0.9	0.3	42	31	179	7	4	21	0.6	135	5			Ne	NR	n	N	N	Y	N	Y	N	PV,INT	L,E	N	Y	N	N	EMF	Phenytoin
3	P3	29	F	Nil	Nil	116	0.6	0.1	21	19	87	6.2	4	29	0.7	139	4.6			Ne	NR	n	Y	N	N	N	Y	N	F ,PF	N,L	N	N	N	N	Acne . Erup	OCP
4	P4	50	F	Nil	Nil	172	1	0.4	39	42	112	6.4	4.2	40	0.9	136	3.9			Ne	NR	FL	Y	Y	Y	N	N	`	BL	L,E	N	N	Y	Y	Liche. Derm	Thiazides
5	P5	40	M	T	Nil	89	0.6	0.1	18	31	123	6.9	3.7	15	0.7	129	3.4			Ne	NR	n	N	N	Y	Y	N	N	PV,INT	L,E	N	N	N	N	Exanthem	CTP drug/Phenytoin
6	P6	65	M	Nil	Nil	131	1	0.4	27	22	89	6.4	3.8	42	1.2	135	3.5			Ne	NR	n	N	N	Y	N	Y	Y	BL	L,E	Y	N	Y	Y	Bullous FDE	NSAID
7	P7	21	M	Nil	Nil	107	0.8	0.5	38	40	151	5.4	3.1	18	0.8	137	3.8	96		Ne	NR	n	N	N	Y	N	N	Y	PV,PA	L,PC,E	Y	Y	N	N	DRESS/SJS	NSAID
8	P8	14	F	Nil	Nil	120	1.2	0.4	40	38	194	6	3.6	30	0.7	132	4.6			Ne	NR	n	N	N	Y	N	Y	Y	PV,INT	L,E	Y	N	Y	Y	GBFDE	NSAID
9	P9	18	F	T	Nil	91	0.5	0.3	66	73	67	6.4	3.3	37	1.2	130	3.3	100		Ne	NR	n	N	N	Y	N	Y	Y	PV,INT	L,E	Y	N	Y	N	SJS	Carbamazepine
10	P1	61	F	Nil	Nil	90	0.2	0.12	22	26	145	7.9	4	18	0.8	142	4.8			Ne	NR	n	Y	N	Y	N	N	N	PV,INT	L,E	N	Y	N	N	Erythroderma	Cephalosporin/NSAID
11	P11	70	M	Nil	Nil	78	0.9	0.3	17	21	58	5.6	3	52	0.9	134	4.2	96		Ne	NR	n	N	N	Y	N	Y	Y	BL	L,E	Y	N	Y	Y	Bullous FDE	NSAID
12	P12	22	M	Nil	Nil	94	0.9	0.3	16	21	111	7.4	4.4	20	0.4	135	5.2			Ne	NR	n	Y	N	N	Y	N	N	F,PF	N,L	N	N	N	N	Acne . Erup	Topical steroids
13	P13	22	F	Nil	Nil	94	0.4	0.1	17	22	104	7.4	4.3	22	0.8	140	4.2	97		Ne	NR	n	N	N	Y	N	N	Y	PV,INT	L,E	N	N	Y	Y	FDE	Paracetamol
14	P14	52	M	Nil	Nil	144	1	0.2	41	27	86	6.2	3.6	17	0.6	140	4.5			Ne	NR	n	Y	N	Y	N	N	N	PV	L	N	N	N	N	Exanthem	Unknown
15	P15	35	M	T	Nil	172	0.7	0.2	22	27	104	6.4	4.2	32	0.8	142	3.9			Ne	NR	FL	N	N	N	N	N	N	F,PF	L,N,E	N	N	N	N	Acne . Erup	Systemic Steroids
16	P16	40	F	Nil	Nil	59	0.3	0.1	68	72	254	7.2	3	20	1.2	131	5.7	105	24	Ne	NR	n	N	N	Y	N	Y	Y	DENSE	N,L	Y	Y	N	N	SJS	Carbamazepine
17	P17	75	M	T	Nil	73	1	0.5	21	23	104	5	2	14	0.7	136	3.5	96		Ne	NR	n	N	N	N	Y	N	Y	PV,DBV	L,E	Y	N	Y	Y	Bullous FDE	Ciprofloxacin
18	P18	55	F	Nil	Nil	85	0.2	0.1	28	22	74	6.4	3.8	66	1.4	135	4	101	27	Ne	NR	n	N	N	Y	N	Y	Y	DENSE	L	Y	Y	N	N	SJS	NSAID
19	P19	62	M	Nil	Nil	132	0.4	0.1	17	12	94	7.2	4.2	37	0.9	141	4			Ne	NR	n	N	N	N	Y	N	Y	PV	L	N	N	Y	Y	FDE	NSAID
20	P20	28	M	T	Nil	88	1.2	0.4	78	69	196	5.4	2.9	34	0.6	140	3.5	90	28	Ne	NR	n	Y	Y	Y	N	N	N	PV,DBV	L	N	N	N	N	Erythroderma	Carbamazepine

				Biochemical parameters															Others			Histopathological examination												Diagnosis	Offending Drug
	Patient	Age (in years)	Sex	Urine albumin	Urin sugar	RBS (mg /dl)	Total bilirubin (mg /dl)	Direct bilirubin (mg/dl)	SGOT (IU / L)	SGPT (IU / L)	ALP (IU / L)	Total protein (gm /dl)	Albumin (gm / dl)	Blood Urea (mg / dl)	Serum Creatinine (mg / dl)	Na+ (mEq / L)	K+ (mEq / L)	Cl- (mEq / L)	HCO3- (mEq / L)	VCTC	VDRL	USG abd	Hyperkeratosis	Parakeratosis	Spongiosis	Acanthosis	Necrotic keratinoytes	Basal cell degeneration	Pattern of infiltrate	Inflammatory Cells	Vesicle / Bulla	Dermal Edema	Pigment incontinence	Melanophages		
21	P21	45	M	Nil	Nil	146	1.2	0.4	62	59	108	6.4	3.9	40	0.9	147	4			Ne	NR	n	N	N	Y	N	N	Y	PV,INT	L,E	N	N	Y	Y	FDE	Ciprofloxacin
22	P22	50	M	Nil	Nil	76	1.2	0.4	36	34	94	7	4.4	26	0.9	138	4.2	99		Ne	NR	n	N	N	Y	N	N	Y	PV,INT	L,E	N	N	Y	Y	FDE	paracetamol
23	P23	13	F	Nil	Nil	70	0.9	0.2	25	31	279	7	4	17	0.4	130	4.1			Ne	NR	n	N	N	N	N	Y	N	PV,INT	L,E	N	Y	N	N	Exanthem	Sodium valproate
24	P24	35	F	Nil	Nil	150	1.2	0.2	70	53	110	6.7	3	30	1	134	4.2	95	22	Ne	NR	FL	N	N	Y	N	Y	Y	PV	L,N,E	Y	Y	N	N	TEN	Unknown
25	P25	51	M	Nil	Nil	114	0.4	0.1	14	17	78	6.9	4.2	17	0.7	139	4.7	92		Ne	NR	n	N	N	Y	N	N	N	PV,DBV	L	N	N	N	N	Exanthem	Ciprofloxacin
26	P26	20	F	Nil	Nil	76	0.9	0.4	24	26	91	6.2	3.6	27	0.9	140	3.6	99		Ne	NR	n	N	N	Y	N	N	N	PV,INT	L	N	N	N	N	Exanthem	Phenytoin
27	P27	13	M	Nil	Nil	68	0.4	0.1	40	37	249	6.9	4.3	12	0.5	142	4.6			Ne	NR	n	N	N	Y	N	Y	N	PV,INT	L,E	N	Y	N	N	EMF	NSAID
28	P28	16	F	Nil	Nil	49	8.4	4.2	335	1296	277	4.9	2.6	61	1.1	132	4	97	25	Ne	NR	HM	Y	N	Y	N	Y	Y	PV	L,E	N	Y	N	N	DRESS	Phenytoin/Lamotrigine
29	P29	21	M	Nil	Nil	60	0.9	0.1	16	16	90	5.4	2.6	60	1.4	128	4.8	96	24	Ne	NR	HSM	N	N	Y	N	N	N	PV	N,L	N	Y	N	N	Exanthem	Arterolane+Piperaquine
30	P30	27	M	Nil	Nil	111	0.7	0.1	14	12	89	6	3.7	36	1	135	4	99	28	Ne	NR	n	N	N	Y	N	Y	Y	PV,INT	L,N,E	Y	Y	N	N	SJS	Cotrimoxazole
31	P31	20	M	T	Nil	96	0.6	0.2	16	14	58	7.3	2.6	35	1.1	130	3.9			Ne	NR	n	Y	N	N	N	N	N	F,PF	N,L	N	N	N	N	Acne . Erup	CTP drug/Steroids
32	P32	66	F	Pr	Pr	325	0.3	0.1	91	205	78	7.3	3.1	205	5.1	127	5	98	25	Ne	NR	FL	N	N	Y	N	Y	Y	INT	L,E	Y	Y	Y	Y	Bullous FDE	Unknown
33	P33	61	M	Nil	Nil	127	0.8	0.3	92	78	662	4.5	2.4	64	1.4	129	4.3	105	23	Ne	NR	n	N	N	Y	N	Y	Y	PV,INT	L,N,E	Y	Y	N	N	TEN	Phenytoin
34	P34	68	F	Nil	T	211	1.2	0.4	30	36	121	6	3.4	42	1.3	147	4.7			Ne	NR	FL	N	N	Y	N	N	Y	PV,INT	L,E	Y	N	Y	Y	Bullous FDE	NSAID
35	P35	65	F	Nil	Nil	113	0.6	0.3	24	22	71	4.8	2.5	47	0.5	134	3.8	102		Ne	NR	n	Y	N	N	N	Y	N	PV,DBV	L,E	N	Y	N	N	Exanthem	Paracetamol
36	P36	14	M	Nil	Nil	88	1.3	0.8	39	34	46	6.5	3.6	58	1.5	163	4	99	27	Ne	NR	n	N	N	Y	N	Y	Y	PV,INT	L,N,E	N	Y	Y	N	SJS/TEN	Carbamazepine

KEY TO MASTERCHART

Ad	–	Adequate
BL	–	Band like
Bl	–	Beau's lines
CTP	–	Chemotherapeutic drug
D	–	Decreased
DBV	–	Dilated blood vessel
DRESS	–	Drug reaction with eosinophilia and systemic symptoms
E	–	Eosinophils
EMF	–	Erythema multiforme
Eo	–	Eosinophilia
F	–	Female
F	–	Follicular
FDE	–	Fixed drug eruption
FL	–	Fatty liver
GBFDE	–	Generalised bullous fixed drug eruption
H	–	Hypochromic
HA	–	Hyperpigmented annular lesions
HM	–	Hepatomegaly
HSM	–	Hepatospleenomegaly
I	–	Increased
INT	–	Interstitial
M	–	Male
Mi	–	Microcytic
N	–	Neutrophils
N	–	No
n	–	Normal
Ne	–	Negative
NR	–	Non reactive
NSAID	–	Non steroidal anti inflammatory drugs

OCP	–	Oral contraceptive pills
P	–	Present
P	–	Purpura
PA	–	Periadnexal
PF	–	Perifollicular
PV	–	Perivascular
S	–	Scaling
SGOT	–	Serum glutamate oxaloacetate transferase
SGPT	–	Serum glutamate pyruvate transferase
SJS	–	Steven Johnson syndrome
T	–	Trace
TEN	–	Toxic epidermal necrosis
TL	–	Target lesions
USG	–	Ultrasonogram
VCTC	–	Voluntary counseling & testing centre
VDRL	–	Venereal disease research laboratory
Y	–	Yes

PROFORMA

Adverse cutaneous drug reactions – A clinicopathological study

Case no :

Name : Age : Sex : M/F

Address :

Occupation :

Date of patient reporting to OPD /casualty :

Date of admission (if admitted):

Presenting complaints :

Date of onset of skin lesions :

Site of onset of skin lesions :

Distribution of skin lesions :

Other symptoms associated with skin lesions :

Mucosal involvement : Y/N

If yes (site):

Constitutional symptoms : Y/N

If yes (symptom) :

Date of onset of illness for which treatment taken :

Type of illness :

Duration of illness :

Treatment taken on date :

Drugs taken : before / after constitutional symptoms

H/o any native medications :

Possible offending drug :

Time interval between drug intake and onset of skin lesions :

Past history :

Any illness : Y/N

Nature of illness :

If yes (drugs taken previously and at present for the disease) :

Any recent change of drug :

Any drug reactions in the past :Y/N

If yes (mention the drug) :

Type of skin lesion:

Duration of illness :

Treatment taken :

Whether admitted :

Personal history :

Any addiction :

Iv drug abuse :

Family history :

H/o of drug reaction : Y/N

If yes (details) :

H/o collagen vascular disorders : Y/N

If yes (details) :

General examination :

Build and nourishment :

Pallor /clubbing /cyanosis/lymphadenopathy/jaundice/pedal edema

Pulse rate : BP :

Respiratory rate : Temp :

I/O chart :

Systemic examination :

CVS : RS :

ABDOMEN : CNS :

Dermatological Examination :

Morphology of skin lesions:

Sites affected (% BSA) :

Mucosal lesions :

Scalp and hair :

Nails :

Palms and soles :

Lab investigations :

Blood R/E :

Hb : TC: DC: ESR:

Platelet count :

Absolute eosinophil count :

Peripheral smear :

Urine R/E : Alb - sugar –

Random blood sugar :

Liver function tests :

Renal function tests :

Serum electrolytes :

VCTC : VDRL :

USG Abdomen :

Skin biopsy report :

Final diagnosis:

Treatment :

INFORMATION SHEET

TITLE : **"CLINICO PATHOLOGIAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS"**

Name of Investigator **: Dr.L.BALAMURUGAN**
Name of Participant :

Purpose of Research : The purpose of this study is to analyse the incidence, various drugs causing adverse cutaneous drug reactions, clinical pattern of the disease and the role of blood investigations and skin biopsy in assessing the severity of the disease

Study Design : Prospective Study

Study Procedures : In this study history of patient will be taken, examination and routine blood investigations,VCTC and VDRL will be done. Biopsy of lesional skin will be done. Ultrasound of the abdomen, if needed will be done. The patients are then advised regarding avoidance of offending drug in future, and will be treated with emollients,topical or systemic drugs according to their need.

Possible Risks : No risks to the patient

Possible benefits :

To patient : Any offending drug will be detected and the patient is provided with any of the above mentioned treatments.

To doctor & to other people : The results of the study will help in confirming the role of drugs in the causation of the disease and emphasis the importance of avoidance of such drugs if alternative drugs available , in preventing such adverse reactions in the future.

Confidentiality of the information obtained from you : The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared

Can you decide to stop participating in the study : Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time

How will your decision to not participate in the study affect you : Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of Participant
Date :
Place :

PATIENT CONSENT FORM

Title of the study: : "**CLINICO PATHOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS"**

Name of the Principal investigator: Dr.L.BALAMURUGAN.

Name of the Institution: Rajiv Gandhi Government General Hospital,Chennai

Patient's Name :
Patient's Age :
OutPatient No :

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

I hereby consent to participate in this study

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests and to undergo treatment.

Signature/thumb impression
Patient's Name and Address:

Signature of Investigator
Study Investigator's Name:
Dr.L.Balamurugan

ஆய்வு தகவல் தாள்

ஆராய்ச்சியின் தலைப்பு : மருந்துகளால் ஏற்படும் தோல் சம்பந்தப்பட்ட பாதகமான பின்விளைவுகள் பற்றிய மருத்துவ மற்றும் மெய்மிநோயியல் ஆய்வு.

ஆய்வாளர் : மரு. இல. பாலமுருகன்

பங்கேற்பாளர் : **வயது :** **பாலினம் :**

ஆராய்ச்சி மையம் : தோல்நோய் துறை,
இராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை.

இந்த ஆய்வில் பங்கேற்பதற்காக தாங்கள் அழைக்கப்படுகிறீர்கள். இந்த ஆவணத்தில் உள்ள தகவல்கள் தாங்கள் இந்த ஆய்வில் பங்கேற்க முடிவு செய்துக் கொள்ள உதவும். இதில் ஏதேனும் சந்தேகம் இருந்தால் வெளிப்படையாக கேள்விகளைக் கேட்டு தெரிந்துக் கொள்ளலாம்.

நாங்கள் இராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் மருந்துகளால் ஏற்படும் தோல் சம்பந்தப்பட்ட பாதகமான பின்விளைவுகள் பற்றிய மருத்துவ மற்றும் மெய்மிநோயியல் ஆய்வை நடத்துகிறோம்.

அதற்கு உங்கள் பங்களிப்பு எங்களுக்கு பெரிதும் உதவக்கூடும்.

இந்த ஆய்வின் நோக்கம்:

இவ்வாராய்ச்சியில் தங்களிடையே அடிப்படை மற்றும் உங்களுடைய நோய் குறித்த விரிவான கேள்விகள் கேட்கப்படும். பின்னர் நீங்கள் மருத்துவப் பரிசோதனைக்கு உட்படுத்தப்படுவீர்கள். பின்பு தோல் சம்பந்தமான வெளிப்பாடுகள் குறித்து மருத்துவப் புகைப்படம் எடுக்கப்படும்.

அனைவரிடமும் இரத்தம் மாதிரி பெறப்பட்டு அது வழக்கமான இரத்தப் பரிசோதனைகளும் CBC, LFT, RFT, VCTC, VDRL, உயிர்திடசுப் பரிசோதனை மற்றும் தேவைப்பட்டால் USG Abdomen & Pelvis பரிசோதனையும் செய்யப்படும்.

தங்களது மருத்துவ சிகிச்சை குறித்த தகவல்கள் இரகசியமாக பாதுகாக்கப்படும். ஆய்வின் போதோ அல்லது முடிவுகளை வெளியிடும் போதோ தங்களது பெயரையோ, அடையாளங்களையோ வெளியிடமாட்டோம் என்பதை தெரிவித்துக் கொள்கிறோம்.

இந்த ஆய்வில் பங்கேற்பது உங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆய்விலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம். இந்த ஆய்வில் பங்கேற்காவிட்டாலும் நீங்கள் வழக்கமான சிகிச்சையை தொடர்ந்து பெறலாம்.

இந்த ஆய்வின் முடிவு தங்களுக்கு ஆய்வின் இறுதியிலோ அல்லது ஆய்வின் போதிலோ தெரியப்படுத்தப்படும்.

ஆய்வாளர் கையொப்பம் பங்கேற்பாளர் / பாதுகாவலர் கையொப்பம்

தேதி :

சுய ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு : **மருந்துகளால் ஏற்படும் தோல் சம்பந்தப்பட்ட பாதகமான பின்விளைவுகள் பற்றிய மருத்துவ மற்றும் மெய்மிநோயியல் ஆய்வு.**

பெயர் : வயது : தேதி : உள்நோயாளி எண் :

..... என்பவராகிய நான் இந்த ஆய்வின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக அறிந்து கொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன். இச்சுய ஒப்புதல் படிவத்தை பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை பற்றி அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில்தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என சம்மதிக்கிறேன்.

இந்த ஆய்வின் முடிவுகளை வெளியிடும்போது எனது பெயரோ, அடையாளமோ வெளியிடப்பட்டாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்று கொண்டேன். இந்த ஆய்விற்காக இரத்தப் பரிசோதனைகளும் (CBC, LFT, RFT, VCTC, VDRL, உயிர்திடசுப் பரிசோதனை மற்றும் தேவைப்பட்டால் USG Abdomen & Pelvis பரிசோதனையும் செய்துக் கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ள வேண்டும் என அறிந்து கொண்டேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்றும் தெரிவிக்கிறேன் என்று புரிந்து கொண்டேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்றும் தெரிந்து கொண்டேன்.

பங்கேற்பாளர் / பாதுகாவலர் கையொப்பம் தேதி :

ஆய்வாளர் கையொப்பம் தேதி :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301A
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.L. Balamurugan
Post Graduate in MD DVL
Madras Medical College
Chennai 600 003

Dear Dr.L. Balamurugan,

The Institutional Ethics Committee has considered your request and approved your study titled **"CLINICO PATHOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS" NO. 19112016.**

The following members of Ethics Committee were present in the meeting hold on **01.11.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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Sources included in the report:

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Instances where selected sources appear:

5

PLAGIARISM CERIFICATE

This is to certify that this dissertation work titled **"CLINICO PATHOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS"** of the candidate **Dr.BALAMURUGAN. L** with registration Number **201530002** for the award of **M.D DERMATOLOGY, VENEREOLOGY & LEPROSY** in the branch of **XX**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **2 percentage** of plagiarism in the dissertation.

Guide & Supervisor sign with seal