A CLINICOEPIDEMIOLOGICAL STUDY ON ADVERSE CUTANEOUS DRUG REACTIONS

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LEPROSY

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CERTIFICATE

This is to certify that this dissertation entitled **'A CLINICO EPIDEMIOLOGICAL STUDY ON ADVERSE CUTANEOUS DRUG REACTIONS'** submitted by **Dr. Koregol Savita** to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfillment of the requirement for the award of M.D., [DERMATO VENEREO LEPROLOGY] and is a bonafide research work carried out by her under direct supervision and guidance.

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I also declared this bonafide work or a part of this work was not submitted by me or any other for any award, degree and diploma to any university, board either in India or abroad.

This is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulation for M.D.,[D.V.L] Degree examination.

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INTRODUCTION

A drug may be defined as a chemical substance, or combination of substances, administered for the investigation, prevention or treatment of diseases or symptoms, real or imagined. An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects and unanticipated adverse manifestations. ADR can also be defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'. ADRs are underreported and are an underestimated cause of morbidity and mortality; it has been estimated that ADRs represent the fourth to the sixth leading cause of death[1],[2]

Adverse Cutaneous Drug Reactions (ACDRs) are probably the most frequent manifestations of all drug sensitivity reactions although their incidence is difficult to determine. Very few published studies[3],[4] have assessed the epidemiological and clinical features of drug reactions in India and still fewer in South India[3]. Hence this study was undertaken to assess the pattern and clinical features of ACDRs and common drugs causing them in South Tamil nadu.

AIM OF THE STUDY

1. To study the clinicoepidemiological pattern of various adverse cutaneous drug reactions in patients attending SKIN OPD, Government Rajaji Hospital.

2. To study the common drugs causing adverse cutaneous drug reactions.

REVIEW OF LITERATURE

EPIDEMIOLOGICAL ASPECTS OF ADVERSE CUTANEOUS DRUG REACTIONS:

Incidence:

The exact incidence and prevalence of cutaneous adverse drug reactions are unknown, but the overall prevalence is believed to be less than 1% of the general population. Estimates between 2.0% to 2.4% have been reported worldwide.[68] Out of this 7% is due to antibiotics. An incidence of 0.38% has been reported from India .[69]

Immunosuppressed patients are most frequently affected.[1]

Age:

Though ADRs can affect any age group ADRs occur in 6–17% of children admitted to specialist paediatric hospitals ,those over 60 years of age comprise only 12% of the population in the USA, 33% of all drugs are prescribed for this age group,[1] [70] and the elderly have a significantly higher incidence of ADRs, related to decreased organ reserve capacity, altered pharmacokinetics and pharmacodynamics, and polypharmacy.

Gender:

Women are more likely than men to develop ADRs.[1]

Classification of adverse drug reactions:[1]

Non-immunological

→ Predictable

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

→Unpredictable

Intolerance

Idiosyncrasy

Immunological (unpredictable)

IgE-dependent drug reactions

Immune complex-dependent drug reactions

Cytotoxic drug-induced reactions

Cell-mediated reactions

Miscellaneous

Jarisch–Herxheimer reactions

Infectious mononucleosis–ampicillin reaction

Criteria for assessment of potential drug reactions have been promulgated, and include:[64][65]

1.recurrence on challenge;

2.existence of a pharmacological basis for the reactions;

3.the occurrence of immediate acute or local reactions at the time of administration,

4.of previously known reactions with a new route of administration, or repeated rare reactions; and

5.the presence of immunological abnormalities .

FIXED DRUG ERUPTION

1. Age:

Fixed drug eruptions have been reported in patients as young as 1.5 years and as old as 87 years. The mean age at presentation is 30.4 years in males and 31.3 years in females.[43]

2. Gender :

One large study of 450 patients by mahboob et al.[43] revealed a male to female ratio of 1:1.1 for fixed drug eruptions.

3.Race:

Fixed drug eruptions have no known racial predilection. A genetic susceptibility to developing a fixed drug eruption with an increased incidence of HLA-B22 is possible. [44]

4. Pathophysiology:

Although the exact mechanism is unknown, recent research suggests a cell-mediated process that initiates both the active and quiescent lesions. The process may involve an antibody-dependent, cell-mediated cytotoxic response. $CD8^+$ effector/memory T cells play an important role in reactivation of lesions with re-exposure to the offending drug[45]

The offending drug is thought to function as a hapten that preferentially binds to basal keratinocytes, leading to an inflammatory response. Through liberation of cytokines such as tumor necrosis factor-alpha, keratinocytes may locally up-regulate expression of the intercellular adhesion molecule-1 (ICAM1).The up-regulated ICAM1 has been shown to help T cells (CD4 and CD8) migrate to the site of an insult.

The newly arriving and residential CD8 cells likely perpetuate tissue damage by

their production of the inflammatory cytokines interferon-gamma and tumor necrosis factor-alpha. CD8 cells isolated from active lesions have also been shown to express alpha E beta 7, a ligand for E-cadherin, which may further contribute to the lymphocyte's ability to localize to the epidermis. Other cell surface molecules, such as CLA/alpha4beta1/CD4a, that bind E-selectin/vascular cellular adhesion molecule-2/ICAM1 help to further attract CD8 cells to the area.

Changes in cell surface markers allow vascular endothelium to select CD4 cells for migration into active lesions. These regulatory CD4 cells likely produce interleukin 10, which has been shown to help suppress immune function, resulting in a resting lesion.As the inflammatory response dissipates, interleukin 15 expression from keratinocytes is thought to help ensure the survival of CD8 cells, helping them fulfill their effector memory phenotypes. Thus, when reexposure to the drug occurs, a more rapid response develops in the exact location of any prior lesions.[45]

5. History:

The initial eruption is often solitary and frequently located on the lip or genitalia. Rarely, the eruption may be intraoral. Lesions are commoner on the limbs than on the trunk; the hands and feet, genitalia and perianal areas are favoured sites. Perioral and periorbital lesions may occur. Genital and oral mucous membranes

may be involved in association with skin lesions, or alone. With the initial fixed drug eruption attack, a delay of up to 2 weeks may occur from the initial exposure of the drug to the development of the skin lesion.Skin lesions develop over a period of hours but require days to become necrotic. Lesions may persist from days to weeks and then fade slowly to residual oval hyperpigmented patches.[46]

The eruption may initially be morbilliform, scarlatiniform or erythema multiforme-like; urticarial, nodular or eczematous lesions are less common.

A fixed drug eruption characteristically recurs in the same site or sites each time the drug is administered; with each exposure, however, the number of involved sites may increase. Subsequent reexposure to the medication results in a reactivation of the site, with inflammation occurring within 30 minutes to 16 hours. The reactivation of old lesions also may be associated with the development of new lesions at other sites.

Patients may not be cognizant that a drug, nutritional supplement, over the counter medication, or, rarely, food (eg, fruits, nuts) triggered the skin problem. They may be convinced that an insect, particularly a spider, may be the culprit. A careful history is required to elicit the fact that a drug has been taken and is temporally related to the onset of the eruption. Medications taken episodically, such as pain relievers, antibiotics, or laxatives, are often to blame. When able to

be identified, patients often report ingestion of one the following types of medications:[67]

- Analgesics
- Muscle relaxants
- Sedatives
- Anticonvulsants
- Antibiotics

In the case of isolated male genital fixed drug eruption (often affecting only the glans penis), the drugs most commonly implicated in one series were co-trimoxazole (trimethoprim– sulfamethoxazole), tetracycline and ampicillin .

Cross-sensitivity to related drugs may occur, such as between phenylbutazone and oxyphenbutazone, between tetracycline type drugs, and between anticonvulsants .

Local symptoms may include pruritus, burning, and pain.Systemic symptoms are uncommon, but fever, malaise, nausea, diarrhea, abdominal cramps, anorexia, and dysuria have been reported.

Further questioning may reveal prior episodes of fixed drug eruption, atopic disease, or other past drug reactions. Family history may render a history of atopy, drug reactions, or diabetes mellitus.

Several cases of fixed drug eruption on the genitalia have been reported in patients who were not ingesting the drug but whose sexual partner was taking the offending drug and the patient was exposed to the drug through sexual contact.

6. Types: Several variants of fixed drug eruption have been described, based on their clinical features and the distribution of the lesions.These include the following:[47]

- Pigmenting fixed drug eruption
- Generalized or multiple fixed drug eruption
- Linear fixed drug eruption
- Wandering fixed drug eruption
- Nonpigmenting fixed drug eruption
- Bullous fixed drug eruption
- Eczematous fixed drug eruption
- Urticarial fixed drug eruption
- Erythema dyschromicum perstans–like fixed drug eruption
- Vulval & Oral fixed drug eruption

7. Differential diagnosis:

- Bullous Pemphigoid
- Cellulitis

- Drug-Induced Bullous Disorders
- Eczema
- Erythema Annulare Centrifugum
- Erythema Multiforme
- Herpes Simplex
- Lichen Planus
- Lichen Planus Actinicus
- Discoid lupus erythematoses
- Pemphigus Vulgaris , Pityriasis Rosea
- Postinflammatory Hyperpigmentation

8. Complications:

Hyperpigmentation is the most likely complication of a fixed drug eruption (FDE). The potential for infection exists in the setting of multiple, eroded lesions. Generalized eruptions have been reported following topical and oral provocation testing.[48]

9. Prognosis:

The prognosis is very good, and an uneventful recovery should be expected. No deaths due to fixed drug eruption have been reported. Residual hyperpigmentation is very common, but this is less likely with the nonpigmenting variant. As healing occurs, crusting and scaling are followed by

pigmentation, which may be very persistent and occasionally extensive, especially in pigmented individuals; pigmentation may be all that is visible between attacks.[49]

MACULOPAPULAR RASH

A drug reaction is suspected when a maculopapular eruption begins within 4 to 12 days of beginning a new medicine. Macules predominate initially, then become confluent patches with papular areas within the patches.[17]

Proposed mechanism :

Morbilliform drug eruption is a non-immediate type IV allergic reaction involving drug-specific T cells (CD4+) with direct cytotoxic effects and release of pro-inflammatory factors.[1]

Clinical features: Most reactions develop within 7 to 8 days, though reactions to aminopenicillins may develop over a longer period (>8 days) & in phenytoin it takes around 3 weeks . This interval is the time needed for an immunological (cell-mediated) delayed-type hypersensitivity reaction to occur.The eruption is characteristically polymorphic, with confluent areas on the trunk, papular areas on the arms, and purpuric areas on the feet.In maculopapular rash, features range from a normal epidermis to local areas of basal cell degeneration with eosinophilic infiltrat Dermis showed congested vessels, mild to moderate

perivascular/periappendageal infiltrate of mononuclear cells.[66]

Moderate pruritus, a low-grade fever, and general malaise may be present. Mucous membranes are typically spared, and lymphadenopathy is mild if present.

The eruption generally fades over 1 to 2 weeks without complication. Post-inflammatory desquamation is common. Antibiotics (sulphonamides, aminopenicillins, cephalosporins) and anticonvulsants are most commonly implicated.[17]

Chemotherapeutic agents, particularly cytarabine, dacarbazine, hydroxyurea, paclitaxel, and procarbazine, have also been associated with maculopapular eruption. Epidermal growth factor receptor inhibitors (EGFRs; e.g., cetuximab) also have a propensity to trigger cutaneous eruptions.

Treatment:

Prompt cessation of the causative drug results in resolution over 1-2 weeks. No specific treatment is required but topical corticosteroids or oral antihistamines may give symptomatic relief of itch.[17]

URTICARIA

Urticaria is a skin rash, also called hives, or nettle rash, which is often accompanied by swelling and itching of the skin.

Classification:

-Immune-mediated

IgE-mediated: penicillin

Complement and immune complex mediated: penicillin, immunoglobulins, whole blood.

-Nonallergic urticarial ACDR

Analgesics/NSAIDs inhibit/block cyclooxygenase in prostaglandin synthesis

Radio contrast media

ACE inhibitors: inhibition of kinin metabolism

Calcium channel blockers

Drugs releasing histamine[13]

Clinical features:

Time from Initial Drug Exposure to Appearance of Urticaria : IgE-Mediated Initial sensitization, usually 7–14 days; urticaria may occur while the drug is still being administered or after it is discontinued. In previously sensitized individuals, usually within minutes or hours. Skin Symptoms consist of Pruritus, burning of palms/ soles, auditory canal. With airway edema, difficulty breathing. Drug-induced urticaria may be allergic (immunologically mediated) or pseudoallergic (nonimmunologically mediated).

Common drugs: Penicillins , Cephalosporins , Sulphonamides , Cytostatic

agents, ACE inhibitors, Calcium channel blockers

Drug-induced urticaria is seen in association with anaphylaxis, angio-oedema and serum sickness.[9]

Differential diagnosis :

Is of acute edematous red pruritic plaque(s):

a) Allergic contact dermatitis (poison ivy, poison oak dermatitis)

b) Cellulitis

c) insect bite(s).

Management :

The offending drug should be identified and withdrawn as soon as possible. Prevention: Previously Sensitized Individuals. The patient should carry information listing drug sensitivities (wallet card, bracelet). Radiographic Contrast Media Avoid use of contrast media known to have caused prior reaction. If not possible, pretreat patient with antihistamine and prednisone (1 mg/kg) 30–60 min before contrast media exposure.

Treatment of Acute Severe Urticaria/Anaphylaxis :

Epinephrine : 0.3–0.5 mL of a 1:1000 dilution subcutaneously, repeated in 15–20 min. Maintain airway, Intravenous access, Antihistamines H1 blockers or H2 blockers or combination.

Systemic Glucocorticoids : Intravenous Hydrocortisone or methylprednisolone

for severe symptoms. Oral Prednisone 70 mg, tapering by 10 or 5 mg daily over 1–2 weeks, is usually adequate.[13]

ERYTHRODERMA

It is most frequently caused by antibiotics, antiepileptic drugs and NSAIDs. [50]

Drug-induced erythroderma accounts for about 10% of all erythrodermas.

Definition: generalized erythema of the skin (more than 90% of the body surface area) accompanied by a variable degree of scaling.

Pathogenesis: The rise in adhesion molecule expression (VCAM-1, ICAM-1, E-selectin and P-selectin) seen in exfoliative dermatitis stimulates dermal inflammation, which may lead to epidermal proliferation and increased production of inflammatory mediators. The complex interaction of cytokines and cellular adhesion molecules such as interleukin-1, -2 and -8; intercellular adhesion molecule-I (ICAM-I); and tumor necrosis factor (TNF) results in significantly elevated epidermal turnover rate, leading to above normal mitotic rate. The amount of germinative cells increases and the transit time of keratinocytes through the epidermis decreases, causing loss of more cellular material from the surface.

Clinical features:

The pattern observed is erythematous patches, which increase in size and

coalesce to form extensive areas of erythema, and eventually spread to involve most of the skin surface.Some studies have shown sparing of the nose and paranasal areas, and this has been described as the "nose sign".

The epidermis appears thin, giving a glossy appearance to the skin. Once erythema has been established, white or yellow scales develop that progress to give the skin a dry appearance with a dull scarlet and grey hue. Induration and thickening of the skin from edema and lichenification may provoke a sensation of severe skin tightness in the patient. The skin is bright red, dry, scaly and warm to touch.

Some patients may experience involvement of their palms and soles, with hair loss and nail shedding. Involved nails are thick, lusterless, dry, brittle, and show ridging of the nail plate. Subungual hyperkeratosis, distal onycholysis, splinter hemorrhages occur; and sometimes, the nails may shed. Shelley described alternating bands of nail plate discontinuity and leukonychia in drug-induced erythroderma.

Laboratory investigations:

Laboratory findings in the erythrodermic patient are usually nonspecific. Common abnormalities are mild anemia, leukocytosis with eosinophillia, elevated sedimentation rate, decreased serum albumin, increased uric acid, abnormal serum protein electrophoresis with polyelevation in the gamma

globulin region and elevated IgE levels.

Management:

To identify & stop the offending drug. Systemic corticosteroids , nutritional replacement, fluid and electrolyte losses. Local skin care measures should be employed, such as oatmeal baths as well as wet dressings to weeping or crusted sites followed by the application of bland emollients and low potency corticosteroids. Known precipitants and irritants are to be avoided.

Secondary infections are treated with antibiotics. Edema in dependent areas, such as in periorbital and pedal areas, may require diuretics.

Hemodynamic or metabolic instability should be addressed adequately. Serum protein, electrolyte and blood urea levels should be monitored.[51]

URTICARIA WITH ANGIOEDEMA

In the past this was called giant urticaria or angioneurotic edema or Quincke's edema. Angioedema is a swelling of the deep layers of the subcutaneous or submucosal tissue or both. Most commonly it occurs on the lips, tongue, face, hands or feet.

The oedema is caused by an increase in capillary leakage as a result of inflammatory mediators. This can be a manifestation of Type I allergic reactions; or a consequence of deficiency in C1-esterase inhibitor or because of failure to metabolise mediators such as bradykinin. Drugs are implicated in all

three mechanisms, although C1-esterase inhibitor deficiency is usually hereditary.

Drug most commonly implicated:

ACE-inhibitors , Bupropion , vaccines , selective serotonin reuptake inhibitors (SSRIs) , COX-II inhibitors , angiotensin II antagonists , other antidepressants , non-steroidal anti-inflammatory drugs (NSAIDs), statins , proton pump inhibitors.

Management:

Primary management is to ensure an adequate airway. Adrenaline, antihistamines, and corticosteroids may be needed. Endotracheal intubation or tracheotomy is required in severe cases.[52]

DRESS

[Drug Rash with Eosinophilia & Systemic Symptoms]

Synonym:

Drug Hypersensitivity Syndrome[DHS]

drug-induced delayed multiorgan hypersensitivity syndrome (didmohs)

Definition: Long-lasting papulopustular or erythematous skin eruption often progressing to exfoliative dermatitis, with fever, lymphadenopathy, and visceral involvement (hepatitis, pneumonitis, myocarditis, pericarditis, nephritis).

Incidence/prevalence:For phenytoin, carbamazepine, and phenobarbital, the

incidence of DRESS has been estimated to 1 reaction per 5,000 to 10,000 exposures.

Race: Reactions to antiepileptic drugs may be higher in black individuals.

Etiology:Most commonly: antiepileptic drugs (phenytoin, carbamazepine, phenobarbital; cross-sensitivity among the three drugs is common) and sulfonamides (antimicrobial agents, dapsone, sulfasalazine).

Less commonly: allopurinol, gold salts, sorbinil, minocycline, zalcitabine, calcium-channel blockers, ranitidine, thalidomide, mexiletine.

Pathogenesis :

Some patients have a genetically determined inability to detoxify the toxic arene oxide metabolic products of anticonvulsant agents. Slow N-acetylation of sulfonamide and increased susceptibility of leukocytes to toxic hydroxylamine metabolites are associated with higher risk of hypersensitivity syndrome.

Clinical manifestation:

Onset : 2–6 weeks after drug is initially used, and later than most other serious skin reactions.

Prodrome: Fever, rash ,malaise.

Skin Lesions:

Early : Morbilliform eruption on face, upper trunk, upper extremities; cannot be distinguished from exanthematous drug eruption. May progress to

generalized exfoliative dermatitis/erythroderma, especially if drug is not discontinued. Eruption becomes infiltrated with edematous follicular accentuation. Facial edema (especially periorbitally) is characteristic. Dermal edema may result in blister formation. Sterile folliculocentric as well as nonfollicular pustules may occur. Eruption may become purpuric on legs. Scaling and/or desquamation may occur with healing.

Distribution : Symmetric, almost always on trunk and extremities. Lesions may become confluent and generalized.

Mucous Membranes: Cheilitis, erosions, erythematous pharynx, enlarged tonsils.

General Examination: Elevated temperature (drug fever).

Lymph Nodes:Lymphadenopathy frequent ± tender; usually due to benign lymphoid hyperplasia. Involvement of liver, heart, lungs, joints, muscles, thyroid, brain also occurs.

Laboratory examinations :

Hemogram and Chemistries: Eosinophilia (30% of cases), Leukocytosis, Mononucleosis like atypical lymphocytes. Signs of hepatitis and nephritis.

Histology of skin shows Lymphocytic infiltrate, dense and diffuse or superficial and perivascular ± Eosinophils or dermal edema. In some cases, bandlike infiltrate of atypical lymphocytes with epidermotropism, simulating cutaneous T cell lymphoma. Benign lymphoid hyperplasia of lymph nodes.

Uncommonly atypical lymphoid hyperplasia, pseudolymphoma.

Liver - Eosinophilic infiltrate or granulomas. Kidney -Interstitial nephritis.

The table given below indicates organ involvement in DRESS syndrome:[53]

Incidence of organ involvement in DRESS syndrome	
Organ	**Percent of patients with involvement**
Liver	80%
Kidney	40%
Pulmonary	33%
Cardiac/muscular	15%
Pancreas	5%
Incidence of hematologic abnormalities in DRESS syndrome	
Abnormality	**Percent of patients with abnormality**
Atypical lymphocyte	63%
Eosinophilia	52%
Lymphocytopenia	45%
Thrombocytopenia	25%
Lymphocytosis	25%

Diagnosis:

Proposed Diagnostic Criteria:[54]

(1) Cutaneous drug eruption;

(2) hematologic abnormalities (eosinophilia >1500/μL or atypical lymphocytes);

(3) systemic involvement [adenopathies ≥2 cm in diameter or hepatitis (SGOT >2 N) or interstitial nephritis or interstitial pneumonitis or carditis]. Diagnosis is confirmed if three criteria are present.

Differential diagnosis :

Early: That of morbilliform eruptions, can mimic early measles or rubella.

Later: Serum sickness, drug-induced vasculitis, Henoch-Schönlein purpura, cryoglobulin-associated vasculitis, vasculitis associated with infection, and collagen vascular diseases.

Rash Plus Lymphadenopathy : Rubella, primary EBV or CMV mononucleosis syndrome.

Course and prognosis:

Rash and hepatitis may persist for weeks after drug is discontinued. In patients treated with systemic glucocorticoids, rash and hepatitis may recur as glucocorticoids are tapered. Lymphadenopathy usually resolves when drug is withdrawn; however, rare progression to lymphoma has been reported. Rarely, patients die from systemic hypersensitivity such as with eosinophilic

myocarditis. Clinical findings recur if drug is given again.

Management:

Identify and discontinue the offending drug.

Symptomatic Treatment :

Oral antihistamine to alleviate pruritus.

Glucocorticoids :

Topical High-potency topical glucocorticoids applied twice a day are usually helpful in relieving cutaneous symptoms of pruritus but do not alter systemic hypersensitivity.

Systemic : Prednisone (0.5 mg/kg per day) usually results in rapid improvement of symptoms and laboratory parameters. [54]

Future Drug Therapy:

Cross-sensitivity between various aromatic antiepileptic drugs occurs, making it difficult to select alternative anticonvulsant therapy.

Prevention:

The individual must be aware of his or her specific drug hypersensitivity and that other drugs of the same class can cross-react. These drugs must never be readministered. Patient should wear a medical alert bracelet.

STEVEN JOHNSON SYNDROME

SJS is a severe illness of usually sudden onset, associated with marked constitutional symptoms of high fever, malaise, myalgia, arthralgia and extensive erythema multiforme of the trunk, with occasional skin blisters and erosions covering less than 10% of the body's surface area. [1]

The skin lesions are variable in extent, and consist of typical maculopapular lesions of erythema multiforme, bullous or, rarely, pustular lesions. New crops of lesions develop over a period of 10 days, or sometimes 3–4 weeks. Mucous membranes:

- Oral: extensive bulla formation, erosions and a greyish white membrane, so that the mouth and lips show characteristic haemorrhagic crusting . [7]
- Eyes: a severe catarrhal or purulent conjunctivitis can be seen. Corneal ulceration, anterior uveitis or panophthalmitis may occur. The eye changes often regress completely, but synechiae, corneal opacities and rarely blindness are possible sequelae.
- Genital : retention of urine due to involvement of the bladder. [1]

Respiratory symptoms may occur, and often the radiological changes within the lungs are far greater than the symptoms. Abnormalities of liver function may be present. Renal involvement with haematuria or even renal tubular necrosis has been reported and may lead to progressive renal failure. [25]

Untreated, this disease used to have a mortality of 5–15% from infection, toxaemia or renal damage, but the mortality rate is now lower. The eruption usually heals without sequelae, although the eyes may be permanently damaged. Eruptive melanocytic naevi are reported to develop after SJS.

Complications :

Acute: Massive fluid and electrolyte loss (3–4L/day) ,prerenal renal failure,Bacterial infection and septicaemia, hypercatabolism: insulin resistance, diffuse interstitial pneumonitis, mucous membrane involvement

Chronic :Ocular complications (up to 35%) Conjunctivitis, ectropion or entropion, corneal scarring , Symblepharon,Sjögren-like sicca syndrome

Other mucous membrane involvement :Oesophageal stricture ,Phimosis. Vaginal synechiae, Orogenital ulcers

Miscellaneous: Wound infection, pigmentary changes, nail dystrophy, hypohidrosis, scarring alopecia, contractures, development of melanocytic naevi.[1]

Management is similar to toxic epidermal necrolysis and has been discussed subsequently.

TOXIC EPIDERMAL NECROLYSIS

TEN: The incidence of erythema multiforme, SJS and TEN was estimated at 1.8 cases per million person years for patients aged between 20 and 64 years; the incidence for patients aged less than 20 years, and 65 years or more, increased to 7 and 9 cases per million person-years, respectively. The incidence of TEN was estimated at 0.5 per million per year.[1]

Aetiology

Immunology

In general, CD4 T cells predominate in the upper dermis, while epidermal CD8 T cells and macrophages are variable and Langerhans' cells virtually disappear. Keratinocytes express HLA-DR and ICAM-1, and there is endo- thelial cell ICAM-1, vascular cell adhesion molecule 1 (VCAM-1) and E-selectin expression. CD3 activated T cells expressing the skin-homing receptor (cutaneous leukocyte antigen; CLA) in both skin and peripheral blood parallel the severity of the disease, and tumour necrosis factor-α (TNF-α), IFN-γ and interleukin-2 (IL-2) are overexpressed in peripheral blood mononuclear cells, suggesting an important role for T cells in TEN . Prominent involvement of the monocyte–macrophage lineage, including factor XIIIa, HLA-DR, dendrocytes and CD68, Mac387, macrophages, before, during and especially after epidermal necrosis has been reported ,with dense labelling of the epidermis for TNF-α.

Mechanisms mediating keratinocyte death:

Cytokines released by activated lymphocytes and/or from keratinocytes may contribute to apoptosis in TEN. Activated lymphocytes may induce apoptosis via an interaction between Fas-ligand (FasL), expressed on the surface of and secreted by lymphocytes, and Fas antigen (CD95), expressed by keratinocytes after exposure to IFN-γ. There is keratinocyte overexpression of Fas antigen in drug-induced erythema multiforme, SJS and TEN . Moreover, peripheral blood mononuclear cells from TEN and SJS patients secreted high levels of soluble(s) FasL on stimulation with the causal drug . Increased sFasL levels precede skin detachment in patients with SJS and TEN . Bcl-2, a protein known to block apoptosis, is strongly expressed along the basal layer and in the dermal infiltrate both in erythema multiforme and SJS/TEN; thus Fas-mediated cell death may be partially suppressed by Bcl-2 protein .

The matrix metalloproteinase MMP2 has a significant role in epidermal detachment, inflammation and re-epithelialization.

Drugs implicated in toxic epidermal necrolysis :

- Antibiotics: Sulphonamides : Co-trimoxazole , Sulfadoxine, Sulfadiazine, Sulfasalazine

  Penicillins : Amoxicillin Ampicillin

  Cephalosporins

- Non-steroidal anti-inflammatory drugs :

  Phenylbutazone

  Oxyphenabutazone

  Oxicam-derivatives

Clinical features:

Typically sheet like erosions involve more than 30% of the body surface with widespread purpuric macules or flat atypical target lesions, and there is severe involvement of conjunctival, corneal, irideal, buccal, labial and genital mucous membranes.[27]

Prodromal period: Flu-like symptoms (malaise, fever, rhinitis and conjunctivitis), sometimes accompanied by difficulty in urination, which usually lasts 2–3 days; however, it may last from 1 day to 3 weeks before signs of skin involvement develop.

Acute phase : Persistent fever, severe mucous membrane involvement and generalized epidermal sloughing to leave large, raw, painful areas, and lasts from 8 to 12 days. There may be an initial 'burning' maculopapular, urticarial or erythema multiforme-like eruption. Most frequently, the initial individual skin lesions form poorly defined macules with darker purpuric or blistering centres, progressively merging on the chin, upper parts of chest and back.

Nikolsky's sign, the ability to extend the area of superficial sloughing by gentle

lateral pressure on the surface of the skin at an apparently unaffected site, may be positive.

Detachment of the full thickness of the epidermis at sites of pressure or trauma, such as the back, shoulders or buttocks, leaves a dark red oozing dermis. However, the entire skin surface may be involved, with up to 100% of the epidermis sloughing off. Only the hairy portion of the scalp is never affected.

The process tends to occur in waves, over a 3- to 5-day period (sometimes a week), but involvement of the whole of the body surface occurs within 24 h in approximately 10% of cases.

Mucous membranes (particularly the buccal, and less commonly the conjunctival, genital, perianal, nasal, tracheal, bronchial, pharyngeal and oesophageal membranes) are involved in nearly all patients (85–95%). Urethritis develops in up to two-thirds of patients, and may lead to urinary retention. Stomatitis and mucositis lead to impaired oral intake with consequent malnutrition and dehydration. Intestinal involvement has been documented . Healing occurs by re-epithelialization; this may occur within a few days on the anterior thorax, but is slower on the back and at intertrigi- nous areas. Most patients' skin lesions are completely healed in about 3–4 weeks, but mucosal lesions take longer and the glans penis may take up to 2 months to heal over.

Investigations:

Increase in serum aminotransferases and serum amylase overt hepatitis.

Anaemia and lymphopenia with a selective and transient depletion of CD4+ T lymphocytes. Neutropenia is observed in approximately 30% of patients, and thrombocytopenia in 15%; eosinophilia is very unusual. Hypophosphataemia , hyperglycaemia,raised urea and creatinine levels, subclinical interstitial oedema is often noted on early chest X-rays.[1]

Prognosis :

There is an appreciable mortality as a result of TEN, increasing from 5% in SJS, to 10–15% in transitional SJS–TEN and 30–40% in TEN.

SCORTEN prognosis score:[1]

Parameters:

1.Age > 40 years

2.Presence of a malignancy

3.Epidermal detachment > 30%

4.Heart rate > 120/min

5.Bicarbonate < 20 mmol/L

6.Urea > 10 mmol/L

7.Glycaemia > 14 mmol/L

1 point awarded for each parameter; SCORTEN derived by totalling scores[1]

SCORTEN	Probability of death (%)
0–1	3
2	12
3	35
4	58
≥5	90

Management of toxic epidermal necrolysis:[1]

Intensive therapy or burns unit, air-fluidized bed,analgesia, maintain fluid and electrolyte balance (replace up to 5 L/day), maintain body temperature, maintain nutrition, oral hygiene.

Frequent ophthalmological assessment :Antiseptic/antibiotic eye drops 2hourly, disrupt synechiae frequently, limitation of infection

Frequent cultures of erosions, and blood cultures, Culture tips of Foley catheters and intravenous lines, Prophylactic broad-spectrum systemic antibiotics (controversial).Topical cleansing/antibacterial agents 0.5% silver nitrate solution on gauze or 10% chlorhexidine gluconate washes orsaline washes or polymixin/bacitracin or 2% mupirocin, wound care :Paraffin gauze or hydrogel dressings ,biological dressings (xenografts, allografts, skin substitutes). Recently plasmaphereses and Intravenous immunoglobulins are being used.

ERYTHEMA MULTIFORME

Erythema multiforme is an acute, self-limited, and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers.

Erythema multiforme may be present within a wide spectrum of severity. The papules evolve into pathognomonic target lesions or iris lesions that appear within a 72-hour period and begin on the extremities . Lesions remain in a fixed location for at least 7 days and then begin to heal.

The clinical description is as follows:[8]

- Erythema multiforme minor - Typical target or raised, edematous papules distributed acrally.
- Erythema multiforme major - Typical targets or raised, edematous papules distributed acrally with involvement of one or more mucous membranes; epidermal detachment involves less than 10% of total body surface area.

Erosions of the oral mucosa may result in difficulty in eating, drinking, or opening the mouth. Conjunctival involvement may cause lacrimation, photophobia, burning eyes, or visual impairment. Genital lesions are painful and may result in urinary retention; painful micturition due to genitourinary tract ulceration may also occur. Shortness of breath or difficulty in breathing may occur due to tracheobronchial epithelial involvement.

Drug hypersensitivity:

The keratinocyte is the ultimate target of this disease process, with keratinocyte necrosis being the earliest pathologic finding.

Patients frequently display an altered metabolism of the responsible drug, and are considered to be slow acetylators, both genotypically and phenotypically. Drug metabolism is directed toward the alternative pathway of oxidation by the cytochrome P-450 system, resulting in increased production of reactive and potentially toxic metabolites. Affected individuals have a defect in the ability to detoxify these reactive metabolites, which may then behave as haptens by binding covalently to proteins on the surface of epithelial cells. This may then induce the immune response, leading to the severe skin reaction.[17]

Sulfa drugs are the most common triggers (30%) followed by the anticonvulsants, including barbiturates, carbamazepine, phenytoin, and valproic acid.

Causative antibiotics include penicillin, ampicillin, tetracyclines, amoxicillin, cefotaxime, cefaclor, cephalexin, ciprofloxacin,erythromycin, minocycline, sulfonamides, trimethoprim-sulfamethoxazole, and vancomycin.

Other drugs : albendazole, arsenic, bromofluorene, quinine, cimetidine, clofibrate, corticosteroids, diclofenac, didanosine, dideoxycytidine, diphosphonate, estrogen, etretinate, fluconazole, gabapentin, granulocyte-

macrophage colony-stimulating factor (GM-CSF), hydralazine, indapamide, indinavir, mefloquine, methotrexate, meprobamate, mercurials, minoxidil, nifedipine, nevirapine, nystatin, nonsteroidal anti-inflammatory drugs (NSAIDs), phenolphthalein,pyritinol, progesterone, potassium iodide, sulindac, suramin, saquinavir, thiabendazole, thiouracil, terbinafine, theophylline, verapamil, and dihydrocodeine phosphate.[13]

Two additional rare clinical forms of erythema multiforme have been reported: [8]

i) Continuous erythema multiforme manifests as a prolonged course with overlapping attacks and may be associated with systemic administration of glucocorticoids.

ii) Persistent erythema multiforme has a protracted clinical course over months, is commonly associated with atypical skin lesions and is commonly resistant to conventional treatment. It has been reported in association with inflammatory bowel disease (IBD), occult renal carcinoma, persistent or reactivated Epstein-Barr virus (EBV) infection, and HSV infection.

ACNEIFORM ERUPTIONS

This pattern of eruption represents a small percentage of drug-induced skin eruptions. Clinically it presents as a papulo-pustular inflammatory eruption on the face and upper trunk resembling acne vulgaris.

Drug-induced acne should be considered if :

- The onset is sudden
- There is worsening of existing acne
- Comedones are absent
- Monomorphic appearance of the papules and pustules
- There is an exposure to a potentially responsible drug

Few drugs can cause acneiform eruption historically, corticosteroids have been a common cause. However, the new EGF receptor (EGFR) antagonists used in cancer treatment, such as erlotinib, are associated with an acneiform eruption that carries a good prognostic factor for the treatment of the underlying condition as evidence of effect on another organ that expresses EGFR. Withdrawal of the culprit drug and treatment with tetracycline or erythromycin antibiotics is often all that is needed in terms of treatment[13].

Adrenocorticotrophic hormone (ACTH), corticosteroids , dexamethasone in neurosurgical patients, anabolic steroids for body building , androgens (in females), oral contraceptives, iodides and bromides may produce acneiform

eruptions.

Isoniazid may induce acne, especially in slow inactivators of the drug . Other drugs implicated in the production of acneiform rashes include dantrolene , danazol , quinidine , lithium and azathioprine.[14]

The fact that acneiform eruptions do not affect prepubertal children indicates that previous hormonal priming is a necessary prerequisite. In cases in which the offending agent cannot be discontinued topical tretinoin may be helpful[17].

DRUG INDUCED PHOTOSENSITIVITY

Phototoxic reactions : Ultraviolet light activates the photosensitizing drug to emit energy that may damage adjacent skin tissue resulting in an intensified sunburn with skin peeling. Factors influencing the intensity and incidence of drug-induced phototoxicity include:

1) the concentration, absorption, and pharmacokinetics of the drug. Higher doses of lipophilic drugs (e.g., amiodarone) known to cause this reaction have a higher incidence, and

2) the “dose” of sunlight (i.e., quantity and spectrum of sunlight).

Phototoxicity is characterized by a rapid onset of erythema, pain, prickling, or burning sensation of areas exposed to the sun, with peak symptoms occurring 12-24 hours after the initial exposure. The hallmark of this reaction is the

appearance of a sunburn-like reaction on areas of skin with the greatest exposure to sunlight. These reactions do not involve the immune system; therefore, prior exposure or sensitization to a drug is not necessary for this reaction to occur.[58]

Photoallergic reactions :

Drug induced photoallergy is less common than phototoxicity, and requires prolonged or prior exposure to the photosensitizing drug. As the name suggests, this type of reaction is immune mediated. UV light reacts with the drug to produce an immunogenic stimuli known as a hapten. This hapten combines with a tissue antigen producing a cell mediated immune response resulting in a skin reaction. This reaction requires a latency period following drug exposure for the immunological memory response to develop after the first drug contact. Subsequent exposures to the drug can elicit a more rapid reaction. Photoallergic reactions are not dose dependent.

Photoallergic reactions are characterized by solar urticaria with eczema-like dermatitis and erythema. Light exposed areas on the skin are the predominant location of the reaction. These eruptions usually disappear spontaneously upon removal of the offending drug.[58]

LICHENOID DRUG ERUPTIONS

Commonly caused due to HMG CoA reductase inhibitors , gold salts, beta blockers, antimalarials, thiazide diuretics, furosemide, spironolactone, and penicillamine.[59]

Clinicalfeatures:

- Extensive rash distributed symmetrically over the trunk and limbs
- Photodistribution – the rash is predominantly in areas exposed to the sun
- Rash may be scaly resembling eczema or psoriasis
- Wickham's striae are usually absent
- Nail and mucous membrane (e.g., mouth) involvement is uncommon
- More likely to resolve leaving marked pigmentation

Prevention and Treatment : [59]

To stop the underlying offending drug

1. Topical steroids such as clobetasol propionate and betamethasone propionate ointments .
2. Hydrocortisone foam can be used.
3. Steroid injections into affected areas may be useful for localised disease.
4. Systemic steroids may also be used.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS [AGEP]

It is characterized by the rapid appearance of many pustules, which are sterile and located subcorneally in the epidermis; the patients have fever, leukocytosis, and sometimes also an eosinophilia. In >90% of the cases it is caused by drug intake, in particular aminopenicillins, anticonvulsants and anti-inflammatory drugs. Lethality in AGEP is 1% for older patients.

The most striking feature of AGEP is the short interval between the drug administration and the onset of the disease.[60]

The main histopathological findings in AGEP are spongiform superficial pustule, papillary edema, polymorphous perivascular infiltrate with eosinophils and leucocytoclastic vasculitis with fibrinoid deposits.

Use of systemic steroid in AGEP is justified.[60]

TOXIC ACRAL ERYTHEMA

Acral erythema is also known as palmoplantar erythrodysesthesia or hand-foot syndrome. It manifests as painful erythema of the palms and soles, with or without bullae. These symptoms can be preceded by dysaesthesia . The pain from this rash may be so severe that daily activities are limited. If recognised early, the usual course of acral erythema is desquamation followed by re-epithelialization. The exact mechanism is unknown, but it is postulated that the

skin of the hands and feet favour a higher level of certain chemotherapy drugs which causes direct toxicity to the skin cells.[61]

Associated drugs include: Cytarabine , Docetaxel , Doxorubicin , Fluorouracil, Cyclophosphamide , Daunorubicin , Vincristine , Vinblastin.

DRUG INDUCED SWEET'S SYNDROME LIKE ERUPTION

It is rare and represent overall less than 5% of all cases. Approximately 50 cases have been reported, mostly as isolated clinical cases. Sitjas et al[62]. observed in a retrospective study of 30 patients with SS that 7 of them had received a new treatment before the rash occurred (non-steroidal anti-inflammatory drugs (NSAIDS), penicillin, carbamazepine). However, these drugs were often given for another confounding cause, especially an infection.

Delay is highly variable, ranging from several days to, exceptionally, 2 years , but mostly within 7 days. Clinical presentation and histology are quite similar to the idiopathic form. Hyperleucocytosis could be less frequent during the drug-induced form. Evolution is favourable after drug withdrawal. Fever vanishes within one to three days, eruption within 3–30 days under corticosteroid ointment and one week with oral corticosteroid therapy. Relapses occur in case of drug reintroduction.[62]

CUTANEOUS REACTIONS TO ANTINEOPLASTIC AND CHEMOTHERAPEUTIC DRUGS

Alopecia**:** is the most common adverse skin manifestation of the chemotherapeutic treatment. There are two types of drug-induced alopecia: the anagen effluvium and the telogen effluvium. In the anagen effluvium hair loss occurs due to the sudden interruption of the mitotic activity of the hair matrix, one to two weeks after the start of chemotherapy, leading to lack of hair production or its thinning (Pohl- Pinkus constrictions). They involve the hair, eyebrows, beard, axillary and pubic hair. It is dose-dependent and reversible. In the telogen effluvium, hairs move prematurely to a resting phase with subsequent loss of normal hair.[40]

The antineoplastic agents that most frequently cause the anagen effluvium lead to diffuse hair loss, of sudden onset, from 7 to 10 days after the start of chemotherapy. Hair loss becomes more pronounced about 1 to 2 months after the start of treatment.

Trichomegaly and hair curling :

Hair alterations with acceleration of growth and shaft changes are observed with the use of epidermal growth factor receptor inhibitors (EGFR)

Ungual, subungual, and periungual alterations :

Nail alterations can present with a reduction of the nail growth speed, fragility,

lines of discoloration (Mees' lines), transverse depressions (Beau's lines), hyperpigmentation, onycholysis with subungual aseptic abcesses, photoonycholysis, paronychia, and pyogenic granulomas of the periungual folds. Hyperpigmentation can occur due to the use of cyclophosphamide, hydroxyurea, fluoropirimidines, such as 5-fluorouracil (5-FU) and specially anthracyclines like doxorubicin and daunorubicin . Painful onycholysis and subungual abcesses are due to the use of taxanes (docetaxel/paclitaxel) and anthracyclines (doxorubicin). Ingrown nails, paronychia, and pyogenic granuloma are associated with the use of tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR), such as erlotinib and gefitinib. The fenestration or avulsion of the lamina should be considered when abscesses that involve more than 50% of the nail bed are present.[40]

Other adverse effects are as follows :

Neutrophilic eccrine hidradenitis

Eccrine squamous syringometaplasia

Acral erythema or palmoplantar erythrodysesthesia syndrome

Toxic erythema caused by chemotherapeutic drugs

Acneiform eruption

Mucous membrane alterations

Stomatitis

DRUG INDUCED PSEUDOLYMPHOMA SYNDROME

Pseudolymphoma syndrome (PS) consists of the triad of fever, generalised rash and lymphadenopathy. In addition malaise, hepatosplenomegaly, arthralgia, congestive cardiac failure, eosinophilia, thrombocytopenia and blood dyscrasias may be present.

Diphenylhydantion, tridione and phenobarbitone etc. can produce a peculiar response of reticuloendothelial system resulting in PS.PS may be either hypersensitivity reaction or possibly a genetically determined enzymatic defect as seen in primaquin sensitivity. PS may present as generalised exfoliative dermatitis. PS may have generalised or localised lesions and may result from non-anticonvulsant drugs. Histopathology may reveal mycosis fungoides or sezary like syndrome.[63]

DRUG INDUCED BULLOUS DISORDER

Approximately 10% of cases of pemphigus are drug-induced or drug-triggered.

The skin lesions are flaccid blisters which break easily and often only erosions +/- crusting are seen. The Nikolsky sign can be positive. In drug-induced pemphigus, mucous membranes are only involved in 10-15% of cases whereas drug-triggered pemphigus is indistinguishable from classic pemphigus.[57]

Skin biopsy shows the typical separation of individual skin cells seen in

pemphigus. Direct immunofluoresence is positive in 90% of drug related pemphigus, compared to 100% in idiopathic classic disease. Circulating antidesmoglein autoantibodies are only detected in the blood in 70% of drug-induced pemphigus.

The onset of drug related pemphigus can be weeks to months after the drug was started. Resolution occurs after drug withdrawal in drug-induced pemphigus but not if drug-triggered.

Drug-induced pemphigus is caused by drugs with a thiol group such as:

D-penicillamine , Captopril ,Gold sodium thiomalate , Pyritinol

Drug-triggered pemphigus follows nonthiol drug use including:

Antibiotics especially betalactams, rifampicin , Pyrazolone derivatives , Nifedipine , Propranolol , Piroxicam, Phenobarbital.[57]

DRUG INDUCED LUPUS ERYTHEMATOSUS

Drug-induced lupus erythematosus is an autoimmune disorder that is brought on by a reaction to medication.The most common medications known to cause drug-induced lupus include: isoniazid, hydralazine, and procainamide.[56]

Other medications known to cause drug-induced lupus, include:

Anti-seizure medications , Capoten , Chlorpromazine , Etanercept, Infliximab , Methyldopa , Minocycline , Penicillamine ,Quinidine , Sulfasalazine

Symptoms tend to occur after taking the drug for at least 3 to 6 months.

Persons with drug-induced lupus erythematosus may have symptoms that affect the joints (arthritis), heart, and lungs. Other symptoms associated with SLE, such as lupus nephritis and nervous system (neurological) disease, are rare.[56]

DRUG INDUCED PSEUDOPORPHYRIA

Skin signs include skin fragility and photosensitivity. Tense blisters form at the sites of minor trauma on sun exposed skin, bursting early to leave scabs and erosions. The blisters are most often seen on the hands and feet. They sometimes heal with some scar formation and milia.A sunburn type rash may also occur.[55]

Pseudoporphyria is due to drugs which interact with sunlight to cause a phototoxic reaction in the skin. These include:[55]

- Non steroidal anti-inflammatory drugs e.g. naproxen
- Antibiotics: doxycyline, nalidixic acid
- Diuretics: chlorthalidone, bumetanide, furosemide and hydrochlorthiazide
- Retinoids – isotretinoin, etretinate, acitretin
- Oral contraceptives

It is important to withdraw the suspected agent where possible and avoid unnecessary exposure to strong light.Sun protection measures may include UVB and UVA blocking sunscreens.Symptoms usually resolve within several weeks but sometimes they are persistent.[55]

MATERIALS AND METHODS

This study was a prospective, observational study conducted at the skin OPD, Government Rajaji Hospital, Madurai Medical College, Madurai during the period from October 2009-September 2011[24 months].

Inclusion criteria:

All consecutive consenting patients diagnosed clinically as a case of adverse cutaneous drug reaction of all age groups, of all genders, during the study period were included in the study.

Exclusion criteria:

Non consenting patients, and patients with morphological pattern of adverse cutaneous drug reaction, but were unable to provide an exact history of drug intake.

Patients satisfying the criteria were included in the study and demographic details were recorded. A detailed clinical history including duration, site of onset, symptoms, drug history, family history were elicited. A complete general examination, systemic examination and dermatological examination were made. Digital photographs were taken.The morphology and distribution of skin lesions, concomitant affection of mucosa, hair, nails, palms, soles, genital involvement was meticulously recorded and presence of any other associated diseases were noted.

OBSERVATIONS AND RESULTS:

1. Incidence of ACDRs : Out of 1,03,536 patients who attended SKIN OPD during the study period of 24 months a total of 163 patients diagnosed with ACDR, fulfilling the inclusion criteria were included in the study. 0.15% was the overall incidence of ACDR during this period found in this study.

2) Occurrence of various clinical types of ACDRs :

Table 1 : Clinical types of ACDRs:

SI.No	Clinical types of drug eruption	Total no. of cases
1.	FDE	84
2.	Urticaria	15
3.	Maculopapular rash	15
4.	Erythroderma	11
5.	Urticaria+Angioedema	10
6.	DRESS	7
7.	SJS	7
8.	TEN	6
9.	EMF	5
10.	Acneiform eruptions	2
11.	Phototoxic reaction	1

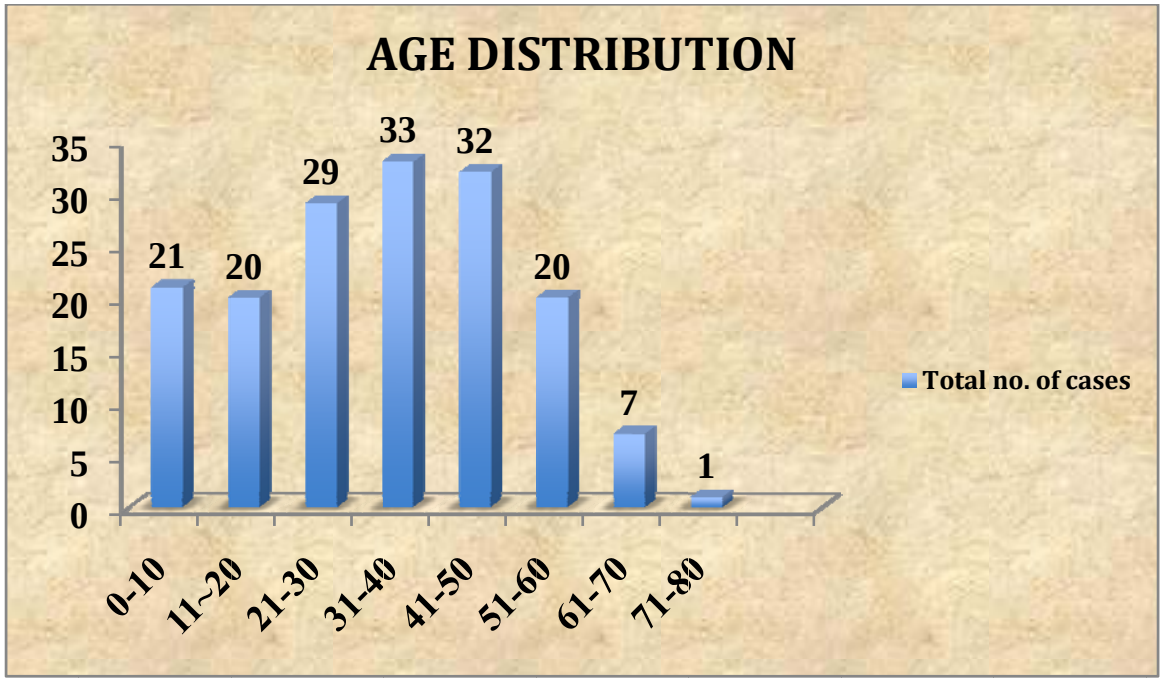
(FDE - Fixed Drug Eruption **, URT –** Urticaria , **URT+A** - Urticaria + angioedema , **DRESS** - Drug Rash with Eosinophilia and SystemicSymptoms , **TEN** - Toxic Epidermal Necrolysis , **SJS** - Steven Johnson Syndrome , **ED** - Erythroderma , **MPR** - Maculopapular Rash , **EMF** - Erythema Multiforme , **AE** - Acneiform Eruption **, PR –** Phototoxic reaction**)**

The most common drug eruption observed is FDE-84cases (51.53%). The other common types of drug eruptions include urticaria (9.25%), Maculopapular rash

(9.25%) and Erythroderma (6.74%). The other ACDRs seen were urticaria with angioedema (6.17%), DRESS (4.32%), SJS (4.32%), TEN (3.7%), EMF (3.08%), Acneiform eruptions (1.23%) and phototoxic reaction (0.61%) as seen in table 1.

3) Age distribution of various ACDRs:

Figure 1: Age distribution of various ACDRs



As shown in figure 1 the highest number of cases were seen in 4th (33 cases) and 5th (32 cases) decades followed closely by 3rd(29 cases) and 1st(21 cases) decades, 20 cases each were seen in 2nd and 6th decade. 7 cases were seen in 7th decade & 1 case was seen in 8th decade.

4) Gender distribution in ACDRs:

Table 3: Gender distribution in various ACDRs

GENDER	FDE	URT	MPR	ED	URT+A	DRESS	TEN	SJS	EMF	AE	PR
MALE	43	8	8	5	2	3	4	5	2	1	-
FEMALE	41	7	7	6	8	4	2	2	3	1	1

There were a total of 82 male and 81 female cases with a gender ratio of 1.01:1. The gender distribution for various drug eruptions is shown in Table 3.

As show in table 3 male patients constituted 43 cases of FDE, 8 cases of urticaria, 8 cases of MPR, 5 cases of ED, 2 cases of urticaria with angloedema. 3 cases of DRESS, 4 cases of TEN, 5 cases of SJS, 2 cases of EMF, 1 case of AE. Female patients constituted 41 cases of FDE, 7 cases of urticaria, 7 cases of MPR, 6 cases of ED, 8 cases of urticaria with angloedema. 4 cases of DRESS, 2 cases of TEN, 2 cases of SJS, 3 cases of EMF, 1 case of AE, 1 case of PR.

5) Site of involvement in various types of ACDRs :

Table 4 : Site of involvement in various types of ACDRs

Site of involvement	FDE	URT	MPR	ED	U+A	DRESS	TEN	SJS	EMF	AE	PR
Skin involvement only	48	15	10	6	-	2	-	-	-	2	1
Both skin & mucosal involvement	36	-	5	5	10	5	6	7	5	-	-
Oral mucosa only	25	-	5	5	5	5	-	-	2	-	-
Genital mucosa only	5	-	-	-	-	-	-	-	-	-	-
Both mucosae	6	-	-	-	5	-	6	7	3	-	-

As seen in table 4 out of total 163 patients 84 [51.53%] cases had only cutaneous involvement without involving the mucosa but 79 [48.46%] cases had both skin and mucosal involvement. In patients having both skin and mucosal involvement, 47[59.49%] cases had oral mucosal involvement only, 5[6.32%] had genital mucosal involvement only & 27[57.44%] had both oral and genital mucosal involvement.

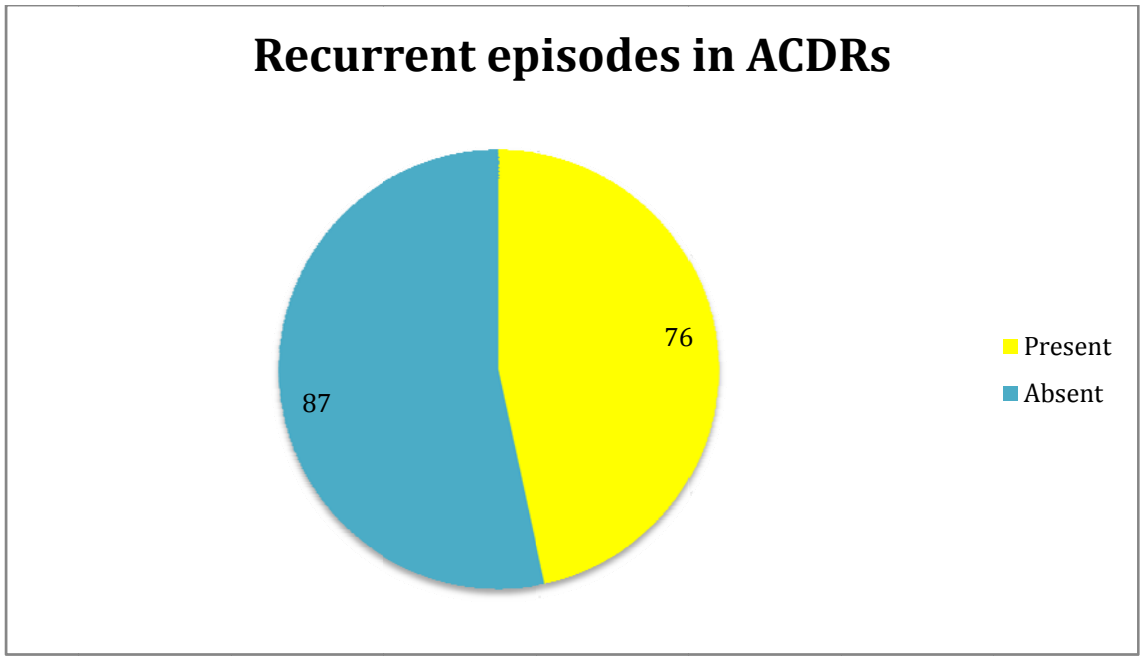
6) Recurrent episodes in various types of ACDRs:

Table 5: Recurrent episodes in various types of ACDRs:

Recurrent Episodes	FDE	URT	MPR	ED	URT+A	DRESS	SJS	TEN	EMF	AE	PR	Total	%
Present	59	7	1	-	5	-	2	-	2	-	-	76	46.62
Absent	25	8	14	11	5	7	5	6	3	2	1	87	53.37

As shown in table 5 , recurrent episodes were seen in 76 cases. Maximum no of these recurrences were seen with FDE, followed by urticaria in 7 cases, Urticaria with angioedema in 5 cases, 2 cases each of SJS & EMF and a single case of maculopapular rash.

Figure 2:



7)Various drug classes involved in ACDRs:

Table 6 : Various drug classes involved in ACDRs

SI.No	DRUG CLASS	SUBCLASS	DRUGS
1.	ANTIMICROBIALS	Antibacterials	Cotrimoxazole, Amoxycillin, Doxycycline, Ciprofloxacin, Cefixime, Cefoperazone, Dapsone, Norfloxacin, penicillin, Antituberculous regimen
		Antifungals	Griseofulvin
		Antivirals	Efavirenz
		Antiprotozoal	Chloroquine,Metronidazole
2.	NON STEROIDAL ANTI-INFLAMMATORY DRUGS		Paracetamol, Aspirin, Nimesulide, Mefenemic acid, Ibuprofen, Diclofenac
3.	ANTICONVULSANTS		Phenytoin, Sodium valproate, Carbamezapine, Phenobarbitone
4.	ANTIDEPRESSANTS		Imipramine
5.	CANCER CHEMOTHERAPY		Imatinib mesylate

In our study the above five classes of drugs were encountered as shown in table 6. A total of 108 [66.25%] cases due to antimicrobials were seen out of these 92 cases were due to intake of antibacterials, 10 cases were due to antivirals, 5 cases were due to antiprotozoal, single case was due to antifungal. 28 [17.17%] cases were due to Non steroidal anti-inflammatory drugs,25 [15.33%] cases were due to anticonvulsants and a single case[0.61%]each was due to antidepressants and chemotherapy.

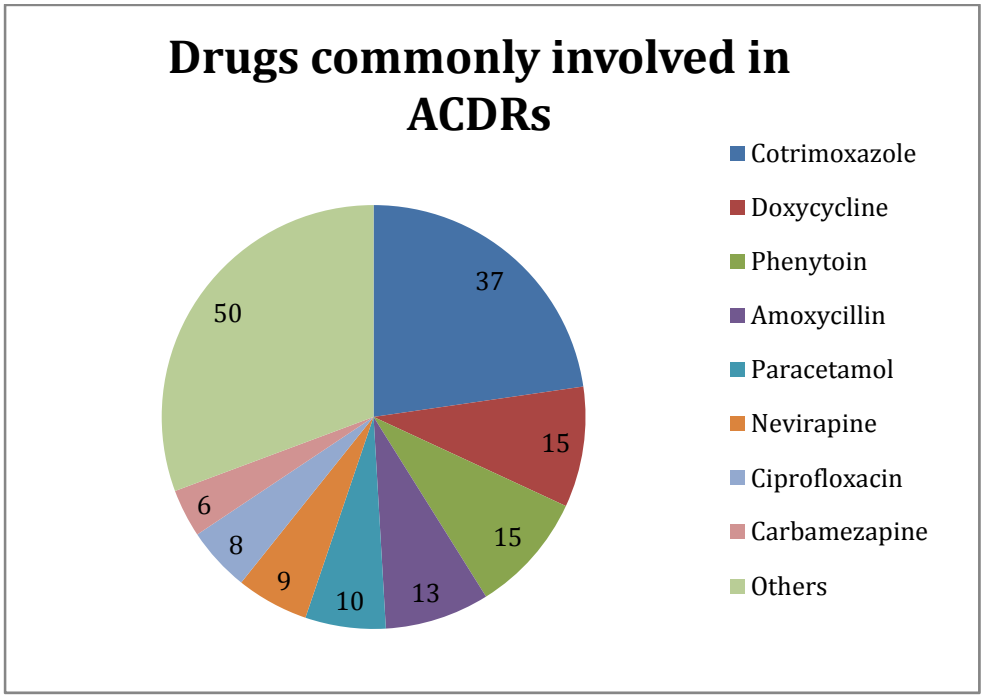
8) Drugs commonly involved in ACDRs

Table 7: Drugs commonly involved in ACDRs

Sl No:	Drugs	No. of Cases	Percentage %
1.	Cotrimoxazole	37	22.69
2.	Phenytoin	15	9.25
3.	Doxycycline	15	9.25
4.	Amoxycillin	13	7.97
5.	Paracetamol	10	6.13
6.	Nevirapine	9	5.55
7.	Ciprofloxacin	8	4.9
8.	Carbamezapine	6	3.68
9.	Cefixime	5	3.08
10.	Diclofenac	4	2.46
11.	Ibuprofen	4	2.46
12.	Penicillin	4	2.46
13.	Sodium valproate	3	1.85
14.	Piroxicam	3	1.85
15.	Aspirin	3	1.85
16.	Nimesulide	3	1.85
17.	Metronidazole	3	1.85
18.	Tetracycline	2	1.23
19.	Cefoperazone	2	1.23
20.	Chloroquine	2	1.23
21.	Isoniazid	2	1.23
22.	Norfloxacin	1	0.61
23.	Efavirenz	1	0.61
24.	Dapsone	1	0.61
25.	Mefenamic acid	1	0.61
26.	Phenobarbitone	1	0.61
27.	Imatinib mesylate	1	0.61
28.	Griseofulvin	1	0.61
29.	Imipramine	1	0.61

As shown in table 7 a total of 29 drugs were seen out of these cotrimoxazole was the most common drug causing ACDRs with 37 cases, second common drugs were phenytoin and doxycycline each involved in 15 cases, amoxicillin in 13 cases, paracetamol in 10 cases, nevirapine in 9 cases, ciprofloxacin in 8 cases, carbamezapine in 6 cases, cefixime in 5 cases, diclofenac, ibuprofen and penicillin each in 4 cases, sodium valproate, piroxicam, aspirin, nimesulide and metronidazole each in 3 cases, Isoniazid, tetracycline, cefoperazone, chloroquine each in 2 cases, single cases were seen with dapsone, imipramine, griseofulvin, imatinib mesylate, phenobarbitone, mefenemic acid, norfloxacin, efavirenz.

Figure 3:



Others- Tetracycline, Cefoperazone, Nimesulide, Dapsone, Mefenemic acid, Aspirin, Griseofulvin, Norfloxacin, Efavirenz, Imatinib mesylate, Chloroquine

9]Drugs and ACDRs caused by them:
Table 8: Drugs and ACDRs caused by them

DRUG	FDE	URT	MPR	ED	URT+A	DRESS	SJS	TEN	EMF	AE	PR	Total	%
CTX	27	5	3	-	-	-	1	-	1	-	-	37	22.69
PHE	-	-	8	-	-	5	1	1	-	-	-	15	9.25
AX	9	1	1	1	-	-	1	-	-	-	-	13	7.97
PCM	4	2	-	-	2	-	-	1	1	-	-	10	6.13
NVP	-	-	4	3	-	-	-	2	-	-	-	9	5.55
CPX	3	1	1	-	1	-	-	-	-	-	-	8	4.9
CBZ	2	-	-	2	-	-	1	1	-	-	-	6	3.68
CFX	1	-	-	-	1	2	2	-	-	-	-	6	3.68
DIC	4	-	-	-	-	-	-	-	-	-	-	4	2.46
IBP	4	-	-	-	-	-	-	-	-	-	-	4	2.46
SV	1	-	-	2	-	-	-	-	-	-	-	3	1.85
PXM	2	1	-	-	-	-	-	-	-	-	-	3	1.85

(CTX- Cotrimoxazole, DOXY-Doxycycline, PHE- Phenytoin, AX- Amoxycillin, NVP-Nevirapine, PCM-Paracetamol, CBZ-Carbamezapine, CPX-Ciprofloxacin, CFX-Cefixime, DIC-Diclofenac, IBP-Ibuprofen, SV-Sodium valproate, PXM-Piroxicam.)

As shown in table 8 it was observed that Cotrimoxazole was found to cause FDE in 26 cases, urticaria in 5 cases, urticaria with angioedema in 3 cases , SJS and EMF in a single case, Phenytoin was found to cause maculopapular rash in 8 cases , DRESS in 5 cases, TEN and SJS each in a single case.Amoxycillin was found to cause FDE in 9 cases, Urticaria, SJS, Erythroderma and Maculopapular rash each in a single case. Nevirapine in 2 cases of TEN, 3 cases of erythroderma,4 cases of maculopapular rash. Paracetamol was seen in 4 cases of FDE, 2cases each of urticaria, urticaria with angioedema & 1 case each of TEN & EMF: total of 10 cases.Carbamezapine was seen in 2 cases each of FDE & Erythroderma and in 1 case each of TEN & SJS : total of 6 cases.Cefixime was

seen with 3 cases of FDE, 1 case each of Urticaria, DRESS & maculo- papular rash. Diclofenac sodium & Ibuprofen were associated with 4 cases each of FDE. Sodium valproate : 1 case of FDE, 2 cases of maculopapular rash, total of 3 cases. Piroxicam : 2 cases of FDE , a case of urticaria :total of 3 cases.

10) Site of involvement for common individual drugs in ACDRs:

Table 9: Site of involvement for common individual drugs

Sl No:	Drugs	Cutaneous involvement	Both skin and mucosa	Total	Percentage %
1.	Cotrimoxazole	12	15	37	22.69
2.	Doxycycline	**6**	9	**15**	**9.25**
3.	Phenytoin	6	9	15	**9.25**
4.	Amoxycillin	**6**	**7**	**13**	**7.9**
5.	Paracetamol	**6**	**4**	**10**	**6.13**
6.	Nevirapine	**3**	**6**	**9**	**5.55**
7.	Carbamezapine	**4**	**2**	**6**	**3.68**
8.	Ciprofloxacin	**7**	**1**	**8**	**4.9**
9.	Cefixime	**1**	**4**	**5**	**3.08**
10.	Diclofenac	**2**	**2**	**4**	**2.46**
11.	Ibuprofen	**2**	**2**	**4**	**2.46**
12.	Sodium valproate	**2**	**1**	**3**	**1.85**
13	Piroxicam	**2**	**1**	**3**	**1.85**

As shown in table 9 Cotrimoxazole was the most common drug causing cutaneous in12 and both involvement in 15 cases, followed by doxycycline and phenytoin each in 6 cases of cutaneous and 9 cases of both. Amoxycillin in 6 cutaneous and both in 7 cases. Paracetamol in 6 cutaneous and both in 4 cases.Nevirapine in 3 cutaneous cases and 6 of both cases. Carbamezapine in 4

cutaneous and 2 case of both. Ciprofloxacin in 7 cases of cutaneous and 1 case of both, Cefixime in 1 case of cutaneous and 4 cases of both, Diclofenac and Ibuprofen each in 2 cases in both categories, Sodium valproate and Piroxicam each in 2 cases of cutaneous and 1 case of both skin and mucosal involvement.

11)Associated diseases in ACDRs:

Table 10 : Underlying associated diseases in ACDRs

Associated disease	**No. of cases**
1. Upper respiratory tract infection	32(19.63%)
2.Seizure disorder	24(14.72%)
3. Fever & Headache	18(11.04%)
4.HIV	10(6.13%)
5. Lower respiratory tract infection	9(5.52%)
6. Dental caries & Gingivitis	9(5.52%)
7. Sinusitis	8(4.9%)
8.Diabetes mellitus [DM]	7(4.29%)
9.Hypertension [HTN]	6(3.68%)
10. Urinary tract infection	6(3.68%)
11.HTN+DM	4 (2.4%)
12. Arthritis & Bursitis	4 (2.4%)
13. Acute & Chronic suppurative otitis media	4 (2.4%)
14. Tuberculous meningitis	3(1.84%)
15. Malaria	3(1.84%)
16. Acute diarrhea	3(1.84%)
17. Typhoid	3(1.84%)
18. Myalgia	3(1.84%)
19. Pyoderma	2(1.22%)
20.Leprosy	1 (0.61%)
21. Depression	1 (0.61%)
22. Chronic lymphocytic leukemia	1 (0.61%)
23. Epididymoorchitis	1 (0.61%)
24.External hordeolum	1 (0.61%)
TOTAL	163

As shown in table 10, maximum number of cases were seen with patients taking drugs for underlying upper respiratory tract infections: 32(19.63%), followed by seizure disorders 24(14.72%) cases, then followed by fever and headache 18(11.04%) cases, HIV was seen in 10(6.13%) cases, equal no. of patients that is 9(5.52%) cases were seen for both lower respiratory tract infections and dental caries & gingivitis. Among chronic long standing diseases Diabetes mellitus was seen in 7(4.29%) cases, Hypertension was seen in 6(3.68%) cases, both diabetes and hypertension were seen in 4(2.4%) cases. Urinary tract infections were seen in 6(3.68%) cases, 4(2.4%) cases each of arthritis and bursitis & acute and chronic suppurative otitis media were seen.

3(1.84%) cases each of tuberculous meningitis, Malaria, acute diarrhea, myalgia & typhoid were seen. 2(1.22%) cases of pyoderma were seen. Single cases each of leprosy, depression, chronic lymphocytic leukemia, epididymoorchitis & external hordeolum were seen.

12] Family history in ACDRs:

None of the cases had any history of family members with ACDRs.

DISCUSSION

1) Incidence of ACDRs:

Out of 1,03,536 total patients during the study period of 2 years, 163 were diagnosed as ACDRs which constitutes 0.15%. The incidence of ACDRs has been found to be 2.6% in a study by chatterjee et al[42] which is higher than our study

2) Occurrence of various clinical types of ACDRs :

The commonest ACDR in our study was FDE seen in 84 [51.53%] patients which is greater than a study by Thappa et al[3] where it was 28 [31.1%] patients. Maculopapular rash was seen in 15 [9.25%] patients in our study which is lesser than the study done by Thappa et al[3] where it was 12.2%. Urticaria was seen in 15 [9.25%] patients in our study which is greater than in the study by Thappa et al [3]where it was 7.8% . Erythroderma in our study included 11[6.74%] cases but according to Thappa et al[3] it was 3.3% which is lesser than our study. Urticaria with angioedema constituted 10[6.17%] cases but Thappa et al[3] recorded 1.1% which is lesser than our study. DRESS cases were 7 [4.32%] in number but in a study by Shear et al[41] 9% of cases were due to DRESS which is higher than our study. SJS constituted 7[4.32%] cases , but was only 3% in a study by Raksha MP et al[4]. TEN cases were 6 [3.7%] in number but only 1% in a study by Raksha MP et al[4] which is lesser than our study. EMF

cases were 5[3.08%] in our study but 6.7% in the study by Thappa et al[3] which is twice the number of cases when compared to our study. Acneiform eruptions were 2 [1.23%] in number whereas Thappa et al[3] recorded 3.3% which is greater than our study.

3) Age distribution of various ACDRs:

The age of the patients ranged from 3 months to 75 years. The majority of patients (33 patients or 20.24%) fall in the age group from 31-40 years followed by age group 41-50 years (32 patients or 19.63%). In a study by Ruchika Nandha et al [15] the maximum number of cases was seen in the age group 21-30 years (25.27%) followed by the age group 31-40 years (23.07%) which is greater than our study.

4) Gender distribution in ACDRs:

In our study, almost equal involvement was noted , 82 patients were males and 81 were females [male to female ratio was 1.01:1] out of 163 total cases , whereas during the study done by Ruchika Nandha et al[15] of the total 91 cases reported 47 (51.7%) were females and 44 (48.3%) were males. The male to female ratio was 0.93:1, which is slightly lesser than ours.

Predominance of males was reported in few studies. Equal ratio has also been reported in other studies.[23]

5) Site of involvement in various types of ACDRs :

Out of total 163 patients 84 [51.53%] cases had only cutaneous involvement without involving the mucosa but 79 [48.46%] cases had both skin and mucosal involvement. In patients having both skin and mucosal involvement, 47[59.49%] cases had oral mucosal involvement only, 5[6.32%] had genital mucosal involvement only & 27[57.44%] had both oral and genital mucosal involvement which is higher than in a study by Faisal et al[35] where about 32.7% of the patients (68/208) had mucosal involvement, the manifestations of which varied according to the type of rash.

6) Recurrent episodes in various types of ACDRs :

Out of 163 patients 76 [46.62%] patients had recurrent episodes which is higher than in a study by Thappa et al[3] where of the 90 consecutive patients, 25 had consumed the same drug earlier, 13 had a similar cutaneous reaction earlier and 12 had no reactions .

7) Various Drug classes involved in ACDRs:

In our study the various drug classes encountered were:

a] Antimicrobials : Cotrimoxazole, Amoxycillin , Ciprofloxacin , Nevirapine , Cefixime ,Tetracycline, Cefoperazone, Griseofulvin, Norfloxacin, Efavirenz, Dapsone- 108 [66.25%] cases.

b] NSAIDs: Paracetamol, Diclofenac, Ibuprofen, Piroxicam, Aspirin, Nimesulide, Mefenemic acid-28 [17.17%] cases

c] Anticonvulsants: Phenytoin, Carbamezapine, Sodium valproate-25 [15.33%] cases

d] Antidepressants: Imipramine -1 [0.61%] case.

e] Cancer chemotherapy: Imatinib mesylate-1 [0.61%] case.

The common offending drug groups in a study by chatterjee et al[42]were antimicrobials (34.10%) which is lesser than our study, anticonvulsants (32.88%) which is higher than our study, anti-inflammatory drugs (21.51%) which is greater than our study.Similar incidence as in our study was seen with antidepressants and chemotherapy drugs.

8) Drugs commonly involved in ACDRs :

Commonest drug causing ACDR was Cotrimoxazole recorded in 37 cases, in a study by Vander Linden et al[19]the most frequent reactions were observed in patients receiving a trimethoprim-sulfonamide combination , which is similar to our study,followed by Phenytoin and Doxycycline each in 15 (9.25%) cases, but Thappa et al[3] observed 7.8% cases for Phenytoin which is lesser than our study. Amoxycillin in 13 cases was the 3rd common drug but in a study by khushwaha et al[30] it was observed that amoxicillinwas 2ndmost common drug, Nevirapine in 9 cases, Paracetamol was involved in 10 cases and was the 5th commonest

drug in our study but in a study by Naldi et al[30] paracetamol was ranked at no.8 to cause ACDRs. Carbamezapine was the 6th commonest drug in our study which is in contrast to a study by Ding et al[29] where Carbamazepine was the most common drug causing severe ACDR. Ciprofloxacin in 6 cases, Cefixime in 5, Diclofenac in 4, Ibuprofen in 4, Sodium valproate , Metronidazole, Piroxicam, Aspirin & Nimesulide in 3(1.85%) cases each where as Thappa et al[3] recorded 2.2% for Metronidazole which is greater than our study. Tetracycline & Cefoperazone in 2 [1.23%] cases each. Mefenemic acid, Griseofulvin, Dapsone, Norfloxacin & Efavirenz each were incriminated in 1[.61%] case, but in a study by Thappa et al[3] Griseofulvin was accounted for 3.3% cases, which is much greater than our study.

9) Drugs and ACDRs caused by them:

a) Cotrimoxazole was found to cause FDE in 26 cases,urticaria in 5 cases, urticaria with angioedema in 3 cases , SJS and EMF in a single case.In a study by Thappa et al[3] Cotrimoxazole was the leading causative agent (29.5%) in FDE cases which is consistent with our study.

b) Phenytoin was found to cause maculopapular rash in 8 cases, DRESS in 5 cases, TEN and SJS each in a single case whereas in a study by Noel et al[34] phenytoin caused maximum no of cases of Maculopapular rash followed by TEN and erythroderma.

c) Amoxycillin was found to cause FDE in 9 cases, Urticaria, SJS, Erythroderma and Maculopapular rash each in a single case, whereas in a study by S Ghosh et al[30], the drug which was attributed to cause maximal number of maculopapular rashes, was amoxicillin.

d) Nevirapine was implicated in 2 cases of TEN, 3 cases of erythroderma,4 cases of maculopapular rash: total of 9 cases, wheras in a study by Ananworanich et al[32] nevirapine most commonly caused maculopapular rash ,TEN.

e) Paracetamol was seen in 4 cases of FDE, 2cases each of urticaria, urticaria with angioedema & 1 case each of TEN & EMF: total of 10 cases.

Noel et al[34] recorded 2 cases of urticaria , 1 case each of FDE and SJS, which is lesser than our study.

f) Carbamezapine was seen in 2 cases each of FDE & Erythroderma and in 1 case each of TEN & SJS: total of 6 cases, whereas in a study by Hung et al[31] the anticonvulsant carbamazepine (CBZ) frequently causes adverse cutaneous drug reactions (ACDRs), including maculopapular eruption (MPE), hypersensitivity syndrome (HSS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

g) Cefixime was seen with 3 cases of FDE, 1 case each of Urticaria, DRESS & maculopapular rash whereas in a study by Shipley et al Cefixime caused urticaria more frequently.[39]

h) Diclofenac sodium & Ibuprofen were associated with 4 cases each of FDE which is consistent with a study by Stern S et al where similar incidence was found.[37]

i) Sodium valproate : 1 case of FDE, 2 cases of maculopapular rash, total of 3 cases, whereas in a study by Patricia et al[38]there were no confirmed serious cutaneous diagnoses in 1,504 new valproate users.

j) Piroxicam : 2 cases of FDE , a case of urticaria :total of 3 cases, whereas in a study by Stern S et al[37] Piroxicam was seen to cause TEN.

10) Site of involvement for common individual drugs in ACDRs:

Cotrimoxazole was the most common drug causing cutaneous in 12 and both involvement in 15 cases, which is similar to a study by Arora et al[27], followed by doxycycline and phenytoin each in 6 cases of cutaneous and 9 cases of both. Amoxycillin in 6 cutaneous and both in 7 cases. Paracetamol in 6 cutaneous and both in 4 cases.Nevirapine in 3 cutaneous cases and 6 of both cases. Carbamezapine in 4 cutaneous and 2 case of both. Ciprofloxacin in 7 cases of cutaneous and 1 case of both, Cefixime in 1 case of cutaneous and 4 cases of both, Diclofenac and Ibuprofen each in 2 cases in both categories, Sodium valproate and Piroxicam each in 2 cases of cutaneous and 1 case of both skin and mucosal involvement. Specfic references involving cutaneous and mucosal involvement for other drugs were not found.

11) Associated diseases in ACDRs:

Maximum number of cases were seen with patients taking drugs for underlying upper respiratory tract infections; 32(19.63%), followed by seizure disorders 24(14.72%) cases, then followed by fever and headache 18(11.04%) cases, HIV was seen in 10(6.13%) cases, equal no. of patients that is 9(5.52%) cases were seen for both lower respiratory tract infections and dental caries and gingivitis.

Among chronic long standing diseases Diabetes mellitus was seen in 7(4.29%) cases, Hypertension was seen in 6(3.68%) cases; both diabetes and hypertension were seen in 4(2.4%) cases. Urinary tract infections were seen in 6(3.68%) cases, 4(2.4%) cases each of arthritis and bursitis & acute and chronic suppurative otitis media were seen.

3(1.84%) cases each of tuberculous meningitis, Malaria, acute diarrhea, myalgia & typhoid were seen. 2(1.22%) cases of pyoderma were seen. Single cases each of leprosy, depression, chronic lymphocytic leukemia, epididymoorchitis & external hordeolum were seen.

In a study by Thappa et al[3] history of a previous systemic illness was present in 44 patients (48.9%); 12 (13.3%) had a major illness while the remaining 32 (35.6%) had a minor one.

Hachem et al[18] reported an incidence of 12% of drug-related rashes among 85

HIV-infected patients which is greater than that found in our study.

12) Family history in ACDRs:

None of the patients in our study had a positive family history whereas according to a recently published study of ACDR during a 5year period by Fernandez et al[16], the risk for developing an adverse cutaneous reaction to drugs in patients with a positive family history for these reactions is 14% compared to 1.2% for those without a family history. In this study only 23% of the patients with an ACDR had a positive personal or family history.

SUMMARY

1) Incidence:

Out of all patients attending SKIN OPD during the study period of 24 months 163 patients were diagnosed with ACDR, which constituted to 0.15 %.

2) Occurrence of various clinical types of ACDRs :

Out of the total 163 patients FDE was the most common ACDR seen in 84 cases, Urticaria and Maculopapular rash in 15 cases each, Erythroderma in 11 cases, Urticaria with angioedema in 10 cases, DRESS & SJS in 7 cases, TEN in 6 patients, EMF in 5 patients, Acneiform eruptions in 2 cases and a single case of phototoxic reaction.

3) Age distribution in various ACDRs:

The maximum no. of cases that is 39.87% of patients were falling between 31-50 years of age group. The youngest patient was 3 months old & oldest patient was 75 years.

4) Gender distribution in ACDRs:

An almost equal incidence of occurrence in both males & females was noted, with a slight male predominance.82 cases were males & 81 cases were females.

5) Site of involvement in various types of ACDRs :

84 patients had only cutaneous involvement.Both cutaneous and mucosal involvement was seen in 79 out of 163 patients. Out of these 49 had oral mucosal involvement only, 5 had genital mucosal involvement only, 24 had both oral and genital mucosal involvement.

6) Recurrent episodes in various types of ACDRs:

Recurrent episodes were seen in 76 patients out of 163. DRESS, TEN, Erythroderma, Acneiform eruption and phototoxic reaction patients never had any previous episodes of recurrences.

7] Various drug classes involved in ACDRs:

The commonest drug class involved was antimicrobials with 11 drugs, followed by NSAIDs with 7 drugs, next common was anticonvulsants with 3 drugs and least common was seen with antidepressants and cancer chemotherapy with a single drug.

8) Drugs commonly involved in ACDRs:

Cotrimoxazole was the commonest drug causing ACDR which was found in 37 cases followed by Phenytoin and Doxycycline in 15 cases each, Amoxycillin in 13cases , Paracetamol in 10 cases , Nevirapine in 9 cases , Ciprofloxacin in 8 cases, Carbamezapine in 6 cases, Cefixime in 5 cases,

Diclofenac, penicillin and Ibuprofen in 4 cases each, Sodium valproate , Piroxicam , Aspirin ,Metronidazole& Nimesulide in 3 cases each. Tetracycline, Chloroquine, Isoniazid & Cefoperazone in 2 cases each. Mefenemic acid, Griseofulvin, Norfloxacin, Dapsone, Phenobarbitone, Imipramine, Imatinib mesylate & Efavirenz each were incriminated in 1 case each.

9) Drugs and ACDRs caused by them:

Cotrimoxazole was found in 26 FDE cases, 5 cases of urticaria, 3 cases of urticaria with angioedema, 1 case each of SJS and EMF.Phenytoin in 8 cases of maculopapular rash , 5 cases of DRESS, 1 case of TEN, 1 case of SJS.Amoxycillin was seen in 9 cases of FDE, 1 case each of urticaria, SJS, Erythroderma, Maculopapular rash.Nevirapine was implicated in 2 cases of TEN, 3 cases of erythroderma,4 cases of maculopapular rash.Paracetamol was seen in 2 cases each of FDE, urticaria, urticaria with angioedema & 1 case each of TEN & EMF.Carbamezapine was seen in 2 cases each of FDE & Erythroderma and in 1 case each of TEN & SJS .Cefixime was seen with 3 cases of FDE, 1 case each of Urticaria, DRESS & maculopapular rash.Diclofenac sodium & Ibuprofen were associated with 4 cases each of FDE.Sodium valproate : 1 case of FDE, 2 cases of maculopapular rash, total of 3 cases.Piroxicam : 2 cases of FDE ,a case of urticaria .

10) Site of involvement for common individual drugs:

Cotrimoxazole was the most common drug causing cutaneous in 12 and both involvement in 15 cases, followed by doxycycline and phenytoin each in 6 cases of cutaneous and 9 cases of both. Amoxycillin in 6 cutaneous and both in 7 cases. Paracetamol in 6 cutaneous and both in 4 cases.Nevirapine in 3 cutaneous cases and 6 of both cases. Carbamezapine in 4 cutaneous and 2 case of both. Ciprofloxacin in 7 cases of cutaneous and 1 case of both, Cefixime in 1 case of cutaneous and 4 cases of both, Diclofenac and Ibuprofen each in 2 cases in both categories, Sodium valproate and Piroxicam each in 2 cases of cutaneous and 1 case of both skin and mucosal involvement.

11) Associated diseases in ACDRs:

Maximum number of cases were seen with patients taking drugs for underlying upper respiratory tract infections; 32(19.63%), followed by seizure disorders 24(14.72%) cases, then followed by fever and headache 18(11.04%) cases, HIV was seen in 10(6.13%) cases, equal no. of patients that is 9(5.52%) cases were seen for both lower respiratory tract infections and dental caries & gingivitis. Among chronic long standing diseases Diabetes mellitus was seen in 7(4.29%) cases, Hypertension was seen in 6(3.68%) cases, both diabetes and hypertension were seen in 4(2.4%) cases. Urinary tract infections were seen in

6(3.68%) cases, 4(2.4%) cases each of arthritis and bursitis & acute and chronic suppurative otitis media were seen.

3(1.84%) cases each of tuberculous meningitis, malaria, acute diarrhea, myalgia & typhoid were seen. 2(1.22%) cases of pyoderma were seen. Single cases each of leprosy, depression, chronic lymphocytic leukemia, epididymoorchitis & external hordeolum were seen.

12) Family history in ACDRs:

There was no positive family history in any of the cases.

CONCLUSION

A total of 163 patients out of 1,03,536 were diagnosed with ACDRs. The incidence of Cutaneous adverse drug reaction in this study was 0.15% during this study period of 2 years.

Maximum number of the patients were in the $4^{th}$and 5^{th} decade, closely followed by patients in 1^{st} and 3^{rd} decades.Both the genders were almost equally involved with a slight predominance of male patients.

Fixed drug eruption was the commonest type of ACDR followed by Urticaria and Maculopapular rash, next closely followed by erythroderma .

Out of all the ACDRs 84 cases had exclusive cutaneous involvement only. Both skin and mucosa were involved in rest of the 79 cases. Out of these 79 cases 47 had only oral mucosal involvement, 5 had genital mucosal involvement only and 27 had both the mucosa involved. Recurrent episodes were seen in 76 patients of all the total cases.

The commonest class of drug causing ACDR was antimicrobials, among these antimicrobials antibacterials were the commonest subclass involved. Non steroidal anti-inflammatory drugs were the second commonest followed by anticonvulsants. Other groups which caused ACDR were antidepressants and cancer chemotherapy.

Amongst all the drugs Cotrimoxazole was the commonest drug causing

ACDR followed by equal involvement of phenytoin and doxycycline .

Among the individual ACDRs, FDE was most commonly caused by Cotrimoxazole. Mucosal involvement was most commonly seen with Cotrimoxazole followed by Phenytoin and doxycycline in succession. None of the patients had a positive family history of drug reaction.

Upper respiratory tract infection was the most common underlying systemic disorder following which patients had consumed the drug and developed ACDR.

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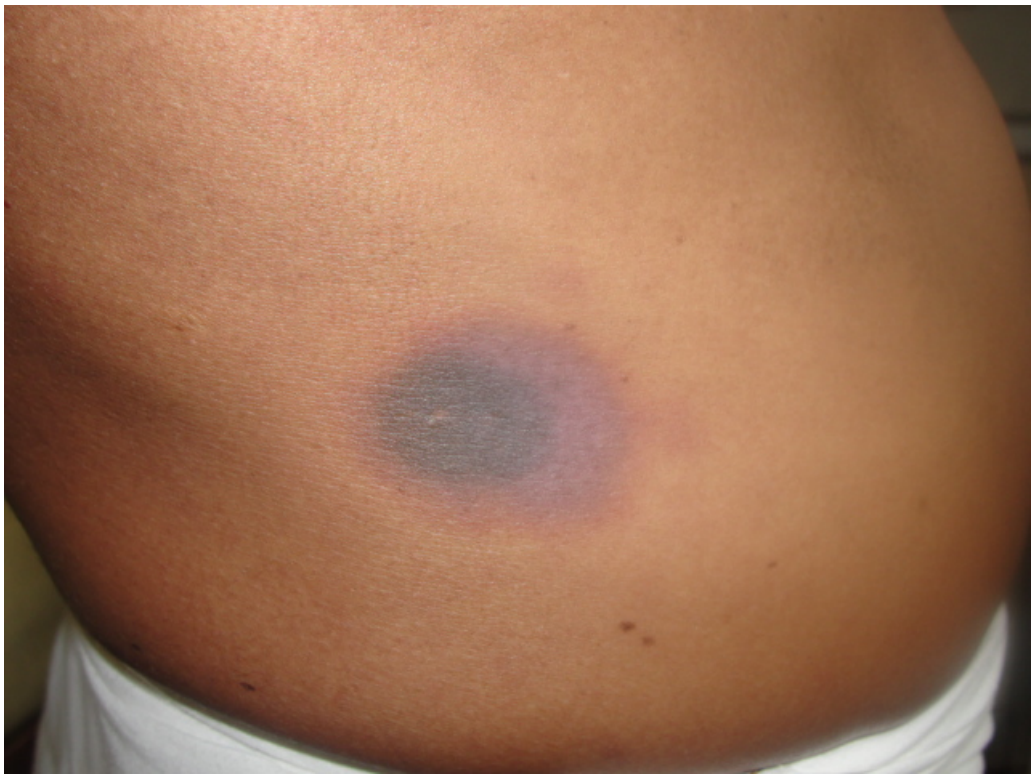
CLINICAL PHOTOGRAPHS



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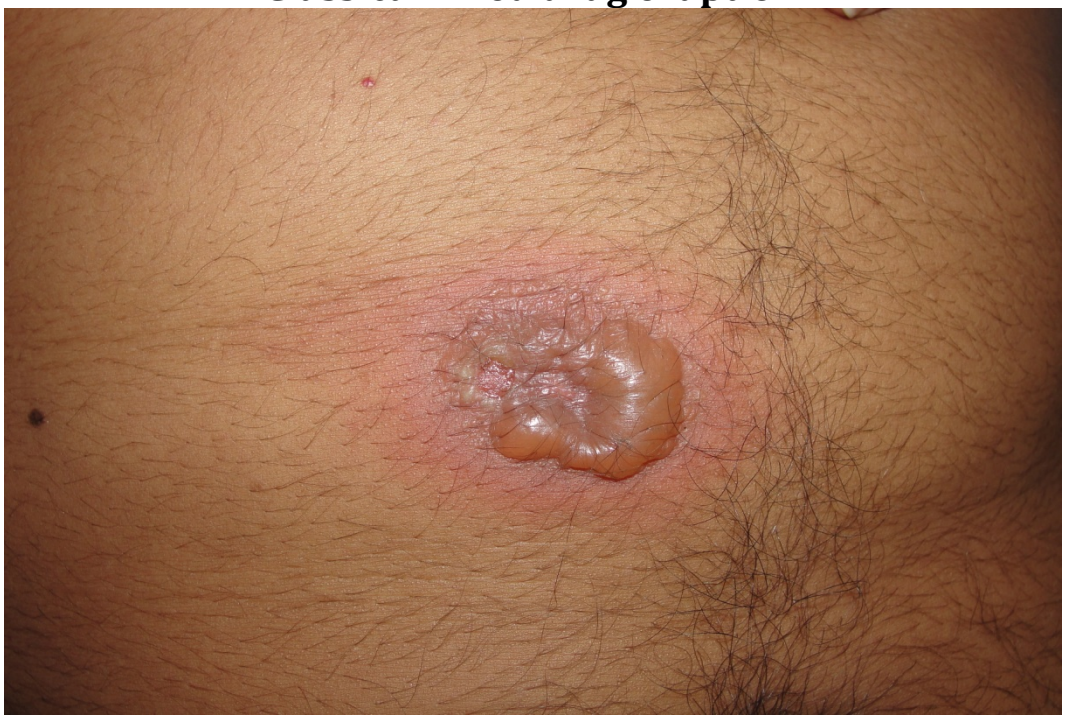

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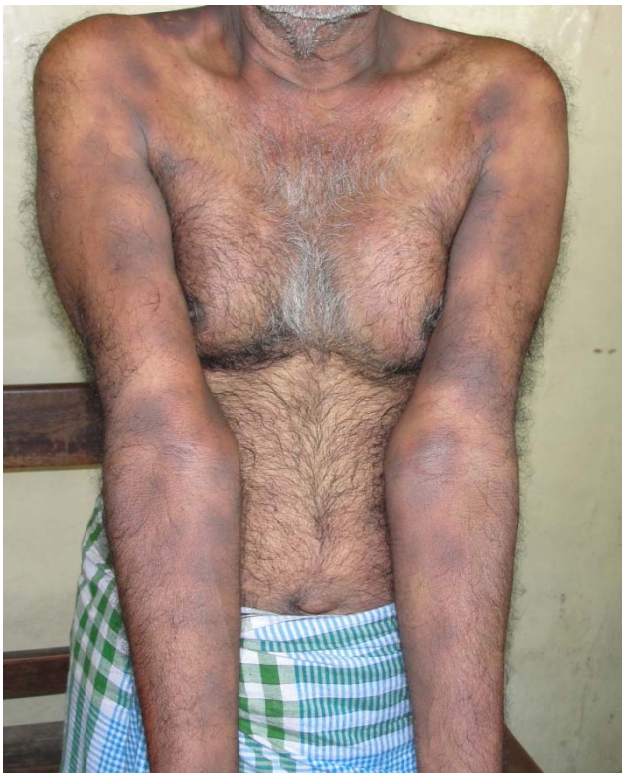

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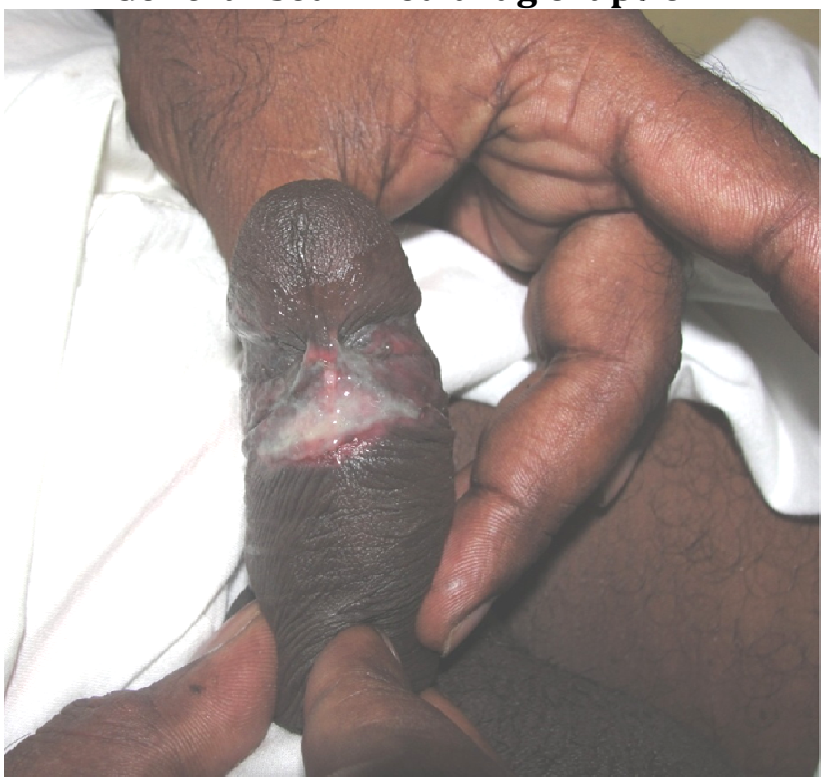

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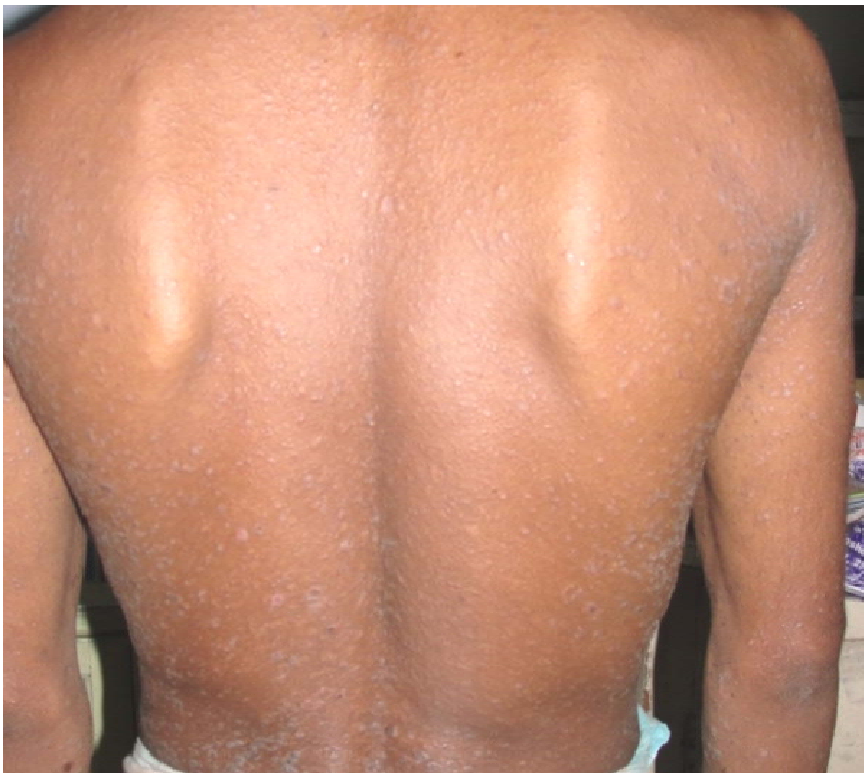

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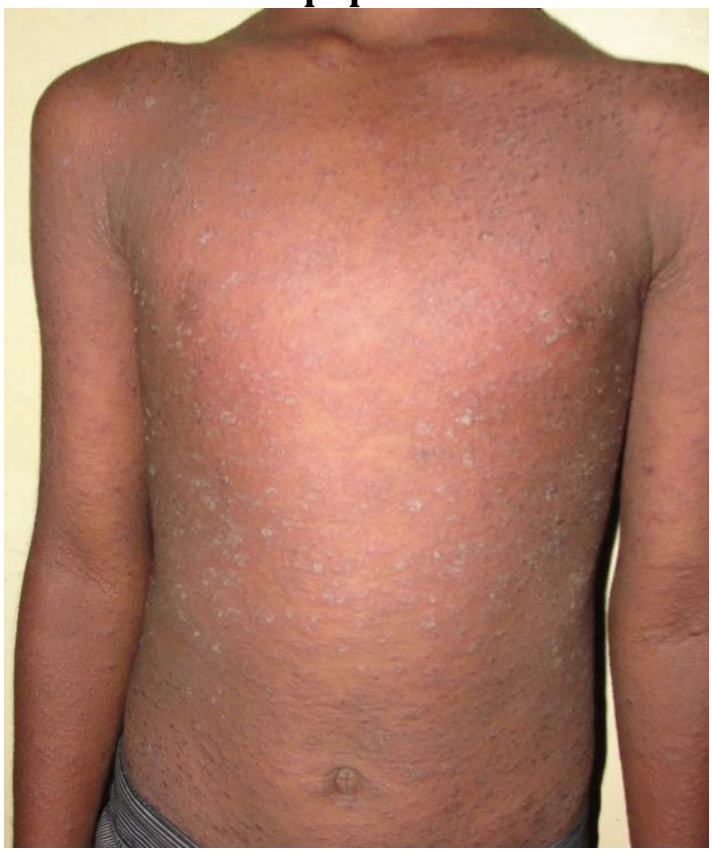

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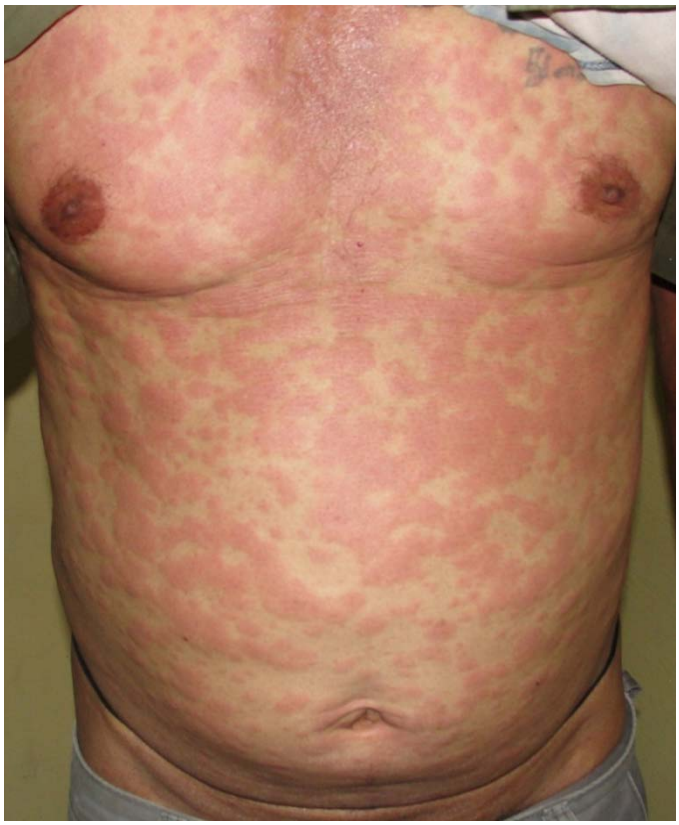

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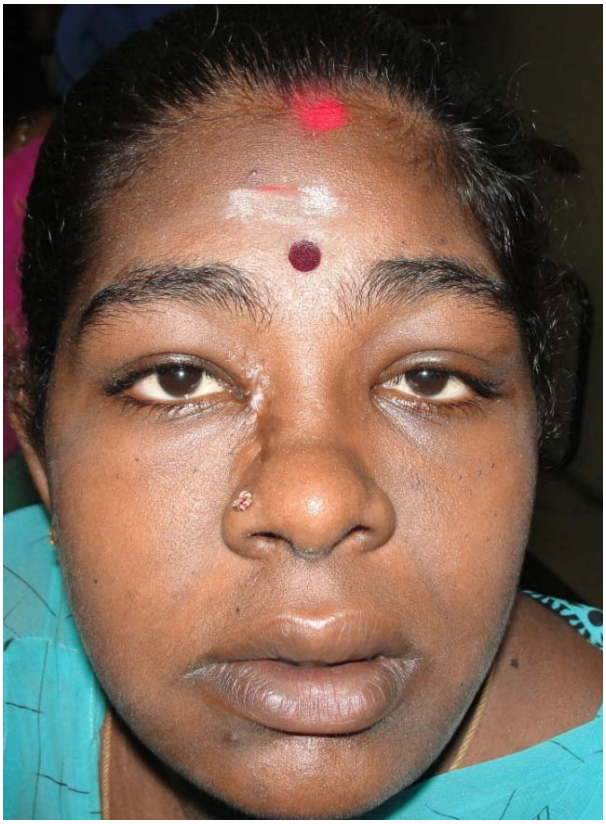

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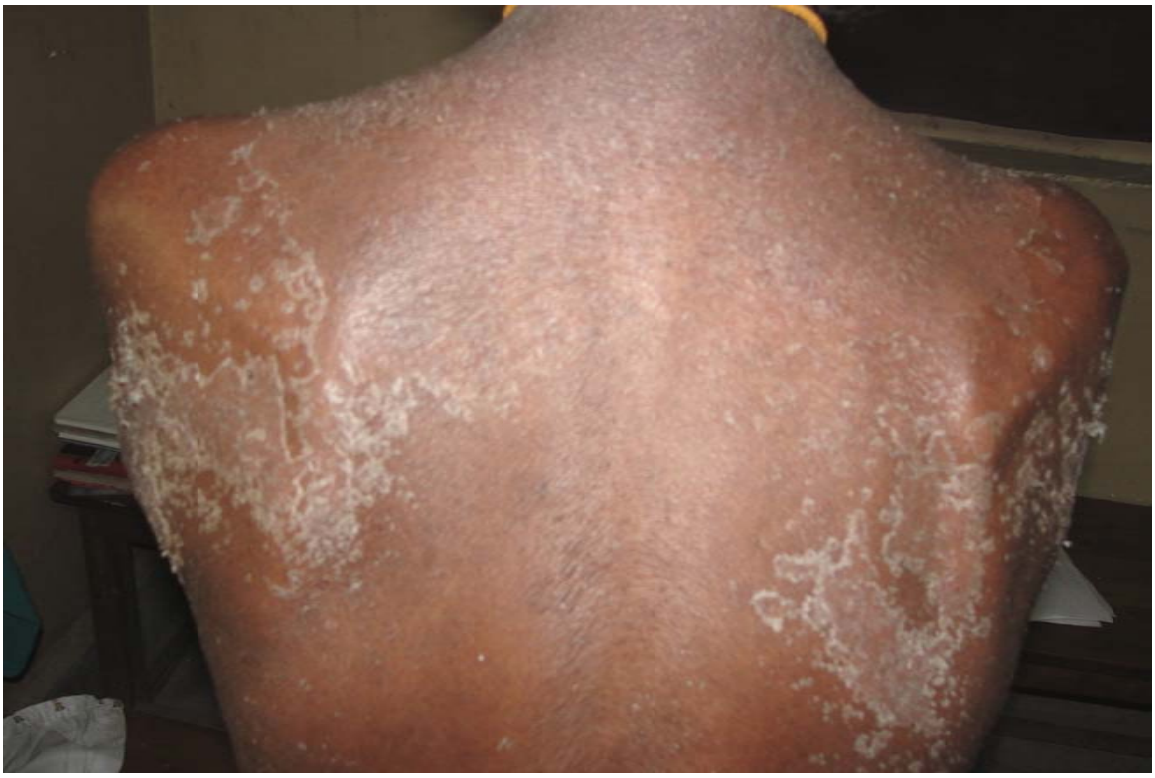

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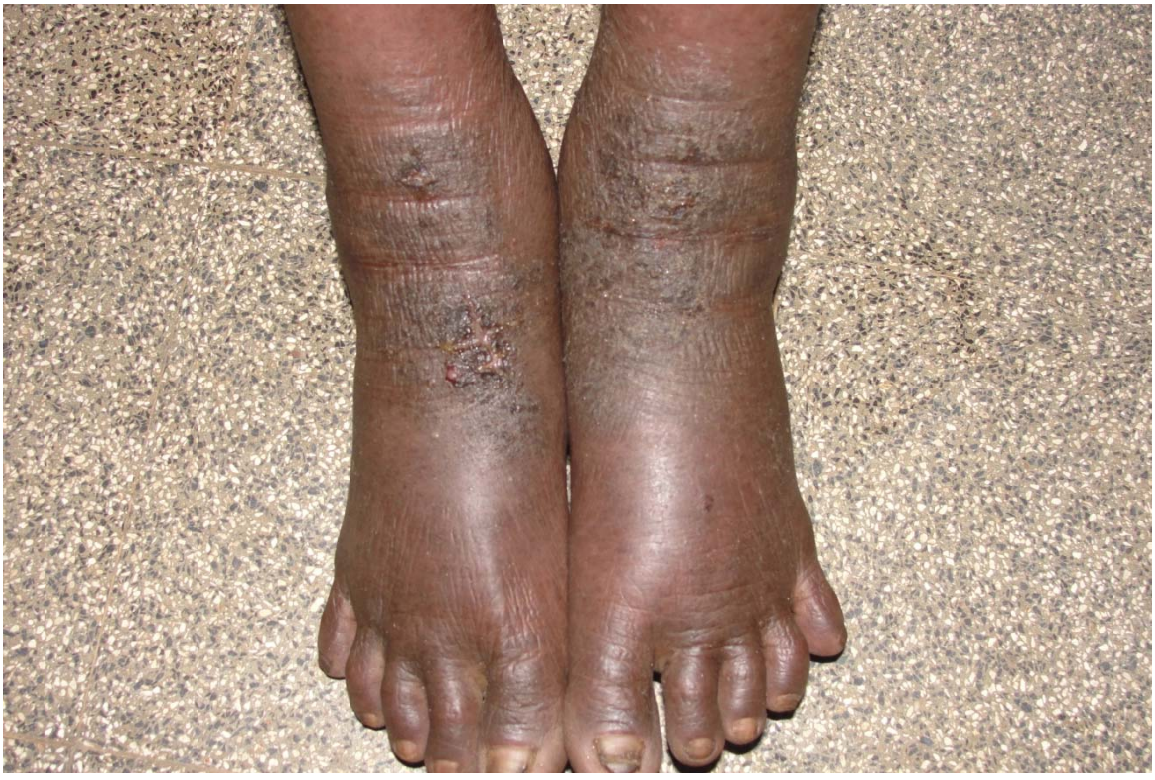

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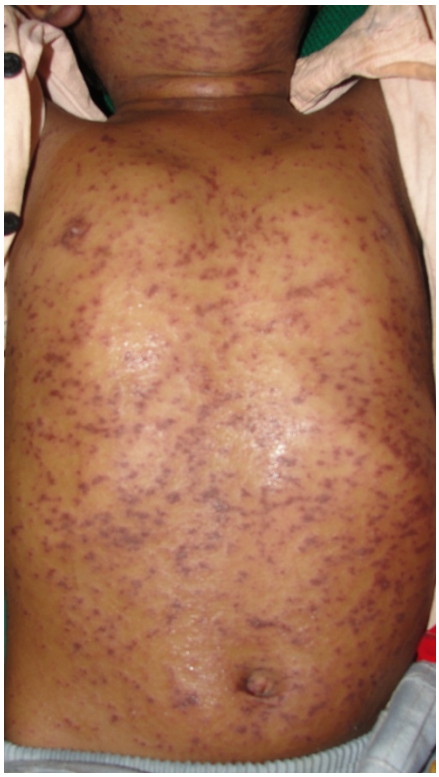
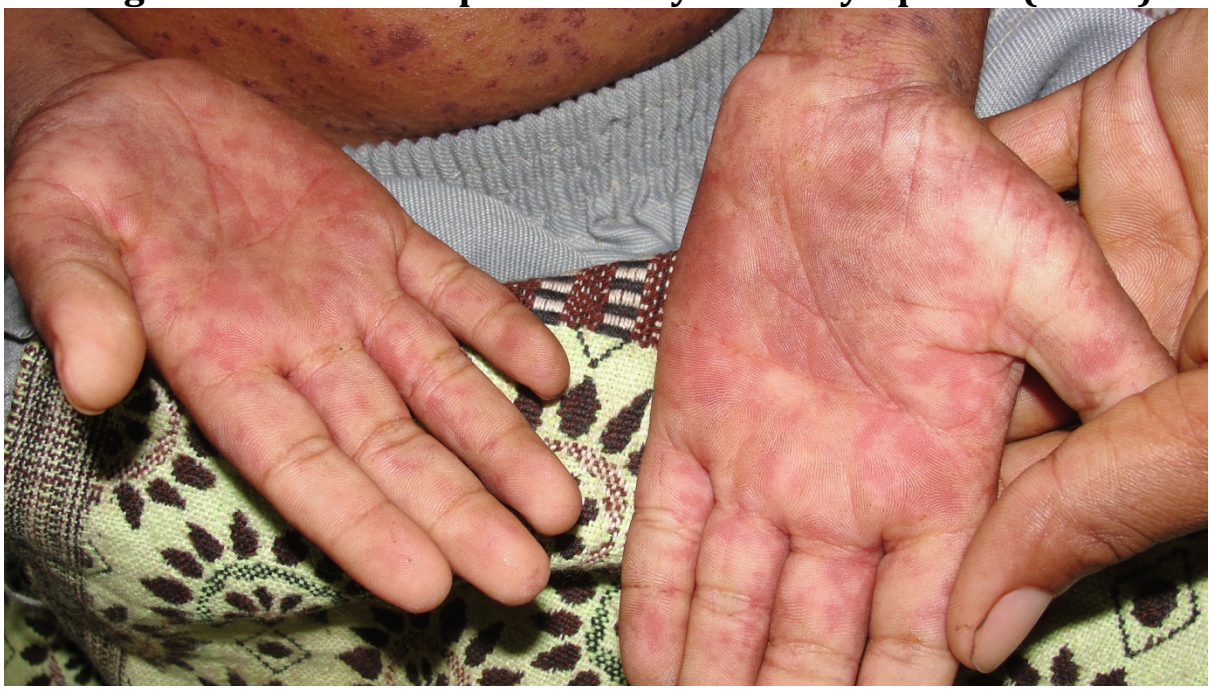
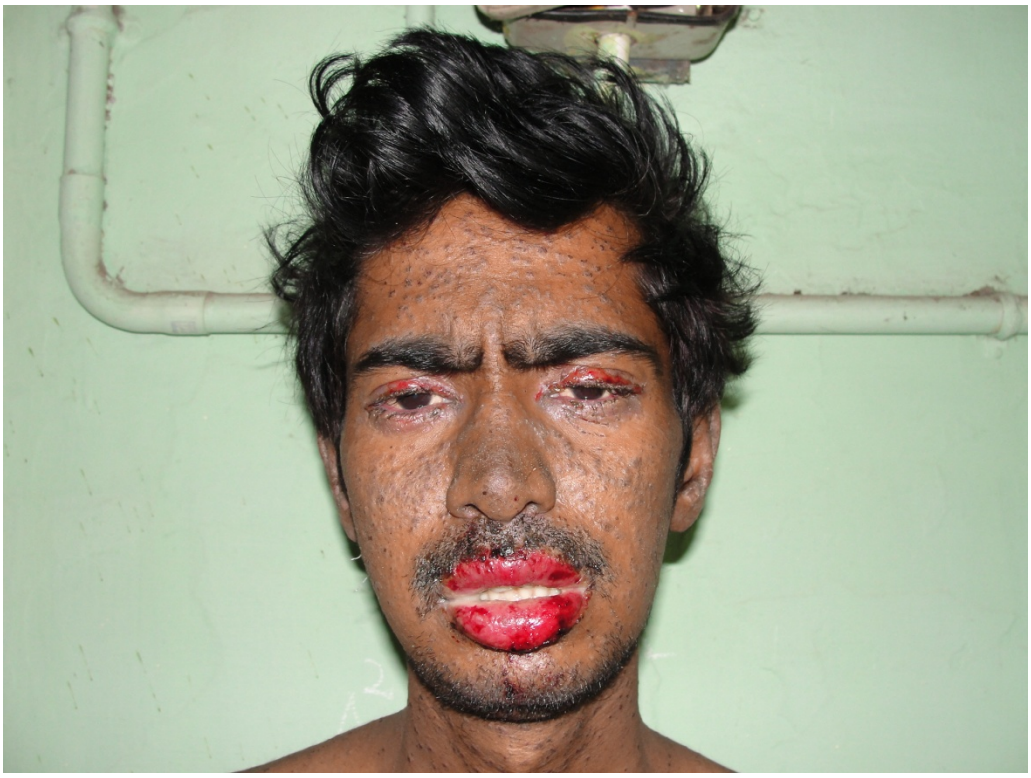


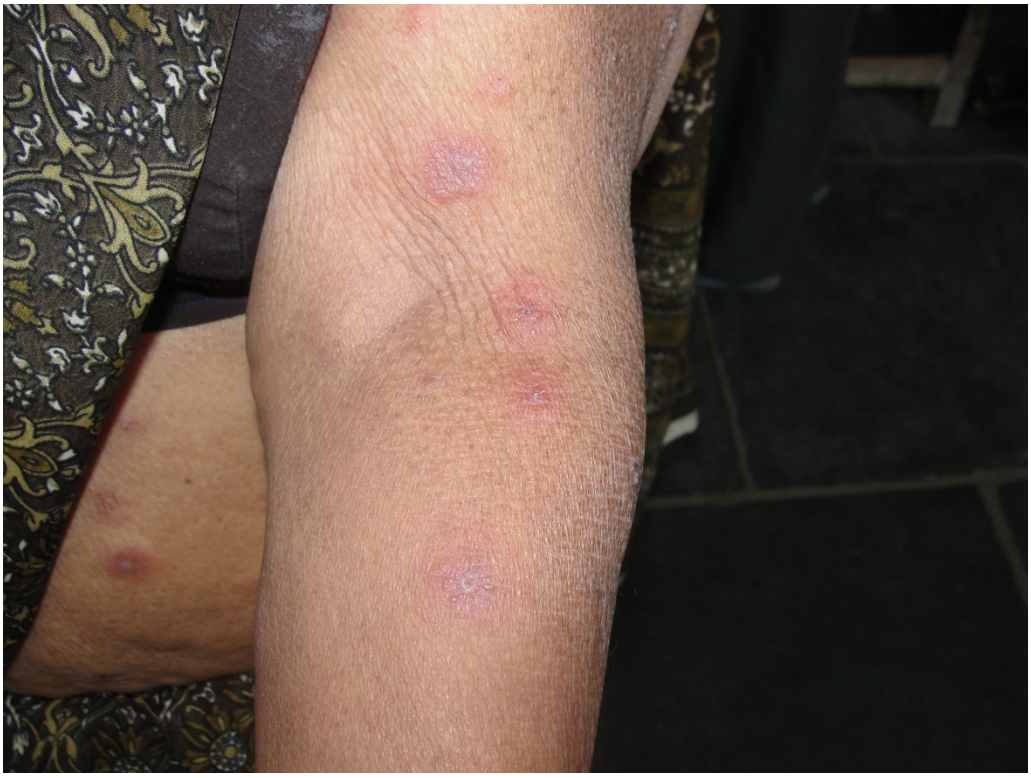
Drug rash with eosinophilia and systemic symptoms (dress)



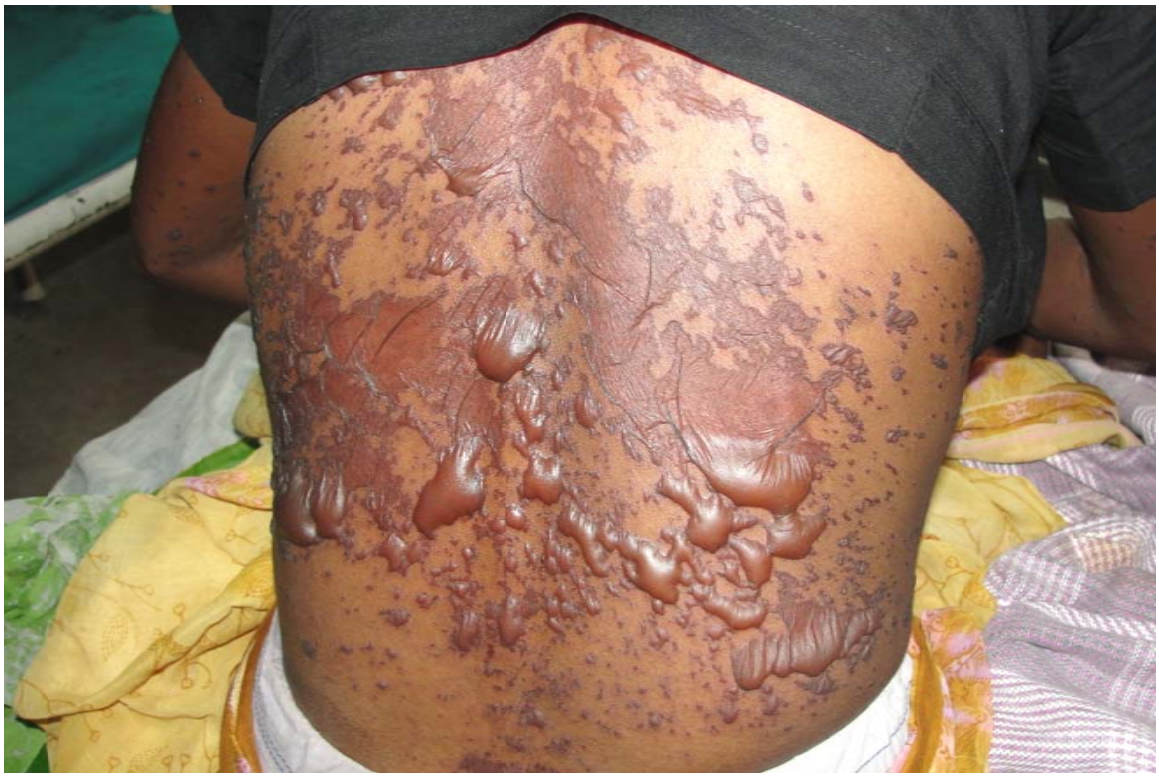
Acral involvement in dress



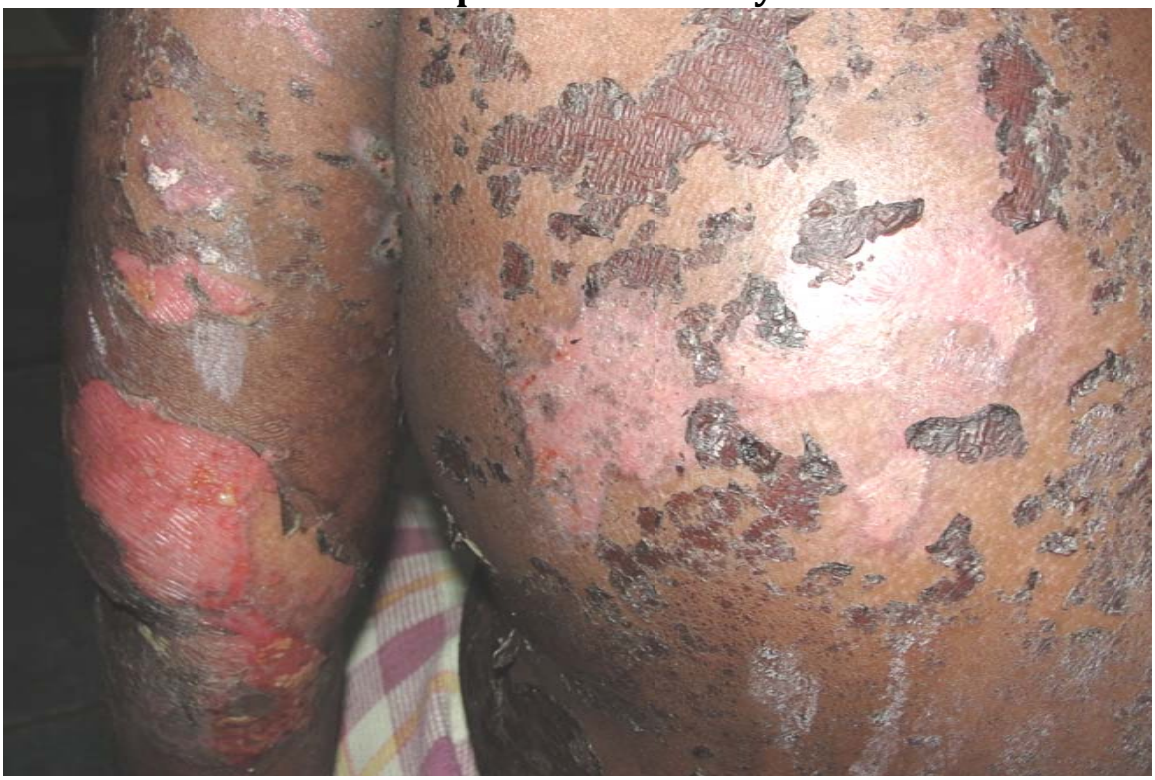
Steven Johnson Syndrome



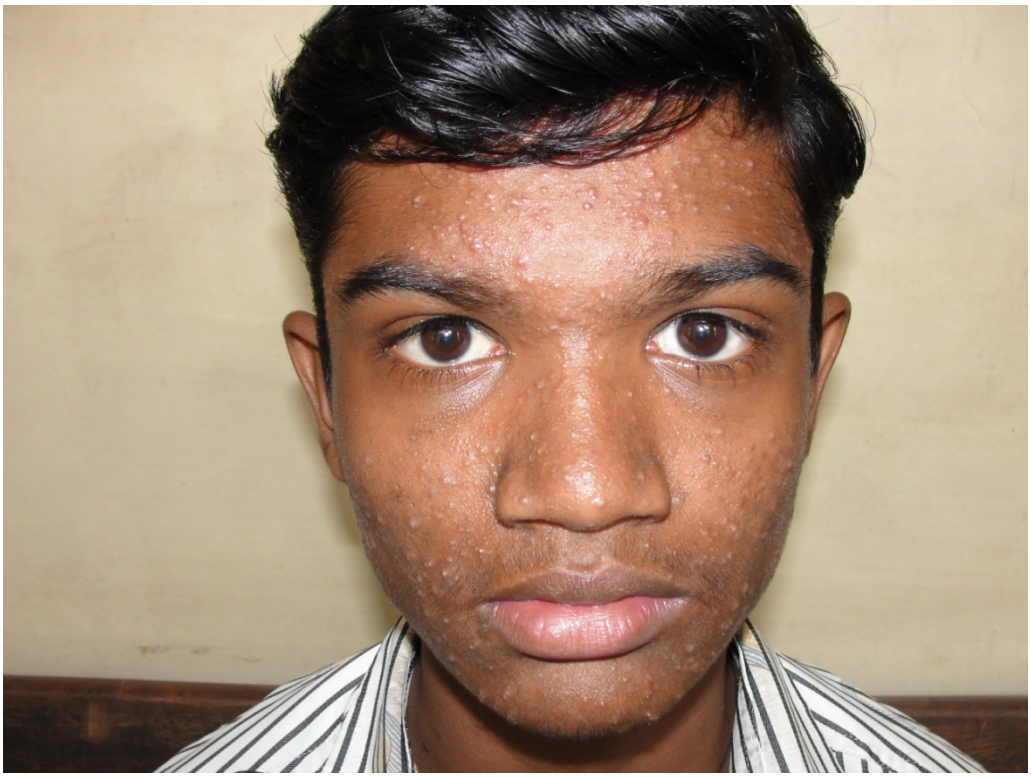
Erythema Multiforme



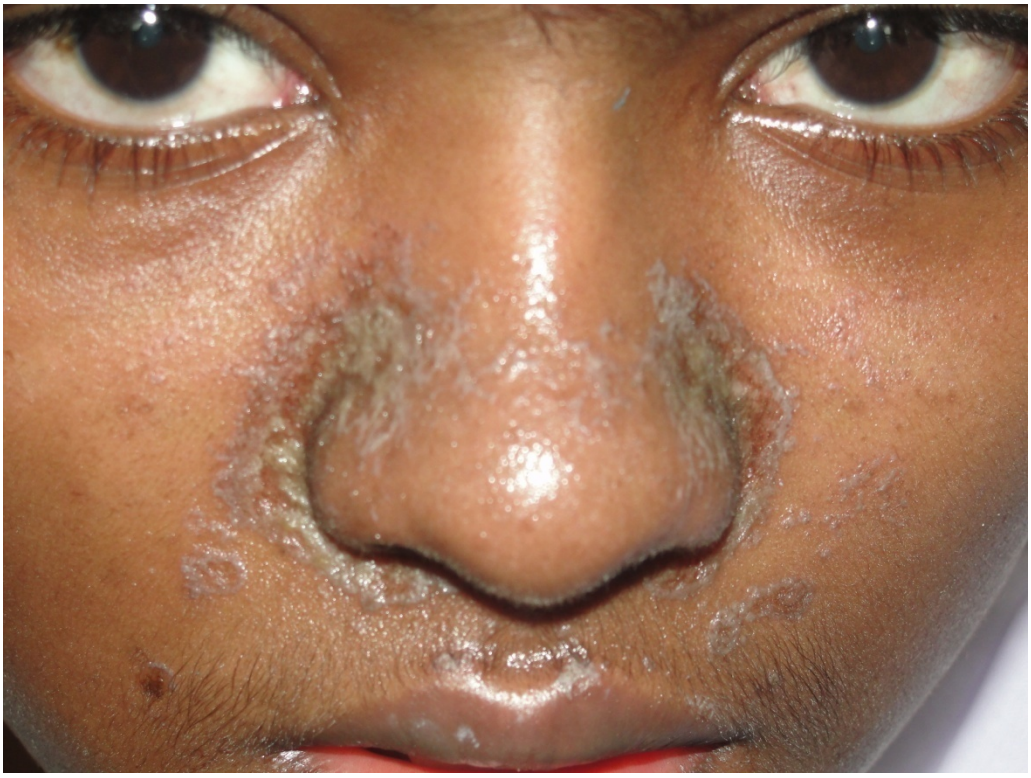
Toxic epidermal Necrolysis



Resolving Toxic Epidermal Necrolysis



Acneiform eruption



Phototoxic reaction

PROFORMA

Name:

Age:

Gender :

Address:

DETAILS ABOUT THE PRESENTING CONDITION:

-Time elapsed between drug intake & onset of first sign/symptom:

-Time since onset of first sign/symptom:

-Type of lesion patient developed:

-Presence of mucosal involvement:

ABOUT THE DRUG:

-Probable drug which caused the onset:

-Mode of drug administration:

-Type of drug taken[allopathic/homeopathic/ayurvedic]:

-Nature of illness for which drug was taken:

-Total number of dose of drug taken:

-Any previous h/o drug interactions:

-Whether taken over the counter/prescribed by RMP:

-Precipitating factors if any:

CONTRIBUTORY FACTORS:

-Any associated systemic illness:

-If the drug was taken for systemic illness:

-Any family h/o drug interactions:

-Associated secondary complications:

-Scalp/hair/nail involvement:

-Similar episodes in the past:

-If yes then details about the condition:

-Extracutaneous manifestations:

-HIV status of the patient:

DERMATOLOGICAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS:

RS:

P/A:

CNS:

RELEVANT INVESTIGATIONS CARRIED OUT:

Complete hemogram:

Liver function test:

Renal function test:

Tzanck smear:

FINAL DIAGNOSIS:

KEY TO MASTER CHART:

FDE	**-**	**Fixed Drug Eruption**
SJS	**-**	**Steven Johnson Syndrome**
TEN	**-**	**Toxic Epidermal Necrolysis**
DRESS	**-**	**Drug Rash with Eosinophilia and Systemic Symptoms**
ASOM	**-**	**Acute Suppurative Otitis Media**
CSOM	**-**	**Chronic Suppurative Otitis Media**
HTN	**-**	**Hypertension**
DM	**-**	**Diabetes Mellitus**
H+D	**-**	**Hypertension+ Diabetes mellitus**
LRI	**-**	**Lower respiratory tract infection**
TB MEN	**-**	**Tuberculous meningitis**
AIDS	**-**	**Acquired Immunodeficiency Syndrome**
CLL	**-**	**Chronic lymphocytic leukemia**
ATT	**-**	**Antituberculous treatment**
UTI	**-**	**Urinary tract infection**
HIV	**-**	**Human immunodeficiency virus**

A CLINICOEPIDEMIOLOGICAL STUDY ON ADVERSE CUTANEOUS DRUG REACTIONS

INTRODUCTION: An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects and unanticipated adverse manifestations.

Very few published studies have assessed the epidemiological and clinical features of drug reactions in India and still fewer in South India. Hence this study was undertaken to assess the pattern and clinical features of ACDRs in South Tamilnadu.

AIM OF THE STUDY:

1. To study the clinicoepidemiological pattern of various adverse cutaneous drug reactions in patients attending SKIN OPD, Government Rajaji Hospital.
2. To study the common drugs causing adverse cutaneous drug reactions.

MATERIALS AND METHODS:

This study was conducted at the skin OPD, Government Rajaji Hospital, Madurai Medical College, Madurai during the period from October 2009-September 2011 [24 months].All consecutive consenting patients diagnosed clinically as a case of ACDR of all age groups, of all genders were included in the study.

RESULTS AND CONCLUSION:

A total of 163 patients out of 1,03,536 were diagnosed with ACDRs. Maximum number of the patients were in the $4^{th}$and 5^{th} decade. Fixed drug eruption was the commonest type of ACDR followed by Urticaria and Maculopapular rash, next closely followed by erythroderma . Out of all the ACDRs 84 cases had exclusive cutaneous involvement only. Both skin and mucosa were involved in rest of the 79 cases. The commonest class of drug causing ACDR was antimicrobials. Other classes were anticonvulsants, NSAIDs, antidepressants & cancer chemotherapy.Cotrimoxazole was the commonest drug causing ACDR. Among the individual ACDRs, FDE was most commonly caused by Cotrimoxazole. Among the individual ACDRs, FDE was most commonly caused by Cotrimoxazole. Mucosal involvement was most commonly seen with Cotrimoxazole followed by Phenytoin and doxycycline in succession. Mucosal involvement was most commonly seen with Cotrimoxazole. None of the patients had a positive family history of ACDR.

Upper respiratory tract infection was the most common underlying systemic disorder following which patients had consumed the drug and developed ACDR.

Key words: ACDRs, Fixed Drug Eruption, Cotrimoxazole.

MASTER CHART									
S.No	NAME	AGE	GENDER	DIAGNOSIS	DRUG	RECURRENT EPISODES	MUCOSA	DURATION BETWEEN DRUG INTAKE & DISEASE ONSET	DISEASE ASSOCIATION
1	Chellapandi	37	M	urt+angioedema	Paracetamol	nil	oral	1hr	fever+headache
2	Poomathy	12	F	urticaria	Chloroquine	nil	nil	0.5hr	malaria
3	Ayyappa	35	M	urticaria	Griseofulvin	nil	nil	12hr	URI
4	Angela	9	F	bullous FDE	Cotrimoxazole	2	nil	1hr	URI
5	M.Ganesan	20	M	EMF	Cotrimoxazole	nil	oral+ genital	2d	URI
6	Anand	11	M	FDE	Cotrimoxazole	nil	oral	12hr	URI
7	Rathna	40	F	bullous+nonbullous FDE	Amoxycillin	1	oral	1hr	Sinusitis
8	Sagairaju	47	M	FDE	Cotrimoxazole	1	oral	1hr	URI
9	Gouri	11	F	FDE	Diclofenac	nil	nil	1hr	Myalgia
10	Fathima	45	F	FDE	Amoxycillin	3	nil	12hr	Sinusitis
11	Arjun	5	M	FDE	Diclofenac	nil	genital	1hr	Myalgia
12	Amaravathi	35	F	FDE	Cotrimoxazole	nil	oral	15min	URI
13	Veershanmathi	6mo	F	FDE	Cotrimoxazole	nil	nil	1day	fever
14	Aadhavan	19	M	bullous+nonbullousFDE	Ciprofloxacin	nil	nil	12hr	Acute Diarrheoa
15	Puspa	38	F	FDE	Sodium valproate	nil	nil	12hr	seizure disorder
16	Khathija	50	F	bullous FDE	Amoxycillin	5	oral	2hr	HTN
17	V Raman	30	M	FDE	Tetracycline	4	genital	12hr	dental caries
18	Thiruvasanan	44	M	FDE	paracetamol	many	genital	2hr	fever
19	Bharathi	26	M	FDE	Ciprofloxacin	1	genital+oral	2hr	typhoid
20	Suguna	18	F	FDE	Amoxycillin	nil	nil	6hr	External hordeolum
21	Chinnan	40	M	FDE	Piroxicam	1	only genital	2d	epididymoorchitis
22	Dhanalakshmi	31	F	FDE	metronidazole	2	oral	6hr	Acute Diarrheoa
23	S Pandi	17	M	FDE	Amoxycillin	2	oral	12hr	Sinusitis
24	Nahur Aniba	30	M	FDE	Doxycycline	4	genital+oral	1hr	dental caries
25	Seethalakshmi	20	F	phototoxic rxn	Ciprofloxacin	nil	nil	3d	Gingivitis

26	Sanjay	1.5	M	maculopapular rash	phenytoin	nil	oral	3 weeks	seizure disor
27	Gnanamoorthy	50	M	DRESS	phenytoin	nil	nil	4 weeks	TB MEN
28	Haridhas	10	M	erythroderma	Paracetamol	nil	nil	7d	fever
29	Vasanth	10	M	TEN	phenobarbitone	nil	genital+oral	8d	seizure disorder
30	Muthalai	35	F	maculopapular rash	Nevirapine	nil	nil	3 weeks	AIDS
31	Sanjay	1.5	M	DRESS	phenytoin	nil	oral	3 weeks	seizure disorder
32	Janaranjini	9	F	DRESS	cefixime	nil	oral	3 weeks	LRI
33	Vijayan	55	M	FDE	cotrimoxazole	3	nil	12hr	URI
34	Prema	42	F	bullous FDE	cotrimoxazole	3	nil	1day	URI
35	Vairmani	13	F	FDE	cotrimoxazole	many	nil	6hr	URI
36	Selvapandi	75	M	bullous FDE	amoxycillin	nil	nil	6hr	DM
37	Mayandi	50	M	FDE	Ibuprofen	3	nil	4hr	DM
38	Maradupandi	30	M	DRESS	phenytoin	nil	oral	3 weeks	seizure disorder
39	Jeeva	11	M	bullous FDE	cotrimoxazole	nil	nil	6hr	URI
40	Arulmary	32	F	SJS	cefoperazone	10	genital+oral	48hr	LRI
41	Chandra	55	F	erythroderma	Imatinib mesylate	nil	nil	2d	CLL
42	Bhagyam	34	F	maculopapular rash	nevirapine	nil	oral	16d	AIDS
43	Adiraja	19	M	TEN	norfloxacin	nil	oral	24hr	UTI
44	Nandini	14	F	Urticaria	mefenemic acid	nil	nil	2hr	fever+headache
45	Joshua	6	M	SJS	carbamezapine	nil	oral	1day	Absent seizures
46	Mookammal	46	F	EMF minor	paracetamol	nil	oral	15day	fever
47	Govindan	25	M	SJS	cotrimoxazole	nil	oral	1day	URI
48	Mariyammal	59	F	FDE	cotrimoxazole	4	oral	2days	DM
49	Vijaya	30	F	FDE	doxycycline	many	nil	6hr	UTI
50	M.Malliga	45	F	maculopapular rash	phenytoin	nil	nil	24days	seizure disorder
51	Kasthuri	30	F	bullous FDE	doxycycline	nil	nil	4days	dental caries
52	Shanthi	35	F	Urticaria	paracetamol	nil	nil	4hr	fever
53	Mayila	56	F	maculopapular rash	efavirenz	nil	nil	3days	HIV
54	Mohan	34	M	maculopapular rash	ciprofloxacin	nil	nil	12hr	typhoid
55	Varadharaj	26	M	maculopapular rash	phenytoin	nil	nil	3 weeks	seizure disorder
56	Prema	33	F	mucosal FDE	cotrimoxazole	3	oral	6hrs	URI

57	Raju	43	M	FDE	carbamezapine	6	nil	6hrs	Absent seizures
58	Saravana kumar	26	M	bullous FDE	doxycycline	1	nil	12hr	dental caries
59	Petchi	47	F	SJS	cefixime	2	oral+ genital	1hr	LRI
60	Valarmathy	28	F	urt+angioedema	cotrimoxazole	nil	oral	6hrs	URI
61	Bose	50	M	erythroderma	nevirapine	nil	oral	10days	AIDS
62	Muneeswari	40	F	urt+angioedema	penicillin	2	oral	2hr	fever
63	Kamakshi	55	F	bullous FDE	Doxycycline	nil	nil	3days	DM
64	Ravi	48	M	FDE	Ibuprofen	6	oral+ genital	30 minutes	Arthritis
65	Gopal	65	M	FDE	cotrimoxazole	1	nil	3days	HTN
66	Palaneeswari	60	F	FDE	Cotrimoxazole	3	nil	1hr	DM
67	Nithish	1.5	M	FDE	cotrimoxazole	nil	oral	24hr	URI
68	K Sundareswari	48	F	FDE	doxycycline	2	oral	30 minutes	UTI
69	Sumathy	38	F	FDE	doxycycline	3	oral+ genital	4hr	dental caries
70	Chandrakala	37	F	bullous FDE	doxycycline	3	nil	12hr	Pyoderma
71	Selvarani	25	F	FDE	Amoxycillin	2	oral	3hours	Sinusitis
72	Alagu	45	F	bullous FDE	cotrimoxazole	3	nil	1 day	URI
73	Premkumar	9	M	FDE	cefpodoxime	1	oral	24hr	LRI
74	Sivamurugan	4	M	bullous FDE	cefixime	3	nil	2 days	LRI
75	Raghukumar	6	M	FDE	penicillin	nil	nil	2hr	Pyoderma
76	R Jagadeesan	29	M	bullous FDE	nimesulide	nil	nil	12hr	Arthritis
77	Chandra	35	F	FDE	piroxicam	3	nil	3days	fever
78	Tamilarasi	55	F	FDE	doxycycline	2	oral	1 day	HTN
79	Aruldas	12	M	FDE	nimesulide	many	nil	1week	fever
80	Sivagami	65	F	FDE	ciprofloxacin	1	nil	2 days	DM
81	Rajasekaran	41	M	FDE	doxycycline	nil	oral	12hr	URI
82	Manikanthan	20	M	bullous FDE	cotrimoxazole	many	nil	1 day	URI
83	Solai	55	F	bullous FDE	nimesulide	many	nil	5 days	HTN
84	Vijaya	32	F	erythroderma	nevirapine	nil	oral	2 weeks	AIDS
85	Ponnammal	57	F	Urticaria	cotrimoxazole	2	nil	2 days	HTN
86	Sathya	6	F	EMF	Amoxycillin	nil	oral+ genital	3days	URI
87	Savithri K S	52	F	erythroderma	nevirapine	nil	oral	3 weeks	AIDS

88	Janaranjini	6	F	DRESS	cefoperazone	nil	oral	2 weeks	LRI
89	Amutha	24	F	maculopapular rash	phenytoin	2	oral	1 month	seizure disorder
90	Prakash	35	M	SJS	phenytoin	nil	oral+ genital	15 days	seizure disorder
91	Rathna	50	F	urt+angioedema	cotrimoxazole	nil	oral	12hr	URI
92	Lokanathan	25	M	Urticaria	ciprofloxacin	nil	nil	4hr	typhoid
93	Panneer selvam	52	M	erythroderma	carbamezapine	nil	nil	1 month	seizure disorder
94	Nagarani	20	F	acneiform eruptions	ATT	nil	nil	3 months	TB MEN
95	Prabhakar	21	M	acneiform eruptions	ATT	nil	nil	20 days	TB MEN
96	Azhagar Raj	48	M	Urticaria	cotrimoxazole	nil	nil	4hr	URI
97	Kashi	70	M	Urticaria	metronidazole	nil	nil	6hr	H+D
98	Pandi	36	M	urt+angioedema	doxycycline	nil	oral+ genital	1hr	dental caries
99	Eswari	17	F	DRESS	phenytoin	nil	oral	2 weeks	seizure disorder
100	Amaravathi	38	F	FDE	paracetamol	nil	nil	3hours	fever
101	Mahalingam	65	M	FDE	ibuprofen	nil	nil	30 minutes	H+D
102	Mohan	47	M	FDE	cotrimoxazole	many	oral+ genital	2hr	URI
103	Dinesh	22	M	FDE	ciprofloxacin	3	nil	3days	Sinusitis
104	Kavitha	25	F	FDE	amoxycillin	nil	nil	2 days	ASOM
105	Pasupathi	25	M	SJS	cefixime	nil	oral+ genital	2 days	LRI
106	Panju	43	F	erythroderma	sodium valproate	nil	oral	2 months	seizure disorder
107	Ayyanar	60	M	urticaria	piroxicam	3	nil	3hours	H+D
108	Chinnakani	40	M	TEN	phenytoin	nil	oral+ genital	1 month	seizure disorder
109	Anushya	17	F	FDE	penicillin	3	nil	3hours	URI
110	Mani	40	F	bullous FDE	cotrimoxazole	4	oral	6hrs	URI
111	Syed Ibrahim	40	M	bullous FDE	doxycycline	2	oral	7 hours	dental caries
112	Parvathi	24	F	erythroderma	chlorpromazine	nil	nil	1 month	seizure disorder
113	Vijaya	32	F	FDE	cotrimoxazole	6	nil	4hr	URI
114	Sumathy	30	F	maculopapular rash	phenytoin	nil	oral	4 weeks	seizure disorder
115	Ammani	6	F	Urticaria	chloroquine	nil	nil	2hr	malaria
116	Alagammal	23	F	Urticaria	Amoxycillin	4	nil	4hr	ASOM
117	Backiaraja	32	M	maculopapular rash	phenytoin	nil	nil	3 weeks	seizure disorder
118	Duraiammal	34	F	urt+angioedema	metronidazole	3	oral+ genital	4hr	Acute Diarrheoa

119	Eswar	45	M	erythroderma	sodium valproate	nil	nil	6 weeks	seizure disorder
120	Thirupathy	16	M	FDE	cotrimoxazole	many	oral	4hr	URI
121	T K Ramesh	41	M	FDE	Amoxycillin	nil	nil	5 hours	Sinusitis
122	Vishith	13	M	FDE	cotrimoxazole	3	nil	6hrs	URI
123	Seema	10	F	bullous FDE	cotrimoxazole	4	oral	12hr	URI
124	Saraswathi	47	F	FDE	cotrimoxazole	2	nil	30 minutes	fever
125	Murugan	37	M	FDE	NSAIDs	6	oral	2hr	fever
126	Ayyava	30	M	FDE	cotrimoxazole	3	oral	8 hours	URI
127	Praveen	36	M	Urticaria	paracetamol	many	nil	6hrs	fever+headache
128	Waheeda banu	32	F	urt+angioedema	ciprofloxacin	4	oral	8 hours	UTI
129	Latha	25	F	maculopapular rash	phenytoin	nil	nil	3 weeks	seizure disorder
130	Umapathy	53	M	erythroderma	carbamezapine	nil	nil	2 months	seizure disorder
131	Sitalakshmi	45	F	urt+angioedema	cefixime	4	oral+ genital	3hours	LRI
132	Kannan	56	M	EMF	Tetracycline	many	oral	6hrs	CSOM
133	Vasanthi	45	F	erythroderma	dapsone	nil	nil	2 months	leprosy
134	Bhuvaneswari	65	F	DRESS	phenytoin	nil	nil	4 weeks	seizure disorder
135	Chinnakalai	45	M	Urticaria	Imipramine	6	nil	5 hours	Depression
136	Asoka	32	M	FDE	cotrimoxazole	2	nil	4hr	UTI
137	Thiyagaraj	43	M	maculopapular rash	nevirapine	nil	nil	2 weeks	HIV
138	Pavan	28	M	EMF	penicillin	many	oral+ genital	48hr	Sinusitis
139	Sangilikalai	54	M	Urticaria	cotrimoxazole	many	nil	12hr	LRI
140	Pandiarajan	34	M	FDE	Aspirin	3	nil	1hr	fever+headache
141	Visheeth	16	M	FDE	cotrimoxazole	nil	genital	2hr	URI
142	Sooryabiwi	60	F	FDE	doxycycline	4	oral	30 minutes	UTI
143	Krishnan	26	M	SJS	Amoxycillin	nil	oral+ genital	3hours	Sinusitis
144	Chinnasamy	30	M	bullous FDE	doxycycline	nil	oral	12hr	dental caries
145	Abdul Rahman	30	M	maculopapular rash	Amoxycillin	nil	nil	1 day	fever
146	Lakshmi	23	F	bullous FDE	ibuprofen	nil	oral	4hr	Myalgia
147	Thiyagaraja	7	M	FDE	aspirin	nil	nil	7 hours	fever
148	Seethalakshmi	50	F	bullous+nonbullous FDE	cotrimoxazole	many	oral+ genital	2hr	URI
149	Lakshmi	28	F	bullous FDE	diclofenac	3	oral	3hours	bursitis

150	Sokkar	57	M	FDE	Aspirin	4	nil	4hr	Arthritis
151	prema	42	F	FDE	doxycycline	2	nil	5 hours	CSOM
152	Md Ibrahim	1	M	FDE	paracetamol	nil	nil	2 days	fever
153	Ponnuthai	67	F	Urticaria	cotrimoxazole	many	nil	4hr	HTN
154	Panchavarnan	55	F	bullous FDE	diclofenac	4	nil	4hr	DM
155	Vijaylakshmi	45	F	FDE	cotrimoxazole	many	nil	2hr	URI
156	Rashida Biwi	53	F	urt+angioedema	paracetamol	many	oral+ genital	2hr	H+D
157	Vedavyas	14	M	TEN	carbamezapine	nil	oral+ genital	8 hours	seizure disorder
158	Samudram	45	M	maculopapular rash	phenytoin	nil	oral	3 weeks	seizure disorder
159	Thangam	46	M	maculopapular rash	nevirapine	nil	nil	12hr	AIDS
160	Devanand	10	M	FDE	carbamezapine	ni.	nil	12hr	Absent seizures
161	Kruthika	3	F	urt+ angioedema	cotrimoxazole	nil	oral	12hr	URI
162	Valli	32	F	TEN	nevirapine	nil	oral+ genital	10days	AIDS
163	Mridula	52	F	TEN	nevirapine	nil	oral+ genital	5 days	AIDS