ESTIMATION OF SERUM THYMUS AND ACTIVATION REGULATED CHEMOKINE (TARC) IN DRUG INDUCED SKIN REACTION AND SEVERE CUTANEOUS ADVERSE DRUG REACTIONS (SCAR)

A dissertation submitted in partial fulfillment of the rules and regulations for M.D (Dermatology, Venereology and Leprosy) examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai, to be held in May, 2022.

ESTIMATION OF SERUM THYMUS AND ACTIVATION REGULATED CHEMOKINE (TARC) IN DRUG INDUCED SKIN REACTION AND SEVERE CUTANEOUS ADVERSE DRUG REACTIONS (SCAR)

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DECLARATION

I hereby declare that the dissertation entitled **"Estimation of serum thymus and activation regulated chemokine (TARC) in drug induced skin reactions and severe cutaneous adverse drug reactions (SCAR)"** conducted at Christian Medical College, Vellore is my original research work done in partial fulfillment of the rules and regulations forthe award of the M.D. degree in Dermatology, Venereology and Leprosy of the Tamil Nadu Dr. M.G.R.Medical University.

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This is to certify that the dissertation entitled "**Estimation of serum thymus and activation regulated chemokine (TARC) in drug induced skin reactions and severe cutaneous adverse drug reactions (SCAR)"** conducted at Christian Medical College, Vellore is a bonafide research work done by **Dr. Lydia Sharon Kati**. This study was undertaken at Christian Medical College, Vellore from **December 2019 to October 2021** under my direct guidance and supervision, in partial fulfillment of the requirement for the award of the M.D. degree in Dermatology, Venereology and Leprosy of the Tamil Nadu Dr. M.G.R. Medical University.

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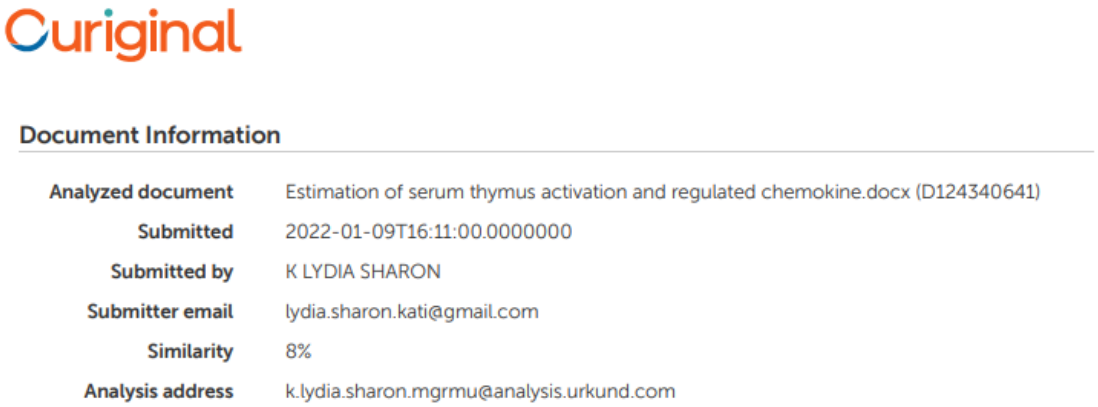

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Abbreviations

ABCD10	(Age, bicarbonate, cancer, dialysis, 10% body surface area)
ADR	adverse drug reaction
AEC	absolute eosinophil count
AENM	acute eosinophilic necrotising myocarditis
AGEP	acute generalised exanthematous pustulosis
ALDEN	Algorithm of Drug Causality in Epidermal Necrolysis
APC	Antigen presenting cell
ARDS	Acute respiratory distress syndrome
ART	Anti-Retroviral therapy
AST	Aspartate aminotransferase
BSA	Body surface area
CADR	Cutaneous adverse drug reaction
CBZ	Carbamezapine
CLEIA	Chemiluminescent immunoassay
CMV	Cytomegalovirus
CRP	C reactive protein
CSF	Cerebrospinal fluid
CTACK	Cutaneous t cell reacting chemokine
CTL	Cytotoxic T lymphocyte
CXCL	Chemokine ligand
CYP	Cytochrome

DAMP	Damage associated molecular pattern
DIC	Disseminated intravascular coagulation
DIHS	Drug induced hypersensitivity syndrome
DNA	Deoxyribose nucleic acid
DRESS	Drug reaction eosinophilia & systemic symptoms
EBV	Epstein Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ELISA	enzyme linked immunosorbent assay
GPS	Glasgow prognostic score
HAV	Hepatitis A
HBV	Hepatitis B
HCV	Hepatitis C
HHV	Human herpes virus
HIV	Human immunodeficiency Virus
HLA	Human leukocyte antigen
HMGB-1	high mobility group protein
IFN	Interferon
IQR	Interquartile range
IRB	Institutional review board
LFT	Liver function test
MAPK	Mitogen activated protein kinase
MDC	Macrophage derived chemokine or CCL-22

MHC	Major histocompatibility complex
MPE	Maculopapular eruption
NLR	Neutrophil lymphocyte ratio
NSAID	Non-steroidal anti-inflammatory drugs
OPD	Out Patient Department
PCR	Polymerase chain reaction
PPI	Proton pump inhibitors
RFT	Renal function test
SCAR	Severe cutaneous adverse reaction
SCORTEN	Severity of illness for toxic epidermal necrolysis
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SGPT	Serum glutamic pyruvic transaminase
SIRS	Systemic inflammatory response syndrome
SJS	Stevens Johnson's syndrome
TEN	Toxic epidermal necrolysis
TARC	Thymus and activation-regulated chemokine
TCR	T cell receptor
TMB	Tetramethylbenzidine
TNF	Tumour necrosis factor
UMC	Uppsala Medical Centre
URI	Upper respiratory infection
WBC	White blood cell
WHO	World health organization

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Estimation of serum thymus activation and regulated chemokine (TARC) in drug induced reactions versus viral exanthem

Introduction

The cutaneous adverse drug reactions (CADR) are commonly classified as non-life threatening or life-threatening reactions (1). The non-life-threatening CADR include maculo-papular exanthem (MPE), fixed drug eruption, etc. The severe cutaneous adverse reactions (SCAR) include Stevens Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP) & drug reaction with eosinophilia and systemic symptoms (DRESS) (1–3). Life-threatening cutaneous drug reactions are rare but cause significant morbidity and mortality. The diagnosis of a CADR is based on a temporal correlation of drug intake with cutaneous and systemic features of CADR, drug probability scoring for adverse reaction (e.g., Naranjo's algorithm, WHO-UMC scale, etc.), investigations (e.g., eosinophilia and transaminitis in DRESS, neutrophilia in AGEP) and supportive histopathology. However, there are no conclusive diagnostic tests for CADR. For instance, an exanthematous or a maculopapular rash could be due to a drug or a viral infection or a connective tissue disorder, etc. Also, a rash due to a drug could be either a benign drug-induced MPE or a serious DRESS. The misdiagnosis of a rash and absence of a follow-up can lead to perilous consequences. In this context identification of a biomarker to differentiate a SCAR from an MPE or a viral exanthem can be beneficial. There are a few reports of serum thymus regulation and activated chemokine (TARC) or CCL17, a Th2 mediated chemokine which has been reported to be a biomarker for SCARs especially for DRESS (4–7).

Aims

a) To describe the clinical profile of patients with drug-induced maculopapular eruptions (MPE) and severe cutaneous adverse reactions (SCARs)

b) To evaluate the role of serum levels of thymus and activation regulated chemokine (TARC) as a potential biomarker in patients with drug-induced maculopapular eruptions (MPE) and severe cutaneous adverse reactions (SCARs)

Objectives

a) To study the clinical profile in patients with drug induced MPE and SCARs

b) To measure the serum TARC values in MPE and SCARs

c) To compare serum TARC levels between drug-induced MPE, drug reaction with eosinophilia and systemic symptoms (DRESS), and viral exanthem

Review of literature:

Background

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as a response to a drug that is noxious and unintended, and it occurs at dosages that are normally given in humans for diagnosis, therapy, or prophylaxis of disease, or modifications of a physiological function (8). Most of the drug reactions are dose-dependent and can be predicted, while a small minority are dose-independent and are not easily predictable (8). The CADRs belong to the "non-dose related" or the dose-independent Type B category of adverse reactions. The exact pathophysiology behind CADR remains incompletely understood nonetheless, it is an immunologically mediated reaction and involves either IgE or T-cells(1,3).

Cutaneous adverse drug reactions (CADR)

Skin is one of the most commonly affected organs in an adverse drug reaction (2,9). These cutaneous adverse drug reactions (CADR) are immunologically mediated inflammatory reactions (3). The early recognition of CADR, especially SCARs, is essential to mitigate the morbidity and mortality associated with these iatrogenic diseases. There are no gold-standards tests for the diagnosis of a CADR. The diagnosis is based on various parameters such as the morphology of the CADR, timing, and duration of drug exposure, latent period, course of the CADR with discontinuation of the drug, a previous history of "drug allergy" and nature and timing of a further eruption with a drug rechallenge, and relevant investigations supporting the diagnosis (10,11). Application of an adverse drug reaction probability scale such as Naranjo's' scale (Appendix V) and algorithm of drug causality in epidermal necrolysis (ALDEN) for

SJS/TEN (Appendix VI) allows removal of only the suspected medication(s) and would permit the use of other medications important for the patient. Early recognition and prompt withdrawal of the culprit drug are chief factors that help to reduce the disease burden (9). The most common differential diagnoses include viral exanthem, connective tissue disorder, graft-versus-host disease, lymphomatous/paraneoplastic eruption, etc. (2).

Epidemiology of cutaneous adverse drug reaction

Cutaneous adverse drug reactions occur in approximately in every 1 in 100 new medication users (12). Of these, the benign drug-induced MPE accounts for more than 95% of cases. Prospective studies on adverse cutaneous reactions from western literature report an overall incidence of 1.8 per 1000 admitted patients (1). In a systematic review from India, the incidence of CADR was reported to be 82.59/1000 cases in inpatient settings and 8.72/1000 cases in outpatient settings (13). In India, SCARs constituted 8% of CADR with phenytoin and carbamazepine being the most commonly implicated drugs and SJS/TEN being the most commonly reported SCAR (13). The incidence of the SJS/TEN spectrum is estimated to be 1-2 cases per million per year. The estimated overall population risk from DRESS is between 1 in 1000 and 1 in 10,000 drug exposures (14). The overall estimated incidence of AGEP is 1-5 per million per year with slight female preponderance demonstrated by EuroSCAR and Bhat et al. (15–17).

Classification of Cutaneous Adverse Drug Reactions

These can be classified as

- Non-immunological- 80-90%
- Immunological 10-20%

Table 1 shows the Gell and Coomb classification of the hypersensitivity reactions.

Table 1: Gell and Coomb's classification

	Immune response	Consequence	Effects	Cells predominantly involved
Type I	IgE	Mast cell degranulation	Urticaria, anaphylaxis	B cells, mast cells
Type II	IgG	Cytolysis	Immune cytopenias	NK cells, B cells
Type III	IgG & complement	Immune complex mediated	Serum sickness, Arthus reaction, vasculitis	B cells, NK cells, phagocytes
Type IV a	Th1 mediated	Monocyte activation by INF-γ and TNF-α	Contact dermatitis, SDRIFE	T cells, macrophages, monocytes
Type IV b	Th2 mediated	IL-4, IL-5, IL-13 induced eosinophilic inflammation	Maculopapular exanthem and DRESS	T cells, eosinophils
Type IV c	Cytotoxic T lymphocyte mediated	Perforin & granzyme mediated keratinocyte killing	Maculopapular exanthem and bullous ADR	T cells
Type IV d	T cells	Neutrophil recruitment from IL-8, IL-17 GM-CSF	AGEP, Behcet's disease	T cells, neutrophils

The drug-induced MPE and the SCARs are type IV delayed hypersensitivity reactions. These can be subclassified as DRESS - type IV b Th2 driven reaction,

SJS/TEN- type IV c cytotoxic reaction, and AGEP- type IV d reactions (18). However, these T-cell mediated ADRs are not mutually exclusive and have significant overlap as in case of drug-induced MPE. Figure 1 shows the effector cells and cytokine profile involved in SCARs.

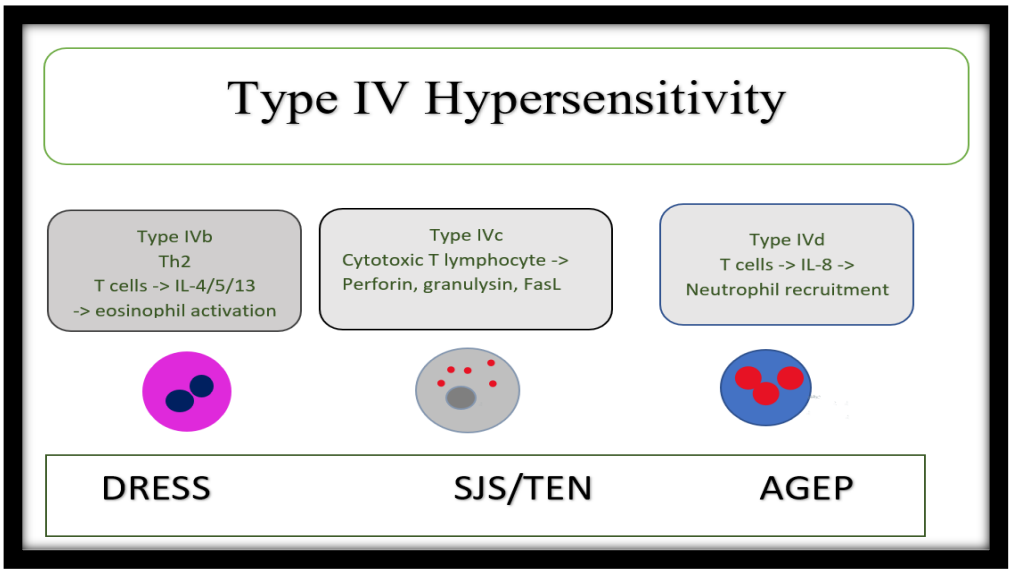


Figure 1: Revised Gell and Coombs classification according to effector cells and cytokine profile involved

The various CADR of interest in this study are the delayed T-cell mediated, non-anaphylactoid reactions which are as follows(3):

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Drug-induced maculopapular eruption (MPE)
- Stevens-Johnson syndrome (SJS), Toxic epidermal Necrolysis (TEN)
- Acute Generalised exanthematous Pustulosis (AGEP)

Causality assessment in Cutaneous adverse drug reactions

A thorough drug history, a drug timeline, and the temporal correlation help in ascertaining the possible culprit drug(s). An assessment of the causality of the

adverse reaction is imperative in the management of the patients with CADRs. Clinical judgment is the first step and it is the most common strategy used in routine clinical practice for causality assessment. However, it is susceptible to pitfalls such as subjectivity, poor reproducibility, and lack of standardization(19). Hence the application of an ADR causality algorithm such as the Naranjo ADR probability scale, Kramer algorithm, Jones algorithm, Karch algorithm, WHO-Uppsala Monitoring Centre (WHO-UMC) etc., helps in assessing the drug causality (19–21). These pharmacovigilance algorithms help clinicians to discriminate the drug(s) capable of the implicated ADR from the medication list of a CADR patient (20,22). Algorithm for assessment of Drug Causality in Epidermal Necrolysis (ALDEN) is a scoring system specific for SJS/TEN with a better ability than the general algorithms that compare all types of drug reaction to find the culprit drug from innocent drugs in SJS/TEN (19). One recent Indian study on patients with CADR utilized ALDEN for causality assessment in DRESS as well (23). Drug causality algorithms are especially useful when multiple drugs have been administered. The advantage of these algorithms is the high intra- and inter-evaluator agreements in determining the culprit drugs (19,20) These ADR causality scales are useful not only for patient management via proper identification of drug responsible for ADR but also for pharmacovigilance and for justification for evaluation of in-vitro mechanisms involved (19).

DRUG REACTION with EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Introduction:

Drug reaction with eosinophilia and systemic symptoms is a SCAR with cutaneous and internal organ involvement that was historically linked to phenytoin and described as 'phenytoin hypersensitivity syndrome' in the 1940s. Various names have been used to describe it, such as hydantoin/phenytoin syndrome, anticonvulsant "Kawasaki syndrome", mononucleosis-like syndrome, pseudolymphoma, graft-versus-host like illness, etc.(14,24). In 1988, Sontheimer suggested "drug-induced delayed multiorgan hypersensitivity syndrome" and Bocquet et al. at the same time coined the term, "drug rash with eosinophilia and systemic symptoms" which subsequently got more acceptance. Later the 'R' in DRESS was changed from rash to reaction as dermatosis is usual and not mandatory and the extent of skin involvement is variable (24). The Japanese consensus group uses the nomenclature 'drug-induced hypersensitivity syndrome' (DIHS) which is DRESS with evidence of HHV-6 reactivation (25). In clinical practice, the diagnosis of DRESS is frequently overlooked due to unfamiliarity with the syndrome and its criteria and especially when cutaneous findings are minimal, making the diagnosis difficult(13).

Commonly implicated drugs in DRESS include aromatic anticonvulsants and sulphonamides. Carbamazepine has been implicated as the most common offender as suggested by Hussain et al. (26) and seen in the results from a multicentric study by Kardaun et al. (27) and a systematic review by Patrice Cacoub et al. (14). Other drugs frequently implicated are phenytoin, antibiotics,

allopurinol, sulfasalazine iodinated contrast media, etc. (11,25,28,29).

Clinical features:

Drug reaction with eosinophilia and systemic symptoms presents with a combination of skin changes and systemic involvement. The lag phase from drug initiation to the onset of symptoms is often 2-6 weeks. The DRESS syndrome is distinguished from a drug-induced MPE by a relatively later onset, a longer duration, multiorgan involvement, activation of lymphocytes in the form of enlarged lymph nodes, lymphocytosis, atypical lymphocytes, and eosinophilia with reactivation of herpesviruses (30). However definite DRESS (RegiSCAR >5) with a short latent period has been described by Soria et al. suggesting a diagnosis of DRESS with a short latent period (of less than 15 days) should be accepted in the appropriate settings (28). Some features such as pruritus, skin pain, fever, and lymphadenopathy may appear even before the skin rash (27). Also, they present with a history of fever and malaise for several days prior to skin changes leading to misdiagnosis of infection (31,32). Clinical features can remain for weeks or months after discontinuing the culprit drug (26). Table 2 compares the demographic and clinical and biological features of patients with DRESS syndrome.

Table 2 Comparison between demographic and clinical features of DRESS in various studies						
Parameter	Kardaun et al. (27)	Hiransuthiku et al. (33)	Walsh S et al. (34)	Avancini et al. (35)	Sasidharanpillai et al. (36)	Choudhary et al. (23)
Country	Europe	Thailand	Europe	Latin America	India	India
Study period	2003-2009	2004-2014	2005-2011	2008-2012	2010-2013	2021
Study design	Prospective	Retrospective	Prospective	Retrospective	Prospective	Prospective
Patients with DRESS	n= 117	n = 52	n= 27	n= 27	n= 26	n= 25
RegiSCAR for DRESS	≥ 4	> 5	≥ 4	> 5	≥ 4	≥ 2
Age	48 ± 32	33 ± 25	40	36 ± 16.4	37.7	43.16 ± 12.8
M:F ratio	1: 0.80	1: 2.47	1: 0.58	1: 0.58	1: 0.8	1: 1.5
Drugs implicated	Carbamazepine Allopurinol	Phenytoin	Phenytoin Carbamazepine	Phenytoin	Phenytoin	Sulfasalazine
Latent period in days	17-31	9- 27	10-49	3-180	7-90	10-44
Fever	90%	78.8%	100%	96.2%	96.2%	100%
Facial oedema	76%	7.7%	85.1%	62.9%	96.2%	88%
Mucosal lesions	56%	-	22%	-	73.07%	100%
Lymphadenopathy	54%	50%	88%	62.9%	50%	76%
Abnormal LFT	75%	94.2%	74%	85.1%	80.8%	80%
Abnormal RFT	37%	15.4%	7%	33.3%	7.69%	32%
Pulmonary involvement	32%	3.8%	-	3.7%	11.5%	12%
Peripheral eosinophilia	95%	60%	92.5%	96.2%	34.6%	56%
Atypical lymphocytes	68%	26.9%		62.9%	19.2%	-
Thrombocytosis	19%	-	-	-	-	-

Clinical features

Skin and mucous membranes: Cutaneous manifestation can be variable. The most common manifestation is a diffuse erythematous maculopapular/morbilliform pruritic eruption which can occasionally be erythrodermic. It usually involves the face, upper part of the trunk, and upper extremities and subsequently involves the lower extremities. In most cases, >50% of BSA is involved (31). Facial oedema is considered characteristic for DRESS (24). Purpuric lesions, erythroderma, and infiltrated appearing lesions are morphologies suggestive of DRESS (37). Rash lasts for more than 15 days in most cases (27). There is increased vascular permeability leading to the passage of plasma in the dermis which results in facial oedema and infiltrated/urticated lesions in DRESS (38). Erythema multiforme (EM) like lesions have been described to correspond to liver damage (34).

The histological features in skin biopsy in DRESS are heterogeneous (34,39). The various features encountered are spongiotic dermatitis, interface dermatitis, apoptotic keratinocytes, perivascular lymphocytic infiltrate in papillary dermis with the presence of eosinophils, atypical lymphocytes, and dermal oedema. The presence of more than one inflammatory reaction pattern is significantly associated with DRESS as compared to an MPE or non-drug-related rash (26,31,39). Apoptotic keratinocytes seen in EM-like presentations have an aggressive course of the disease and an increased risk of liver damage (38,39).

Systemic involvement: Multiple organs can be involved in DRESS which includes but are not limited to lymphatic, hematological, and hepatic systems. There are recognized patterns of organ involvement with specific drugs but individual drugs can affect any organ system (31). Figure 2 shows the evolution of clinical features in DRESS.

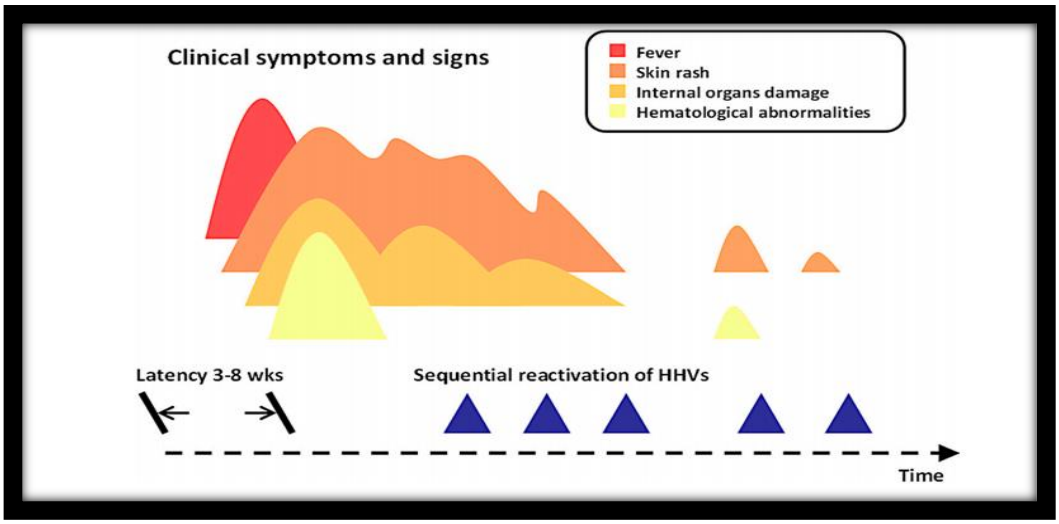


Figure 2 Clinical course in DRESS syndrome Adapted from Int. J. Mol. Sci. 2017 (40)

- **Lymphadenopathy**: In addition to fever (occurring in >95% cases) and malaise, about 50-70% of cases are reported to develop diffuse lymphadenopathy (25,26). Lymph node involvement can be discrete or generalised affecting cervical, axillary and inguinal regions. Lymph node biopsy can show 2 distinct patterns (31):
    - benign lymphoid hyperplasia which has preserved architecture of lymph node
    - pseudolymphoma with normal architectural disruption by polymorphous infiltrate consisting of eosinophils, plasma cells,

histiocytes, atypical cells, mitotic figures, and necrotic areas without capsular invasion or Reed-Sternberg cells.

Histological examination of other organs infrequently done can be nonspecific with the accumulation of eosinophils in damaged tissue

- **Haematological**: Around 30- 90% of cases present with eosinophilia which is thought to play a role in medicating visceral organ damage through the release of proteins toxic to many tissues (26,40). Absolute eosinophil count (AEC) of ≥ 1500 is characteristically seen in DRESS as compared to MPE and other CADR and AEC values of ≥700 and ≥1500 carry a score of 1 and 2 respectively in the RegiSCAR validation score for DRESS (37). Marked leucocytosis with atypical lymphocytes can be seen in 27-67% of patients that can be preceded by leukopenia or lymphopenia (40). Monocytosis, thrombocytosis and secondary hemophagocytic lymphohistiocytosis or macrophage activation syndrome can occur (27,41). Atypical lymphocytes and enlarged lymph nodes in more than 2 sites also carry weightage (a score of one point each) in the scoring system by RegiSCAR scoring for DRESS (37).

- **Hepatic**: Involvement ranges from mild transient transaminitis to fulminant hepatic failure. Phenytoin, dapsone, and minocycline are commonly implicated in liver injury (26). Liver abnormalities such as elevated AST/SGPT has been reported in 70 to >95% of cases (25,26,37). Hepatitis is often anicteric without cholangitis. Liver biopsy can show eosinophilic

infiltrate and granulomas with hepatocyte necrosis and cholestasis (26). Flare in liver dysfunction can be associated with HHV reactivation during the course of illness. Hepatic necrosis leading to coagulopathy & sepsis is a primary cause of mortality in DRESS and may necessitate liver transplantation (42).

- **Renal**: Mild, transient renal impairment with oliguria, elevated urea, creatinine and reduced creatinine clearance in the setting of a normal renal ultrasound is seen. Eosinophils may be present in urine analysis. However, severe interstitial nephritis and renal failure can occur needing temporary haemodialysis (26). Allopurinol, followed by carbamazepine and dapsone are the most common offending drugs in renal impairment (14). A kidney biopsy can show interstitial lymphohistiocytic and eosinophilic infiltrates.

- **Respiratory:** Patients most commonly present with sudden onset breathlessness. Other presenting symptoms can be cough, chest pain and hypoxemia. Most patients usually recover without lung damage. Reported pulmonary complications include impaired pulmonary function, interstitial infiltrates, pneumonia, effusion & ARDS (43). Minocycline is the most frequently implicated drug in lung involvement (44). Lung biopsy may have interstitial and alveolar infiltration by lymphocytes and eosinophils (26).

- **Cardiovascular:** Patients can present with cardiac involvement anytime from the onset of DRESS till 4 months later (45). Two clinical variants have been described (26,31). One is the hypersensitivity myocarditis, (mild, self-

limiting, and responsive to immunotherapy), and the other is an acute eosinophilic necrotising myocarditis (AENM) (with a greater left ventricular dysfunction associated with >50% mortality). Patients present with congestive cardiac failure or elevated cardiac biomarkers or non-specific T wave changes on ECG, impaired systolic function, reduced ejection fraction, and pericardial effusion on ECHO (26,31). Commonly implicated drugs are ampicillin and minocycline. In DRESS with erythroderma, increased cutaneous blood flow can present cardiac failure, especially in the elderly and patients with existing cardiac dysfunction.

- **GI manifestations:** Common manifestations are diarrhoea gastroenteritis. Proton pump inhibitors have been associated with GI manifestations (46). Upper GI bleed can occur due to stress ulcer, corticosteroid use, or CMV involvement (26).

- **Neurological:** Meningitis and encephalitis often develop 2-4 weeks after onset of DRESS and may be associated with HHV reactivation (32).

- **Endocrine:** Usually occur as long-term sequelae, rarely as acute reactions. These include thyroid disease, pancreatitis and type I diabetes mellitus, xerostomia etc. A symptom-free period between apparent resolution of DRESS and the onset of the autoimmune conditions ranges from months to years. Autoimmunity is probably related to viral reactivation that is seen in DRESS (26,47). Monitoring of thyroid function is advisable during DRESS

syndrome as it is the most commonly reported long term sequelae in DRESS syndrome (24).

Diagnostic criteria for DRESS**:** There are 3 separate diagnostic criteria for DRESS/DIHS. The European Registry of Severe Cutaneous Adverse Reaction study group proposed the RegiSCAR scoring system with an "inclusion criteria" (Appendix III) for all potential cases and "validation criteria" for confirmation of diagnosis (37). (Appendix IV). The study group expanded the diagnostic criteria proposed by Bocquet et al. (Appendix V) (48). The Japanese call DRESS syndrome as 'DIHS' (i.e., drug induced hypersensitivity syndrome) and have J-SCAR criteria for it (Appendix VI) (49).

Differential Diagnosis: The common differentials for DRESS syndrome include other SCAR's like SJS/TEN, AGEP, erythroderma & viral exanthem. Angioimmunoblastic T cell lymphoma, Sezary syndrome, pseudo-lymphoma, hyper-eosinophilic syndrome, and acute cutaneous lupus may be considered as differentials. DRESS is a diagnosis of exclusion and each point in the RegiSCAR validation score is applicable if there is no other possible explanation/diagnosis for it (37). Potential differentials including infections, malignancy and autoimmune diseases need to be excluded by the treating physician.

Management of DRESS

Following recognition of DRESS syndrome, prompt withdrawal of the offending drug is essential. In cases where more than one drug is suspected, a detailed medication history is essential and drugs should be taken off according to the

index of suspicion and severity of the condition, the drug causality scores are useful for the same. Systemic corticosteroids are usually initiated at a dose of 1m/kg and gradually tapered over 6 months (31). Delay in withdrawal of the offending drug and institution of corticosteroids can lead to worse outcomes (50). Other potential drugs that can be administered when corticosteroids are contraindicated are intravenous immunoglobulin, cyclosporine and plasmapheresis (14). When DRESS syndrome is complicated by erythroderma, admission is required for provision of vital support therapy and monitoring organ system involvement as the syndrome progresses. Markers of inflammation such as systemic inflammatory response syndrome (SIRS), Glasgow prognostic score (GPS), C- reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) are useful to evaluate the hyper-inflammatory immune responses in SCARs (51,52).

Drug induced maculopapular eruption (MPE)

Drug induced maculopapular eruptions (MPE) are also called exanthematous or morbilliform eruptions. These form the most common cutaneous “drug rashes” accounting for more than 80% of CADR (2,9). Drug induced MPE presents with erythematous changes in skin without blistering, pustulation or systemic symptoms (2). It also includes patients with systemic symptoms but with a RegiSCAR score of 3 or less, and not qualifying as DRESS. Such patients are more likely to have less protracted course than those with DRESS (RegiSCAR $\geq$ 4) (38). These patients could also be categorized as DRESS-minor or mini-DRESS to lay emphasis; while setting a demarcation in terms of a better prognosis than DRESS syndrome (38,53). Thorough clinical and biological

workup should be done, lest a SCAR is wrongly labeled as drug induced MPE. Drug induced MPE in its virtue of being a benign or mild rash makes it eligible for ‘treating-through’, a possibility, rarely if ever present in SCAR (54).

Clinical features: Drug induced MPE presents with erythematous macules, papules with rarely if ever pustules and vesicles (2,12). The distribution predominantly involves trunk and proximal extremities. Acral sites and mucosae are spared. Redness without ulceration in mucosae can be seen and presence of ulceration should arouse suspicion of severe SCAR such as SJS/TEN, DRESS or a viral exanthem. A rash usually develops in 5-14 days, in a previously sensitized patient, it can occur within 1-2 days and fades in less than 15 days.

Management: Withdrawal of drug is the mainstay of treatment with supportive measures such as antihistamines and topical steroids (2). In cases of drug(s) urgently necessary for the patient with no potential alternative, treating through under vigilance of a treating physician with experience in managing ADR is a possible option (54).

Acute generalised exanthematous pustulosis (AGEP)

Introduction:

Acute generalized exanthematous pustulosis is characterized by the rapid onset of sheets of sterile non-follicular pustules over large areas with oedema and erythema. It is a self-limiting phenomenon, resolves without permanent sequelae localized to flexures mostly (17). The eruption usually begins within 48 hours of ingestion of the offending medication along with fever and leukocytosis. Antibiotics are the most common implicated culprits. It was initially thought to

be a form of pustular psoriasis till in 1968 Baker and Ryan suspected it to be an entirely separate entity and in 1980 Beylot et al. proposed to the said name "acute generalised exanthematous pustulosis" for this condition (55).

Associations: Around 90% of cases of AGEP are drug related. The most commonly implicated drugs are: - pristinamycin, aminopenicillins, quinolones, aminoquinolines (chloroquine, hydroxychloroquine), terbinafine, diltiazem. Less commonly macrolides, corticosteroids, oxicam class of NSAIDs, anti-epileptics except for valproate can be implicated. For antibiotics the interval between administration and onset of disease is 2-3 days while for other drugs it is 3-18 days (15,56). In an Indian study, the most commonly implicated drug was penicillin followed by cephalosporins and NSAIDs (16). Few cases are thought to be associated with infections like Mycoplasma pneumoniae, coxsackievirus, parvovirus B19, and cytomegalovirus (CMV). Rarely, mercury exposure and spider bites have also been associated with AGEP (16,17,55).

Clinical features:

Acute generalized exanthematous pustulosis is characterized by high fever and facial and/or intertriginous lesions with dissemination in a few hours. There are hundreds of small, less than 5mm, non-follicular sterile pustules over a large area with edema and erythema. It is distributed over the face, trunk and intertriginous areas with or without associated pruritus and burning sensation. It lasts for a few days followed by superficial desquamation. Edema of hands and face, mucosal lesions, blisters, EM-like lesions, purpura can also be seen (15). Mucosal lesions if present mostly involves a single site, usually lips and buccal mucosa. A

characteristic feature is its rapid evolution, within hours and quick remission in a few days. Systemic involvement is infrequent and can be seen with liver, kidney and rarely lungs. Elevated CRP and absolute neutrophil count have been linked to internal organ involvement. Hepatic involvement can be either hepatocellular (raised liver enzymes) or cholestatic pattern (increased alkaline phosphates and γ-glutamyl transferases) (14). Hepatomegaly or steatosis may be seen on an ultrasound abdomen. The chest can have bilateral pleural effusion resulting in hypoxia requiring oxygen. Patients with mucocutaneous involvement and comorbidities have highest risk of death. However, mortality is < 5% in AGEP and death if occurs is typically a result of disseminated intravascular coagulation (DIC) and multiple organ dysfunction (57)

Diagnosis of AGEP is based on clinical features and histology. A validation score based on clinical course, morphology and histopathology has been developed by EuroSCAR group for AGEP (Appendix VII) (55). Patch test for incriminated drugs are positive in a relatively high number of cases (50-60%) (56). Histopathology shows subcorneal or intraepidermal pustule with neutrophilic infiltrates (18). Spongiosis, neutrophil exocytosis, necrotic keratinocytes and dermal edema can occur.

Management:

It is a self-limiting disorder with a good prognosis with the removal of causative drug is the main treatment and it leads to improvement of symptoms within days (56). Antiseptic solution and moist dressings can help during the pustular phase to prevent infection (55). Potent topical steroids reduce inflammation and

pruritus and have been correlated with reduced duration of hospital stay. In severe cases, systemic corticosteroids can be used (56).

Stevens Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)

Introduction:

Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN) are acute blistering and epidermal sloughing diseases. Stevens-Johnson syndrome has less than 10% involvement of body surface area (BSA) while TEN has more than 30% and SJS/TEN overlap is in between 10-30% of BSA involvement (58). Stevens-Johnson syndrome/Toxic epidermal necrolysis spectrum is a devastating disease with multisite mucositis, epidermal loss with systemic complications which may proceed to multiorgan failure. It has perilous mortality in the acute phase and also has a long-term sequelae. The majority of cases of SJS/TEN group are caused by drugs, frequently implicated high-risk drugs are sulphonamides, anticonvulsants like carbamazepine, phenytoin NSAIDs especially oxicam group, allopurinol, nevirapine and lamotrigine (59). In children, mycoplasma infection and cytomegalovirus (CMV) are well-known triggers.

Clinical features

Diagnosis of SJS/TEN is clinical. Initial prodrome includes URI-like symptoms, fever and conjunctivitis followed by detachment of mucosa (oro-pharyngeal, nasal, conjunctival and ano-genital) More than 2 mucosae are involved usually. Skin presents with dusky erythematous macules/purpura and/or flat target or

targetoid lesions associated with burning sensation and pain. Raised typical target lesions seen in erythema multiforme (EM) are usually absent. The lesions appear and extend predominantly over the trunk and proximal limbs within 2-3 days. Appearance of flaccid blisters is followed by a sheet like detachment of the epidermis. Shearing force over the involved erythematous area can lead to epidermal detachment (pseudo-Nikolsky's sign). Perilesional erythema indicates disease activity and helps to monitor response to treatment. Systemic symptoms are usually associated with SJS/TEN overlap and TEN. Thermoregulation is impaired, energy expenditure is increased. Mucosal involvement leads to photophobia, respiratory distress, impaired alimentation, diarrhoea and painful micturition. Re-epithelialization occurs after cessation of disease activity and usually completes within 3 weeks except for mucous membranes and pressure sites which take longer (60).

Management

Prompt withdrawal of drug and administration of immunomodulators such as systemic steroids, cyclosporine and intravenous immunoglobulins are useful in halting the disease progression (59). Prognostic markers such as Score for Toxic Epidermal Necrolysis (SCORTEN) (Annexure X1V) are useful to assess the mortality of patients with SJS/TEN. A new risk prediction model ABCD10 (i.e., abbreviated for "age, bicarbonate, cancer, dialysis, 10% body surface area") was compared with SCORTEN. In a retrospective analysis comparing ABCD 10 and SCORTEN, in their calibration and discriminatory ability, it was found that the performance of SCORTEN is superior to ABCD10 in predicting mortality.

(61,62). Supportive treatment care includes multidisciplinary treatment care in a hospital setting, if available patient should be managed in specialized centers such as dermatology department or burn unit (63). Management should involve a multidisciplinary team that should also include, ophthalmology, oto-rhino-laryngology, psychology/psychiatry, gynecology. Wound care should involve anti-shear measures such as non-adherent dressings, avoiding the application of tapes over the body, limiting dressing change, avoiding unnecessary manipulation of the wounds (63,64).

Pathogenesis of severe cutaneous adverse reactions

Severe cutaneous adverse reactions are T-cell mediated, drug specific, delayed type IV hypersensitivity reactions. The understanding of immunopathogenesis and genetic risk factors has significantly advanced in the last 15 years (63). Each clinical phenotype of SCARs results from a complex interaction involving genetic factors, environmental factors and the immune system. Adaptive immune cells involved are T-helper type 1 (Th1), Th2, cytotoxic T lymphocytes (CTLs), Th17, and regulatory T cells (Treg) etc. Innate immunity cells involved are NK cells, lymphoid cells, monocytes, macrophages and dendritic cells. Tissue-resident cells such as keratinocytes release cytokines that attract proinflammatory cells and thus contribute to epidermal damage (18). The pathogenesis can be subdivided as follows:

1) Genetic predisposition

a) Human Leukocyte Antigen (HLA) drug specific immune response

2) Drug detoxification mechanisms

3) **Viral reactivation**

4) **Immunopathogenesis in SCAR**

   a) Mechanism of development of drug specific T cells

   b) Soluble mediators, cytokines and leukocyte population in each SCAR phenotype

   c) Danger associated molecular patterns (DAMPs) in SCARs

   d) Regulatory T cells (Tregs) in SCARs

5) **Cell death in SCARs: Apoptosis and necroptosis**

Genetic predisposition:

Ethnic predisposition due to variation in certain Human leukocyte antigen (HLA) alleles. For example, abacavir hypersensitivity syndrome is restricted to HLA B*57:01 and exclusion of abacavir introduction to these patients led to the disappearance of this syndrome. The Asian population is a significantly affected population by SJS/TEN and a lot of progress has been made in the area of genetic markers (63).

There are 3 postulated mechanisms proposed by which HLA molecules present the 'drug' to the lymphocyte in the immunopathogenesis of SCAR's as demonstrated in Figure 3 (24,65,66). These include

- **Hapten/pro hapten model**: - drug such as beta-lactam binds covalently to an endogenous peptide e.g., albumin and forms a new molecule which is processed by antigen processing cells (APCs) and present it as short peptide fragments in MHC binding cleft.

- **Pharmacological interaction**: drugs such as – Carbamazepine, allopurinol, sulphonamides etc., bind noncovalently to certain MHC molecules or TCRs, stimulating specific TCRs and thus generating drug reactive T cells.
- **Altered peptide repertoire model,** a drug (e.g., abacavir) binds to MHC molecule (HLA B*5701) noncovalently altering its conformation allowing an array of self-peptides to occupy it and stimulate T cells leading to drug induced activation of autoimmunity (e.g., abacavir hypersensitivity reaction). The resultant effector mechanism contributes to the characteristic clinical manifestation of each condition i.e., eosinophil-mediated injury in DRESS, CD8+ cytotoxic T-cell mediated injury in SJS/TEN (65)

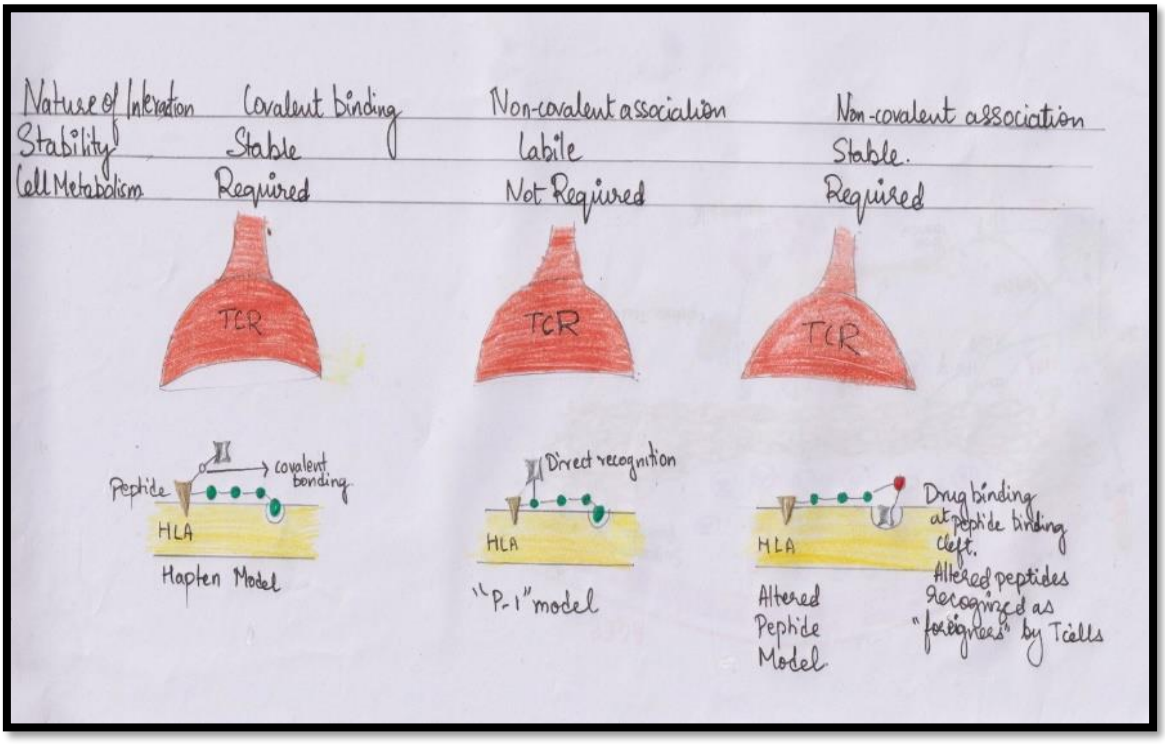


Figure 3 Various models of T cell activation

Drug detoxification enzymes: The deficiency or an abnormality of the enzymes such as epoxide hydroxylase and glutathione transferase that detoxify the drug-metabolites can lead to accumulation of the toxic drug-metabolite causing a direct toxic/immune response. Drugs competing for the same enzyme for their metabolism leading to a drug interaction can also increase the occurrence of an ADR for example, concurrent administration of lamotrigine and valproic acid which are metabolized via hepatic glucuronidation increases the half-life and risk of ADR by lamotrigine (67).

Herpes virus reactivation: Human herpes virus-6 (HHV-6) infects almost all humans by the age of 2 years (67). The HHV reactivation occurring in DRESS is detected by viral DNA PCR and generally occurs 2 weeks following the onset of symptoms. HHV-6 reactivation exclusively occurs in DRESS and is not seen in SJS/TEN (67). There are 2 possible mechanisms described for the role of herpes virus reactivation. One is the T-cell activation which begins as an allergic response to a drug. These activated T-cells also house the HHV genome, hence leading to HHV reactivation in the process. Another possibility is the cross reactivity between the viruses and drugs leading to expansion of T-cells specific to the drugs (and the virus) which persists well beyond drug withdrawal due to persistence of viral antigens. Other than HHV-6, HHV-7, EBV, CMV may also be reactivated. This late viral reactivation is also a result of immune dysregulation, in particular regulatory T-cell dysfunction which provides a 'danger signal' that leads to excessive clonal expansions of CD8+ and CD4+ nonspecific T-cells. Reactivation is not essential but tends to aggravate the

clinical condition and is a marker of severity and leads to a protracted course of disease (24,40). Viral reactivation is associated with flaring up of symptoms such as hepatitis and fever (65,68). Ogawa et al. demonstrated elevated serum TARC levels correlated with HHV-6 reactivation i.e., patients with HHV-6 reactivation had serum TARC levels as compared to those without the reactivation suggesting that the TARC chemokine probably plays a pathogenic role in viral reactivation (18).

Regulatory T cells in SCARs: Treg cells are CD127-CD4+ T cells with high surface expression of CD25 and induced expression of nuclear transcription factor FoxP3 (18). They help in maintaining self-tolerance and immune homeostasis. Foxp3+ Treg cells are expanded in DRESS during the acute phase and suppress the memory T cells. This expansion of Treg during acute DRESS probably leads to delayed onset of DRESS as infiltration of skin by Treg limit the epidermal damage by effector T cells (67). It also leads to a negative lymphocyte transformation test during acute phase of DRESS. In SJS/TEN Treg cells are present in normal numbers but are functionally impaired (67). This lack of Treg function in TEN is implicated for excessive activation of effector T cells and subsequent epidermal damage. In HIV patients, loss of skin protective CD4+CD25+ Treg cells contributes to an increased risk of developing SJS/TEN in them(18).

Mechanisms for the development of drug specific T cells

- **De novo immune response:** Naïve T cells need at least 2 signals to be activated via stimulation of TCR (signal 1) and costimulatory signal by professional APCs such as mature dendritic cells (signal 2). Dendritic cells can metabolize certain drugs and enable them to induce a T-cell response. Mitogen-activated protein kinase (MAPK) signaling pathway is involved in drug-induced maturation of the dendritic cells (18).
- **Heterologous immunity model**- The pre-existing memory T cells responsible for drug hypersensitivity response: Immune system defends the body against a vast microbial universe via polyspecific T cells which recognise antigens derived by more than one pathogen(Figure 4) (65,66). In DRESS the drug specific T cells are derived from the cross reactivity of previously sensitized pathogen-specific effector memory T cells. On exposure to the drug, the effector memory T cells generated much earlier due to infectious agent and maintained by re-exposure or latency, cross react with drug modified proteins. Among the pathogens, HHV, CMV and EBV are thought to be most likely implicated in heterologous immunity in DRESS (15). Heterologous immunity is not dependent on presence of active pathogen replication (as in the case of DRESS where HHV reactivation is seen) but endogenous peptide-drug epitope that drives the T-cell response (66).

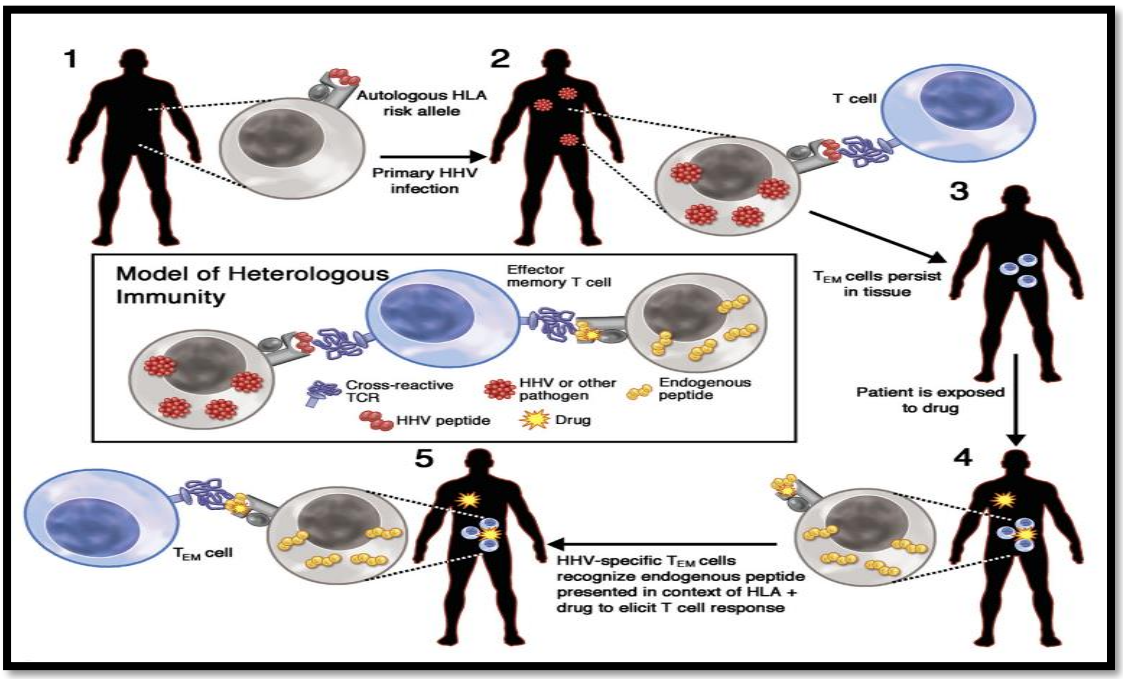


Figure 4 Heterologous immunity. Adapted from J ALLERGY CLIN IMMUNOL 2015 White et al.

Soluble mediators, cytokines, chemokines and leukocyte population in SCARs

In drug reaction eosinophilia and systemic symptoms, skin has dense infiltration of CD4+ T cells, eosinophils in DRESS corresponding to Th-2 cytokine profile and IL-5, IL-4, IL-13 and TARC(CCL17) are produced. However, CD8 + T cells, and granzyme B + T cells also infiltrate the skin. TNFα, INF-γ, Innate type 2 lymphoid cells (ILC2s) expressing the IL-33 receptor ST2, high serum concentrations of soluble ST2 and IL-33 are also expressed in DRESS during the acute phase. Increased levels of TNF-α and IL-6, proinflammatory cytokines prior to treatment correlated significantly with HHV-6 DNA during the clinical course(69,70). Plasmacytoid dendritic cells (pDCs) playing a defensive role against viruses are significantly reduced in number around the time of viral reactivation thereby depressing the antiviral capacity of patients with DRESS (71). Figure 1.5 shows skin infiltrated in DRESS with CD8+, CD4+, Tregs, monomyeloid

cells such as plasmacytoid dendritic cells and monocytes. The TARC chemokine recruits CCR4+Th2 T cells. High levels of IL-5 and Th2 chemokines lead to peripheral and tissue eosinophilia (72). Various chemokines that are elevated in SCARs, table 3 shows the biomarkers found to be elevated in DRESS syndrome.

Table 3 Biomarkers in DRESS in human studies (18,47,69,73)

Biomarker	Detected in
TARC/CCL17	Serum
TNF-α	Serum
IL-6	Serum
IL-5	Serum, Skin
CXCL-10/IP-10	Skin, Serum
HMGB1	Serum, skin
IL-33	Serum
MDC/CCL/22	Serum
CTACK/CCL27	Serum

In AGEP the characteristic feature in the pathophysiology is the neutrophilic inflammation and a cooperation of IL-8/CXCL8 and Th17 lymphocyte for production of same (18). Following exposure of the culprit agent, APC using MHC molecules present the antigen, which leads to activation of drug specific CD4+, CD8+ T-cells (55). Neutrophil chemotactic factor IL-8/CXCL8 activates and mobilizes the neutrophils from bone marrow causing neutrophilia. These cells migrate to the dermis and cause apoptosis of keratinocytes leading to the

production of vesicles and due to the release of an increased level of CXCL8, a neutrophil recruiting cytokine, transforming to sterile pustules. Interferon-γ & granulocyte colony stimulating factor (Th1 cytokine profile) increase the neutrophil survival and induce keratinocytes to release CXCL8 leading to further neutrophil accumulation. Mutation in a gene coding for IL-36 receptor antagonist (IL36RN), an anti-inflammatory cytokine, predisposes the development of AGEP. Patients with AGEP having IL36RN mutation have been described to more likely have lip and oral involvement than patients of AGEP without this mutation (74).

Danger associated molecular pattern: (DAMP) or alarmins (18): These are endogenous agonists of pattern recognition receptors. These are released from damaged tissues after injury to alert the immune system and initiate response following interaction with pattern recognition receptors and Toll like receptors (68). High mobility group box (HMGB-1) is a DAMP elevated in DRESS which recruits monomyeloid precursors that harbour latent HHV-6 and transfer it to the CD4+ cells infiltrating the dermis. Hence leading to the hypothesis of skin being the cryptic site of HHV reactivation in DRESS.

6) Cell death in SCARs especially SJS/TEN (18)**:**

- **Apoptosis** The complete thickness of the skin – which includes all the layers of the epidermis along with detachment at the dermo-epidermal junction is characteristic of SJS / TEN. Apoptosis or programmed cell death, which is a well-regulated homeostatic pathway of the cell is **dysregulated** in SJS / TEN.

The 2 main pathways which are implicated in the apoptosis of keratinocytes are

- **Extrinsic** – where an extrinsic chemical often called **death ligand**– causes a cascade of cellular level reactions causing cell death
- **Intrinsic** – where the mitochondria: an organelle within the cell, by the disruption or break of its outer membrane leads to cytochrome release and brought about by the **activated lymphocytes upregulated in SJS/TEN**

Both these pathways lead to activation of an enzyme called **Caspase -3** which cleaves the DNA and ultimate cellular destruction as demonstrated in figure 5 the intrinsic pathway and in figure 6 the extrinsic pathway.

- **Necroptosis:** Another cellular pathway – which is tightly regulated cellular homeostatic which is dysregulated in SJS / TEN brought about by extrinsic chemical as in extrinsic pathway. This is also thought to be mediated by a **chemical compound Annexin- 1** which acts as a death ligand as shown in figure 7 as a flow chart.

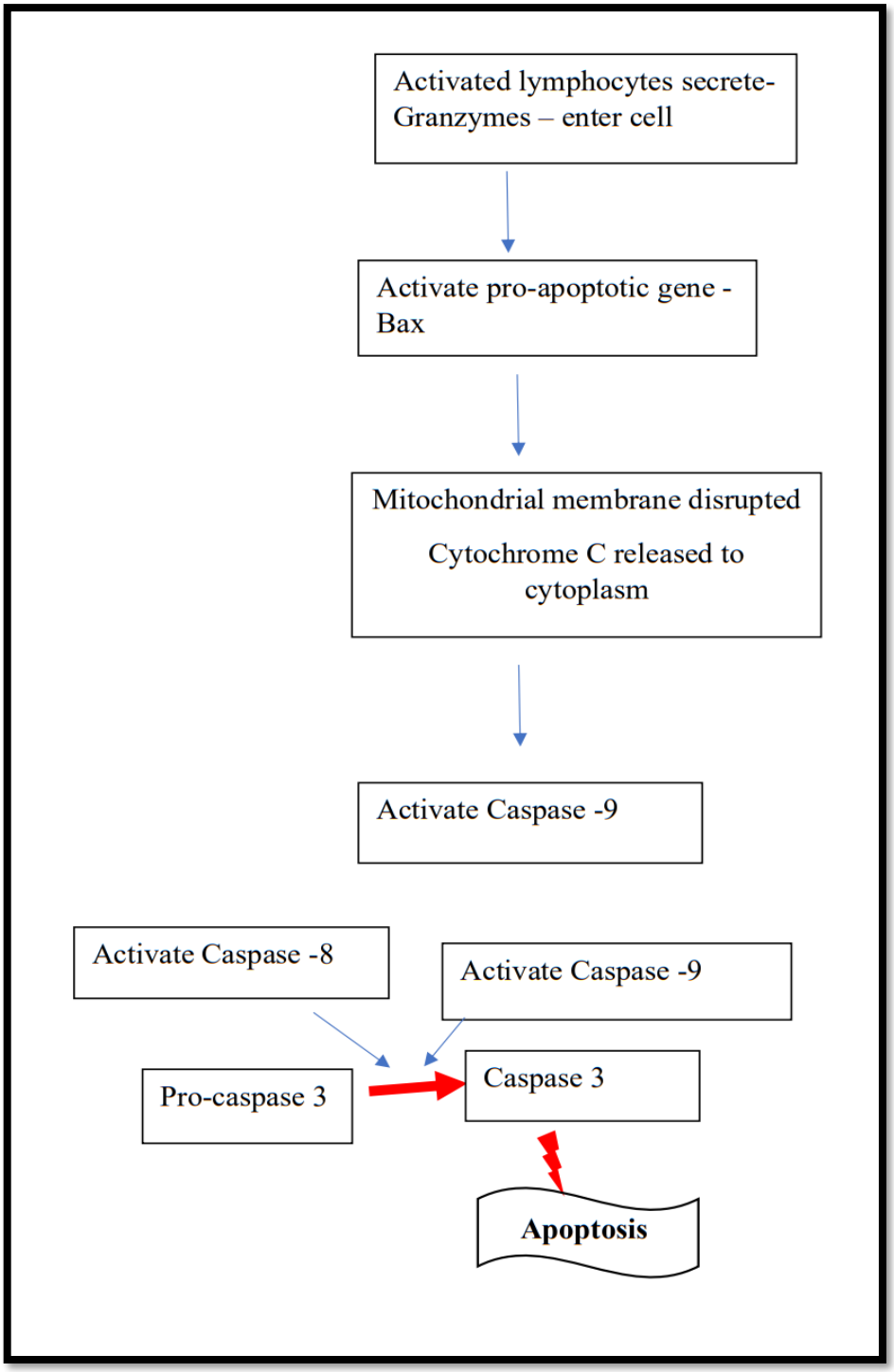


Figure 5 demonstrating the sequences in Intrinsic pathway

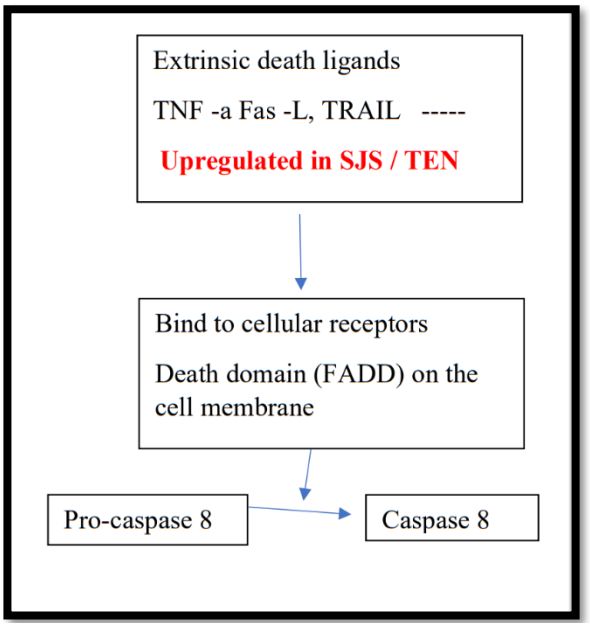


Figure 6 Flowchart demonstrating sequences in extrinsic pathway

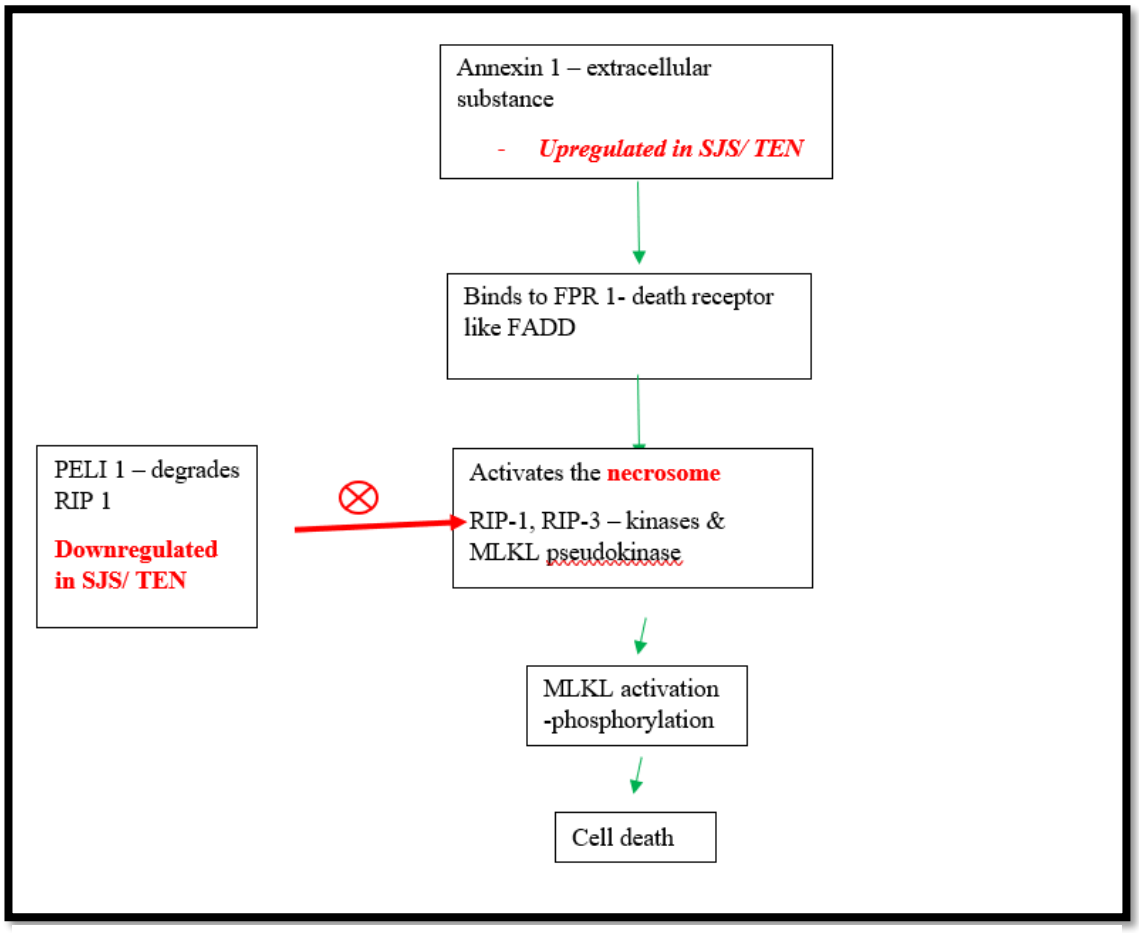


Figure 7 Flowchart showing sequences in Necroptosis

Role of serum TARC in SCARs

Thymus and activation- regulated is a chemokine that is constitutively expressed in thymus, keratinocytes, & dendritic cells, and also elevated in various Th2- dominant inflammatory skin disorders such as atopic dermatitis, bullous pemphigoid, mycosis fungoides etc. (75). Ogawa et al. initially demonstrated elevated serum TARC levels in DRESS, and in a subsequent publication they showed a correlation of TARC with HHV reactivation in DRESS and that patients with HHV reactivation in DRESS have higher TARC levels than those with DRESS without HHV reactivation (5,76). This small molecule belonging to the CC chemokine family which correlates strongly with peripheral eosinophilia and serves as a prognostic marker in CADR especially DRESS(73,77,78). It also parallels with flare-ups seen during DRESS syndrome (73). TARC recruits Th2- polarized lymphocytes to sites of inflammation such as skin in SCARs (78). It binds to the CCR4 receptor in Th2 cells and has also been demonstrated in lesional skin biopsy of DRESS patients where it was shown to be expressed by the dermal dendritic cells (5,73). Other studies demonstrated elevated levels of TARC in SJS/TEN and MPE but to a lesser extent than DRESS (6).

Viral exanthem:

A viral exanthem frequently presents as a morbilliform or a maculopapular eruption. An enanthem may or may not be present. In many cases, it may follow an intake of a drug leading to a diagnostic dilemma. Viral exanthems are more common in children. In adults, Dengue and chikungunya infection caused by Arbovirus is a frequent cause of blanching erythematous or a maculopapular/morbilliform rash (79,80). 3-6 days following onset of illness there is a vascular leak mediated by cytokines such as TNF-

α leading to endothelial dysfunction which is the hallmark of dengue (82). In Chikungunya, rash develops within 3-4 after following onset of fever coinciding with bouts of viremia (80). Viral exanthem often occurs more frequently after taking a medication in the course of a viral infection and mimics a drug exanthem. It is estimated to be perceived as a drug allergy in 10% of cases. In most cases, the distinction between virus-induced and drug-induced skin eruption during the acute phase is not possible (11). A detailed history and through clinical examination and a timeline of the medications taken is crucial to differentiate between a viral exanthem and drug rash. Table 4 shows the differences between drug eruption versus a viral exanthem.

Table 4 Drug eruption versus viral exanthem (11,81)

	Maculopapular drug eruption	*Viral exanthem*
Definition	Most common drug hypersensitivity reaction with symmetric macules and macules usually one week after initiation of culprit drug	An eruption of erythematous macules and papules associated with systemic infection, fever and lymphadenopathy
Epidemiology	Adults, increased incidence in women and HIV positive population	Childhood, no sex predilection
Etiology	Drugs- most common antibiotics, anticonvulsants, NSAIDs	Measles, Rubella, Parvovirus, Adenovirus, EBV, CMV,

	etc.	parainfluenza etc.
Mechanism	Delayed type IV hypersensitivity	After the entry of virus and a brief period of incubation, there is dissemination of viral particles. Rash occurs as a result of perivascular inflammatory reaction in the skin
Onset	Usually after 7-10 after ingestion of the offending drug. Starting from the upper trunk and upper extremities then progressing caudally	Associated with prodromal symptoms such as fever, rhinorrhoea, conjunctivitis, cough, arthralgias, myalgias with cephalocaudal progression of rash
Temperature	Low grade to moderate fever	Low grade fever in rubella, measles, EBV, CMV. High grade fever Adenovirus (Dengue) etc.

Cutaneous manifestations	Symmetric confluent erythematous maculopapular rash over trunk and upper extremities. Petechiae and purpura over legs secondary to hydrostatic pressure. Facial oedema in DRESS Severe mucosal involvement – SCAR Lesions mostly pruritic	Measles, rubella - cephalocaudal rash with sparing of palms, soles. -Kolpik's spots in measles -Slapped cheek appearance in erythema infectiosum -Islands of sparing in Dengue -Appearance of rash -after intake of amoxicillin in infectious mononucleosis. Rash is characteristically non pruritic
Diagnosis	Clinical diagnosis. Requires a high index of suspicion with temporal correlation to drug intake. Patch testing, appearance of rash on rechallenge is confirmatory	Clinical diagnosis based on seasonal prevalence, symptoms, distribution of rash, lymphadenopathy. ELISA IgM for specific viruses Leukopenia/leukocytosis, thrombocytopenia
Histopathology	Dermal eosinophilic infiltration: 36-62.5% Dermal lymphocytic infiltrate: 50-100%	Dermal eosinophilic infiltration: 16.6-20% Dermal lymphocytic infiltrate: 20.8%

MATERIALS AND METHODS

Study design: This study was performed as a single center, prospective, case-control study on patients with cutaneous adverse drug reactions and probable viral exanthem serving as controls.

Study setting: The study was conducted at Christian Medical College and Hospital, Vellore, Tamil Nadu, a tertiary care, 2858 bedded hospital. The study was carried out at the Dermatology, Venereology and Leprosy Unit-2 OPD and ward, consultations seen in Department of Medicine and Department of Neurosciences; Department of Clinical biochemistry for estimation of TARC levels, Christian Medical College, Vellore

Study subjects: Adult patients with suspected drug-induced maculopapular eruptions (MPE) and severe cutaneous adverse reactions (SCAR) based on clinical, hematological, biochemical or histopathological examination were taken as cases and patients with clinical features and investigations suggestive of viral exanthem served as controls.

Inclusion criteria:

Inclusion criteria:

(i) Cases: Patients with drug-induced MPE / SCARs above 18 years of age and who are willing for participation in the study.

(ii) Controls: Patients with viral exanthem

Exclusion criteria: Patients with atopic dermatitis, asthma, alopecia areata, Hodgkin's lymphoma, mycosis fungoides and bullous pemphigoid will be excluded from the study.

Period of recruitment: Study subjects were recruited from January 2020 to October 2021 (21 months)

Recruitment: Adults with suspected drug induced exanthems MPE and SCAR (severe cutaneous adverse reactions) based on clinical and biochemical examination, fulfilling the inclusion criteria were included in the study. Informed consent was obtained from all cases and controls eligible for the study (Annexure VI). Among the in-patients recruited for the study, if the patient was indisposed due to the illness to provide consent, it was obtained from the patient's attendant. The nature of the study and the investigations being done were explained to the patients and their attenders. The flowchart of the study protocol is demonstrated in figure 8.

Data collection: After obtaining the consent, the details of the patient, including demographic details, history of the illness, clinical examination findings and relevant investigations were documented in a clinical research form (Annexure IV).

Demographic details: The name, age, gender, address, occupation, contact number and hospital number of the patient were noted.

History: A detailed history of all the drugs ingested and the symptoms experienced by the patients was noted which included: -

- Latent period from the ingestion of the drug to appearance of the first symptom
- The number of days since the onset of the first symptom of the adverse drug reaction
- Details of rash and associated symptoms features like itching, burning sensation, mucosal involvement, swelling of face, hands and feet
- Systemic symptoms such as fever, jaundice, cough, arthralgia and breathlessness
- Drug details such as the possible causative drugs and their indication, duration of drug

intake, concurrent drugs used

• History of previous drug allergies and the type of previous CADR

Clinical examination: General examination with vital signs including temperature, blood pressure, pulse rate, respiratory rate and systemic examination were recorded.

Cutaneous examination: The below mentioned clinical parameters were recorded.

- Morphology of the skin lesions - blanching erythema, macular, maculopapular, papular, targetoid, purpuric, pustular, vesiculobullous, erosions, infiltration, exfoliations
- The involvement of rash according to body surface area (BSA) as calculated by the "Rule of Nine"
- Presence of facial oedema
- Mucosae involved- number, type of involvement
- Palms and soles involvement
- Associated nail or hair changes
- Photographs of the relevant skin lesions were taken.

All the patients will be examined by the principal investigator and also by the guide/co-guide and the cutaneous findings will be recorded.

Scoring systems:

- Causality:
    - Naranjo assessment (Annexure V) for all cases
    - ALDEN score (Annexure VI) for SJS/TEN cases
- Diagnosis:

    - RegiSCAR validation scoring for MPE and DRESS. Score of 4 more was considered as DRESS and less than 4 as MPE
    - EuroSCAR scoring for AGEP
    - Bastuji Garin classification for SJS/TEN
- Prognosis:
    - SCORTEN for SJS/TEN patients (Annexure XIV)
- Markers of systemic inflammation
    - Glasgow Prognostic score (Annexure XII)
    - Systemic Inflammatory response score (SIRS) (Annexure XIII)
    - Neutrophil-lymphocyte ratio (NLR)

In patients with doubtful diagnosis, other conditions with similar morphology such as connective tissue disease will be ruled out on a case-to-case basis as per protocol.

Data collection: After taking patient's/patient's attender consent, the details of the patient was documented in the research form (Annexure VII) which included demographic details, history of the illness, drug history, clinical examination and relevant investigations.

Demographic data: The name, age, gender, occupation, hospital number and contact details of the patient were written.

Investigations: Routine hematological evaluation included counts, platelets and hemoglobin, liver function tests, CRP

Histopathological examination: Skin biopsy was performed on a case-to-case basis according to protocol, to rule out differentials like viral exanthems and connective tissue disorders. The biopsy was performed from the most representative skin lesion at the

first assessment by the attending dermatologist. A skin punch of size 4 to 6 millimeters was used to do the biopsy and the specimen was transported to the department of Pathology in the routine skin fixative solution. The specimen was processed and then stained with eosin and hematoxylin stain. The slides were examined under light microscopy in the pathology laboratory by a pathologist. The following features in the specimens were noted – orthokeratosis**,** parakeratosis, necrotic keratinocytes, spongiosis, focal basal cell vacuolization, the type of inflammatory infiltrate and lymphocytic exocytosis.

Diagnosis:

The final diagnosis was made by the principal investigator and the guide on each included case after reviewing the history, clinical features, photographs and investigations.

All patients were classified under:

- Drug-induced maculopapular exanthem (MPE)
- DRESS
- SJS/TEN spectrum
- AGEP
- Viral exanthem (controls)

  Drug reaction eosinophilia and systemic symptoms syndrome: RegiSCAR validation scoring were used to classify patients with or without DRESS syndrome. Cases with RegiSCAR ≥ 4 were classified as DRESS.

  Each of the parameters in RegiSCAR criteria were defined as follows:

1) Rash referring to any skin eruption which had an erythematous component and /or macular/ papular component. Rash of more than 50% body surface area was considered as 1 point. Features suggestive of DRESS were erythroderma, infiltration, purpura (not including the legs), and facial edema.

2) Lymphadenopathy was present if at least 2 non-contiguous sites were involved and the size of lymph nodes was more than 1 cm.

3) Fever was defined as a temperature above 100.4°F (38°C).

4) Transaminitis: Liver involvement was defined by the serum level of alanine aminotransferase or aspartate transferase greater than twice the upper limit of the normal values on at least one occasion (>80U/L)

5) Kidney involvement: Creatinine was considered abnormal if the serum level was more than 1.6 mg %

6) Other organ involvement: Lungs, heart, gastrointestinal, pancreas, nervous system etc.

7) Blood count abnormalities:

- ¬ Absolute lymphocytes above 5000 /cubic mm (lymphocytosis) or below 1500/cubic mm (lymphopenia).
- ¬ Absolute eosinophils above 700/ cubic mm or >10% was considered to be peripheral eosinophilia.
- ¬ ¬ Platelets below 100,000/ cubic mm was considered to be thrombocytopenia.

Further, RegiSCAR scoring was used to classify patients as no case, possible DRESS, probable DRESS or definite DRESS. RegiSCAR scoring for DRESS

syndrome is outlined in **Annexure VIII**.

Drug induced maculopapular eruption: The cases with an acute cutaneous eruption, not fulfilling the RegiSCAR validation score (RegiSCAR < 4) were classified as drug induced MPE.

Stevens-Johnson syndrome/Toxic epidermal Necrolysis spectrum: The diagnosis was made on the basis of characteristic mucocutaneous findings, drug history and systemic symptomatology. Patients with purpuric, targetoid or atypical target lesions, vesiculobullous lesions or erosions with involvement of ≥ 2 mucosae, with a temporal relationship to a drug known to produce a severe cutaneous drug reaction were included in this group. Patients were

further subclassified based on the percentage of detachment as SJS (BSA <10% + widespread macules and flat targets), SJS-TEN overlap (BSA 10-30% + widespread macules and flat targets) or TEN with spots (BSA>30% + widespread macules and flat targets) and TEN with spots (BSA >10% with large epidermal sheets without atypical macules and targets) (58). SCORTEN scoring was used to prognosticate patients with SJS/TEN (Annexure XIV).

Acute Generalised Exanthematous Pustulosis: EuroSCAR criteria for AGEP- Annexure XI, was used for the diagnosis of AGEP.

Controls: Nine patients with viral exanthem over the age of 18 years were recruited as controls. The controls were inducted from patients with fever and rash with clinical features of viral infection and/or a lab investigation confirming a case of viral infection.

Demographic details were entered in the proforma. Individuals with a history of previous skin disease/ malignancy/ transplant or any other recent illnesses were not included.

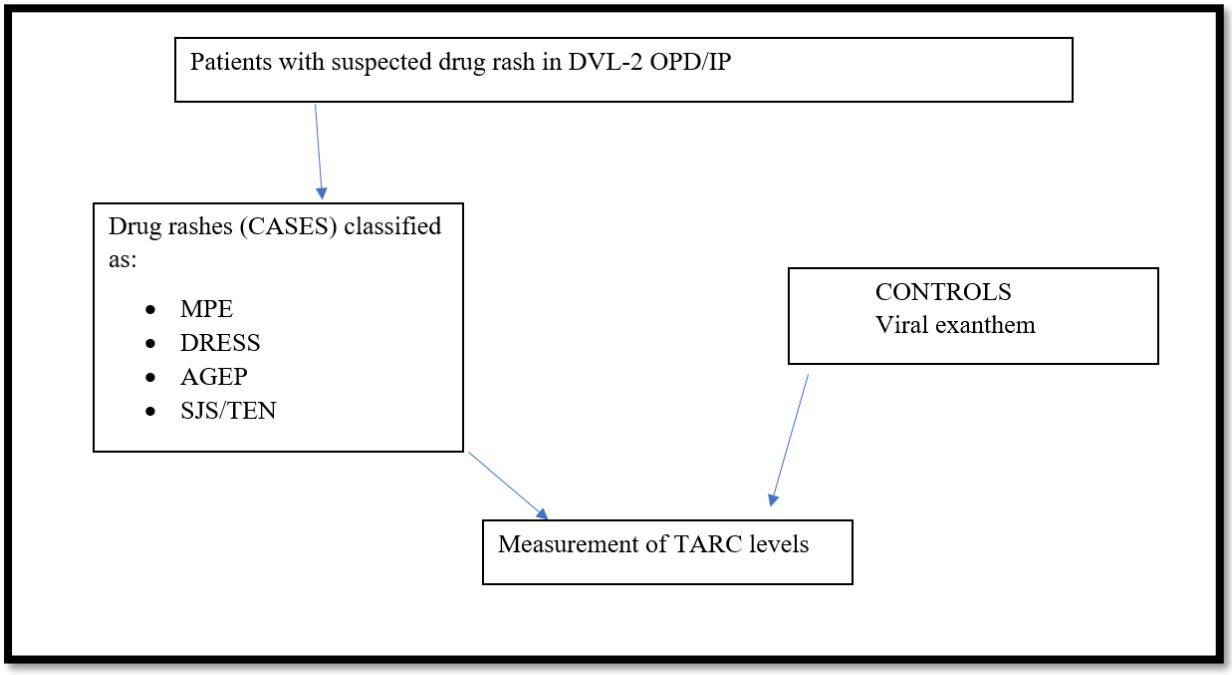


Figure 8 Algorithm for classification of the study subjects

Measurement of serum TARC: A blood sample was obtained for the measurement of serum TARC for all the study patients at initial presentation. Samples were collected in clotted tubes and transported to the Department of Clinical biochemistry at Christian Medical College, Vellore, for all study subjects. The serum was frozen and stored at -70 degree Celsius in the laboratory till the time of the assay. The TARC levels in the serum samples was measured with Abcam ab100644-TARC Human ELISA kit. The assay employed an antibody specific for TARC coated on a 96-well plate. Standards and samples were pipetted into the wells and TARC present in the sample was bound to the wells by the immobilized antibody. The wells were washed and biotinylated anti-Human TARC antibody was added. After washing away unbound biotinylated

antibody, streptavidin-conjugated horseradish-peroxide is pipetted to the wells. The wells were again washed, a tetramethylbenzidine substrate solution was added to the wells and color developed in proportion to the amount of TARC bound. The solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm. The minimum detectable dose of TARC was < 5 pg/mL**.** The test results were verified by a senior biochemist.

Statistical analysis:

Sample size calculation was done based on study of Komatsu Fujii et al. where serum TARC in various drug eruptions was evaluated as a potential biomarker for systemic inflammation(77). Reference laboratory values for serum TARC was 112 pg/ml ± 28. We expected a mean increase of 1000 in the drug rash population. With 80% power and 5% significance levels we needed to recruit a total of 60 patients.

The sample size formula for comparing two means is given by:

Calculation of sample size:

$$n = \frac{2\sigma^2 \, (Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

The data entry was performed using Epidata software and analysis by using SPSS software. The independent sample t test was used for the comparison of two categories with normal variables The data was summarized as mean and standard deviation for normally distributed numerical variables and median and range/Interquartile range (IQR) for non-normally distributed numerical variables. Categorical data has been presented as counts and percentages. Two sample t-test or Mann-Whitney U-test was used for comparing TARC levels according to two groups. Kruskal-Wallis test was used for comparing TARC levels according to 3 or more disease sub groups. Spearman rank correlation was carried out for correlation between TARC level and laboratory and physical parameters.

IRB approval: This study was approved by the Institutional Review Board of Christian Medical College, Vellore, bearing IRB Min number 12355 dated 5.11.2019 and was funded by the Fluid research grant of the institution (**Annexure I**).

To assess the utility of serum TARC measurements for prognosis of systemic inflammation including GPS (with score of 2) SIRS (with a score of 2), a receiver operating characteristic curve was carried out. Sensitivity and specificity were calculated.

Results

Forty-four patients with drug induced rashes were recruited during the study period from February 2020 till October 2021(21 months). Among the 44 patients, there were 23 patients with drug-induced MPE, 13 with DRESS, 5 with SJS/TEN, and 3 with AGEP.

Nine patients with probable viral exanthem were included as controls.

1. **Demographic Profile**

   a. **Age**

   Out of 44 patients with CADR recruited for the study, majority (n=26, 59%) of the patients were in the age group of 18-40 while a third of the patients (n = 15, 34%) were in 40-60 years and 10% (n =5) belonged in >60 years age groups. Figure 9 shows the age distribution among the cases i.e., patients with CADR recruited in this study in a pie chart diagram. The mean age among patients with drug-induced MPE and SCARs were similar in our study with 42.21± 13.28 years and 40.14±14.19 years respectively. The mean age among patients with DRESS was 41.38± 15.91, with SJS/TEN was 39± 14.38, and with AGEP was 36.66 ± 7.09. The mean age in patients with viral exanthem was 35.77± 16.38.

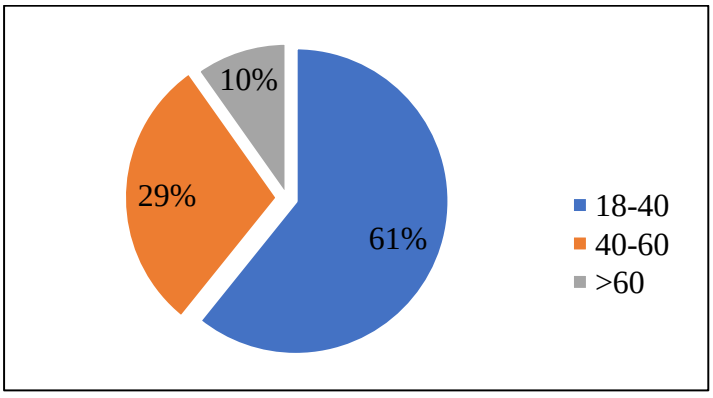


Figure 9 Age distribution in CADR

b. Gender

Both drug-induced MPE and SCARs groups showed a female preponderance with 65% (15/23) in MPE and 57.14% (12/21) in the SCARs group comprising of women. In subgroup analysis, there was an almost equal gender distribution in DRESS. The gender distribution of CADR subgroups is represented in figure 10. Women with DRESS had a younger age of onset (31.50 years) as compared to men with DRESS (49.85 years) with p-value of 0.07 (by independent t- test for means).

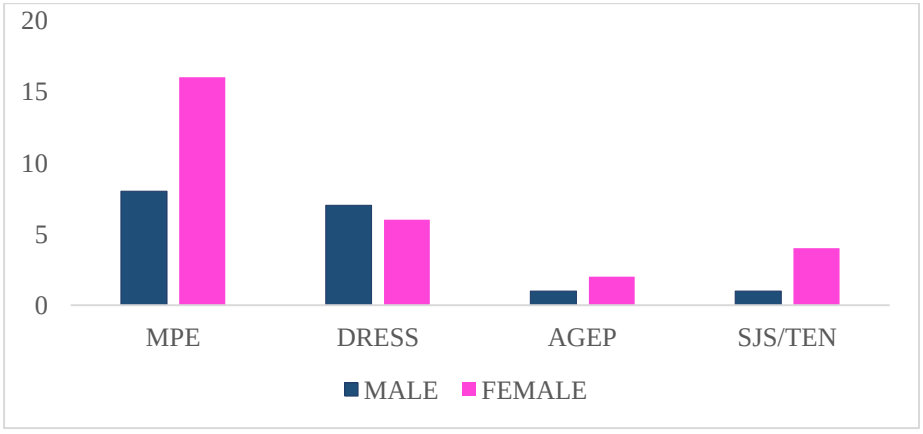


Figure 10 Gender distribution in CADR

c. Place of origin

The majority of the patients hailed from Tamil Nadu (n=32, 60.38%) followed by Andhra Pradesh (n=6, 11.32%) followed by Jharkhand (n=5, 9.43%). There were 3 patients from West Bengal, 2 from Bihar, and one each from Kerala, Manipur, Arunachal Pradesh and, Bhutan. State-wise distribution is represented in figure 11.

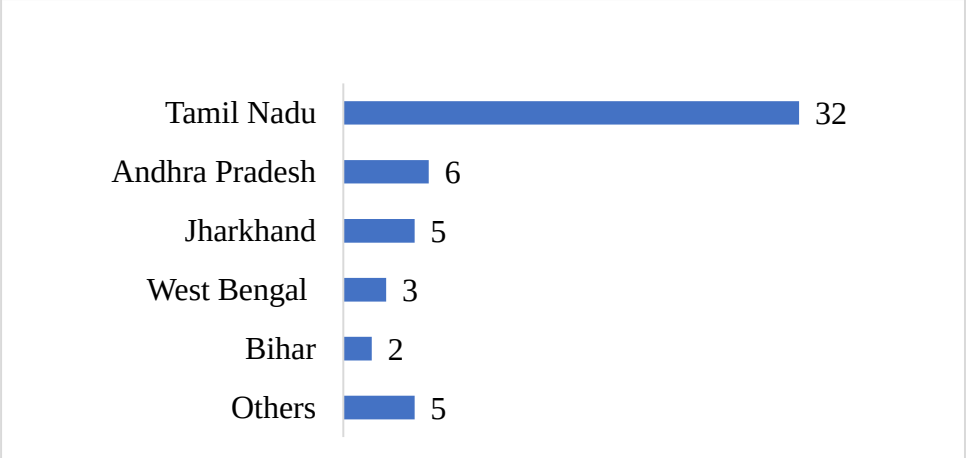


Figure 11 State wise distribution of subjects

2. Clinical profile

a. Presenting symptoms

- **Pruritus:** All patients with MPE and 90% of DRESS (19/21) had pruritus on presentation.
- **Burning sensation**: Only 21% (5/24) patients with MPE reported burning sensation as opposed to 57.14 % (12/21) with SCARs (p-value 0.015).
- **Fever:** Ninety-two percent of patients with DRESS had a fever (12/13) as opposed to 21.7 % (5/23) in MPE with p-value of <0.0001. One patient with DRESS who didn't have a fever was on steroids and had received Rituximab for her inflammatory myositis that could have possibly masked a fever. In the SJS/TEN group, 4 out of 5 patients (80%) had fever.

  All 3 patients of AGEP that were included in the study also had a history of fever, however one patient had presented with a history of fever and rash 6 days ago following a single dose intake of

metronidazole, she had discontinued it immediately followed by subsidence of fever; hence was afebrile on presenting to us.

b. Characteristics of cutaneous eruption

The morphology of cutaneous lesions in CADR were varied. Most common was a maculopapular rash 79% (34/44). Pustules were seen only in SCARs in all the patients with AGEP and in 2 patients with DRESS (p value 0.021). Vesicles were seen only in patients with SJS/TEN and AGEP. Exfoliation and scaling were seen significantly more among SCARs as compared to MPE (p value 0.077). Figure 12 demonstrates the distribution of rash morphology among CADR. One patient with DRESS having Hansen's disease had characteristic sparing of the rash over the leprous skin patches as shown in figure 33.

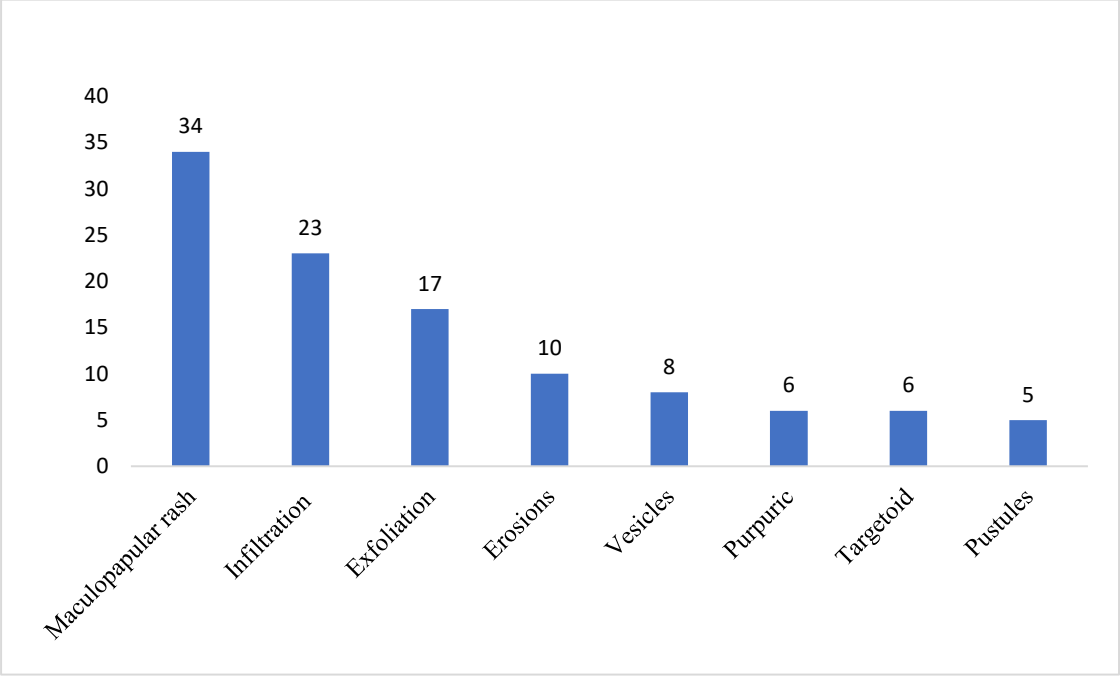


Figure 12 Rash morphology in CADR

c. Body surface area:

The mean body surface area (BSA) among patients with DRESS was 63.5± 23.78 and the mean BSA for MPE was 55.79± 20.22. Thirty patients (68%) with CADR had body surface involvement of >50%. Three patients presented in erythroderma (all 3 had DRESS). In SJS/TEN the mean BSA involvement was 34 ± 16.73 and in AGEP 46±38.57. Table 5 shows the mean and standard deviation of BSA in patients with CADR.

Table 5 Body Surface Area Involvement

Types Of CADR	AGEP	SJS/TEN	MPE	DRESS
Mean	46	34	55.60	65.07
Standard Deviation	38.57	16.73	20.65	22.87

d. Facial involvement: Facial involvement was seen in 30.4% (7/23) of patients with MPE, while all patients with SCAR (100%, n= 21) had facial involvement (p-value <0.0001). The various morphologies of facial lesions were oedema, scaling, presence of papules, targetoid lesions, exfoliation. Facial oedema was seen in 69.2% (9/13) of patients with DRESS, while only in 8% (2/23) patients with MPE. The presence of facial edema was significantly more in patients with DRESS than patients with MPE with a p-value of <0.001

e. Lesions over palms and soles: The most common palmoplantar lesion among patients with CADR was palmar erythema. Other features that

were seen were atypical targets, presence of papules, extension of rash over palms and exfoliation. Lesions were more frequently noted over palms as compared to soles. Sixty-one percent (27/44) of patients with CADR had involvement of palms and soles. Involvement of palms and soles were seen in 66.6% of SCARs versus 56.5% of patients with MPE.

f. Mucosal lesions: All patients with SJS/TEN (5/5) had mucosal lesions while only 3 patients with DRESS and one patient with MPE had mucosal lesions. Mucosal lesions were notably seen more in SCARs than MPE with p-value of 0.0003. Severe mucosal ulcerations were seen only in SJS/TEN. Other SCARs and drug-MPE had relatively milder mucosal lesions.

i. **Eye involvement:** Conjunctival congestion was seen in 1 patient with MPE, while 4 out of 5 patients with SJS/TEN had ocular involvement. Conjunctival congestion, circumcorneal congestion, lid edema, discharge and crusting were seen. Corneal ulceration was not seen.

ii. **Oral involvement:** Oral involvement was seen in the form of erosions, haemorrhagic crusting, cheilitis, buccal mucosa ulceration and coated tongue. All patients with SJS/TEN had oral involvement (5/5). Four patients with DRESS had oral involvement in the form of cheilitis and superficial erosions. CADR patients also had a secondary infection in the form of herpes simplex viral infection and oral candidiasis. Disseminated

herpes simplex infection was seen in one patient with DRESS syndrome.

iii. **Genital involvement**: Genital erosions and ulcers were seen only in patients with SJS/TEN (5/5).

g. Nail involvement: One patient with DRESS to sulfasalazine had dystrophic nails involving all finger and toenails with Beau's lines. This patient had the longest index day of presentation.

h. Scalp and Hair involvement: Scalp and hair involvement was seen in 35% of patients with SCAR versus 8.3% of patients with MPE. Three patients each had alopecia, and scaling over the scalp. One patient with AGEP had pustules over the scalp. One patient with DRESS to Sulfasalazine who had nail changes mentioned above also had greying of all scalp and eyebrow hairs.

3. Latent period

The mean latent period for patients with DRESS was 24.92 ±13.85 days with a minimum of 5 days and a maximum of 54 days. Two out of 13 patients with DRESS had a latent period of ≤ 15 days. The drugs implicated in these cases were dapsone and phenytoin. AGEP, on the other hand presented within 1 day in all 3 patients recruited. The shortest and the longest latent period of MPE was less than 1 day and a maximum was 20 days respectively. Figure 13 shows the distribution of latent period among all CADRs recruited in the study with DRESS having a significantly longer latent period as compared to MPE (p-value of <0.0001)

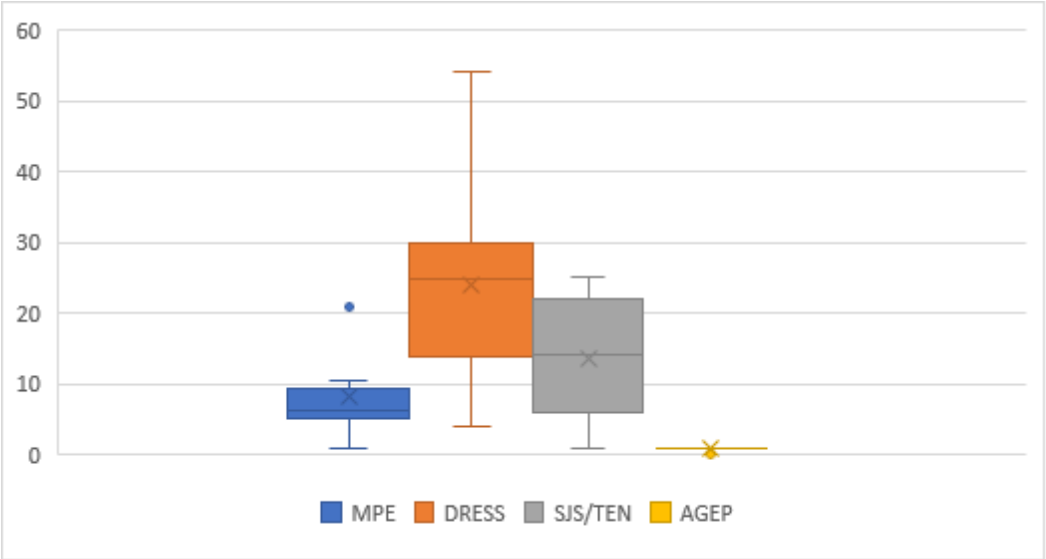


Figure 13 Latent period in days

4. Index day of presentation

Index day of presentation is the number of days after which a patient presented following the onset of symptoms for the CADR. One patient with DRESS to sulfasalazine presented in erythroderma after 7 months since the onset of symptoms; she was treated elsewhere before presentation, with recurrence of symptoms each time following a rapid tapering of steroids. Figure 2.6 shows the index day of presentation among the CADR. The median 'day of presentation' after the onset of symptoms of all patients with CADR was 5 days (IQR 2-7). The mean value of the day of presentation of patients with DRESS was 24.46±56.33 days versus MPE who presented much earlier with a mean of 4.30±3.77 days (p-value 0.09)

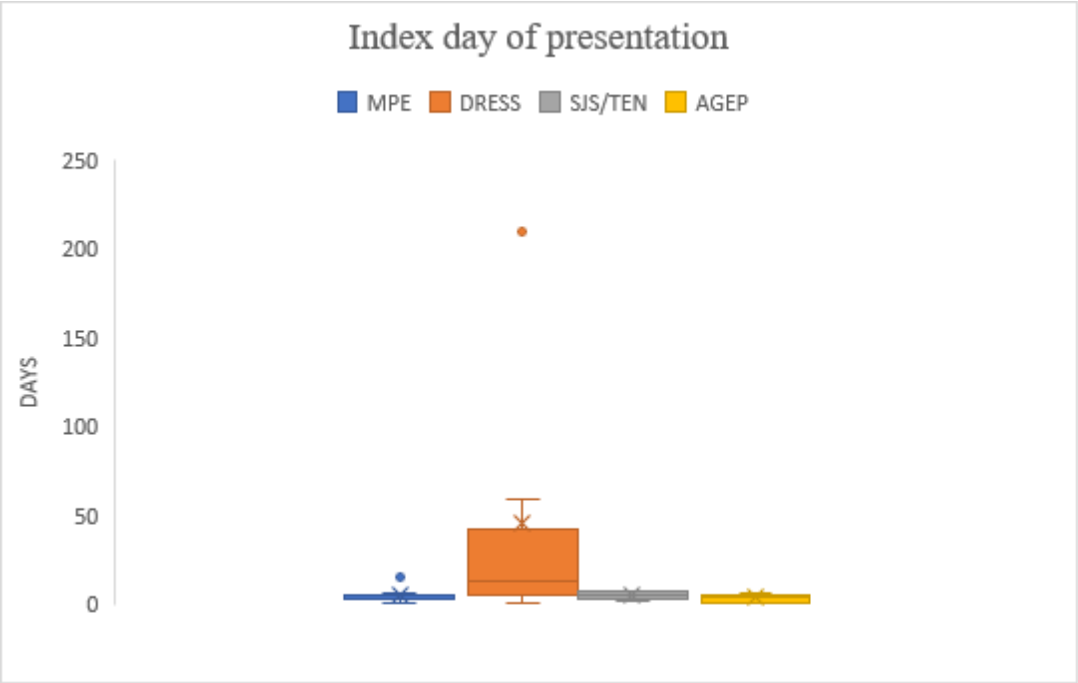


Figure 14 Index Day of presentation in various CADR

5. Comorbidities

A majority of subjects had comorbidities (n=37/53). Diabetes and hypertension were seen in 11 patients (20.7%). In cases (n=44) 7 ((15.9%) patients had tuberculosis, 5 patients (11.36%) had chronic kidney disease, 3 patients (6.8%) had seizure disorder, 2 patients each (4.5%) had HIV and Hansen's disease. Figure 15 shows the distribution of comorbidities among patients with various CADR subgroups. Diabetes, hypertension, and stroke were the common comorbidities among subgroups of CADR. Rheumatoid arthritis and hypothyroidism was seen in one patient each with drug-induced MPE.

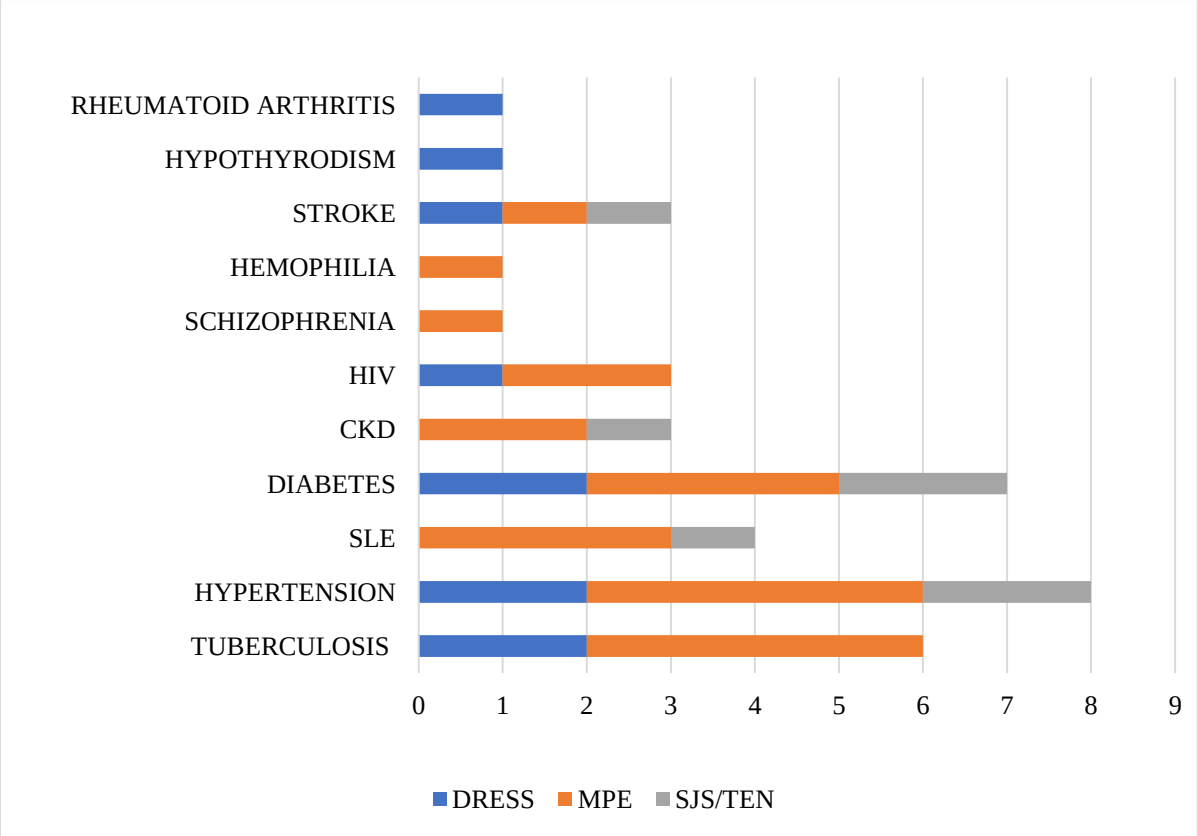


Figure 15 Comorbidities among patients with CADR

6. HLA testing

There were 3 patients in our study with CADR to dapsone, HLA*B13 testing was done in 2 and both these patients had genetic polymorphism. Two patients with CADR to carbamazepine were tested for HLAB15, however no genetic polymorphism was detected.

7. Drug details

a. Commonly implicated drugs in Cutaneous adverse drug reactions

Antibiotics were the most common implicated drugs in CADR (31%). Betalactams (8) were the most common antibiotics responsible for CADR accounting for 18.1%. Antiepileptics were implicated in 10 (22.72%) patients with CADR. Sulfa-containing drugs (i.e., Sulfasalazine,

cotrimoxazole and dapsone) were implicated in 10 patients (22.7%). Anti-tuberculous medications were implicated in 3 patients and all 3 patients underwent drug rechallenge and a single culprit was identified. The latent period of drug categories as displayed in table 6 shows that DRESS has longer latency than MPE caused by the same drug. The drugs implicated in DRESS are shown in a pie chart in figure 16.

Table 6 showing the Indication of drugs that caused CADR with phenotype of CADR

Drugs, number of patients in parentheses	Indication	CADR phenotype
Betalactams • Penicillin (2) • Piperacillin-tazobactam (2) • Meropenem (2) • Ertapenem (1) • Amoxycillin (1)	Pyelonephritis Cellulitis Urinary tract infection	6 MPE (1 patient received both ertapenem and amoxycillin and one patient received penicillin and piperacillin)
Contrast • Ioxehol (3) • Iodixanol (1) • Iodoquinol (1)	Coronary angiogram Computed Tomography scan	5 MPE
Phenytoin	Seizure disorder Stroke Head injury Cerebral venous thrombosis	1 SJS/TEN 3 DRESS 3 MPE

Cotrimoxazole	Prophylaxis	3 MPE 1 DRESS
Sulfasalazine	Psoriatic arthritis Rheumatoid arthritis	2 DRESS
Dapsone	Hansen's disease Prurigo nodularis Bullous lupus erythematosus	2 DRESS 1 MPE
Carbamazepine/Oxcarbazepine	Paresthesia Neuromyelitis Optica	1 DRESS 1 SJS/TEN 1 AGEP
Antituberculous drugs • Isoniazid (1) • Rifampicin (1) • Ethionamide (1)	Tuberculosis	1 DRESS 2 MPE
Proton pump inhibitors • Pantoprazole (1) • Esomeprazole (1)	Pyrosis Steroid adjuvant	2 DRESS
Chlorpromazine	Schizophrenia	1 MPE
NSAID • Diclofenac (1)	Pain relief	1 MPE
Terbinafine	Onychomycosis	1 MPE
Lamivudine	HIV	1 MPE
Gentamycin	Reason not clear	1 SJS/TEN
Doxycycline	Unknown bite	1 AGEP
Allopurinol	Hyperuricemia	1 SJS/TEN

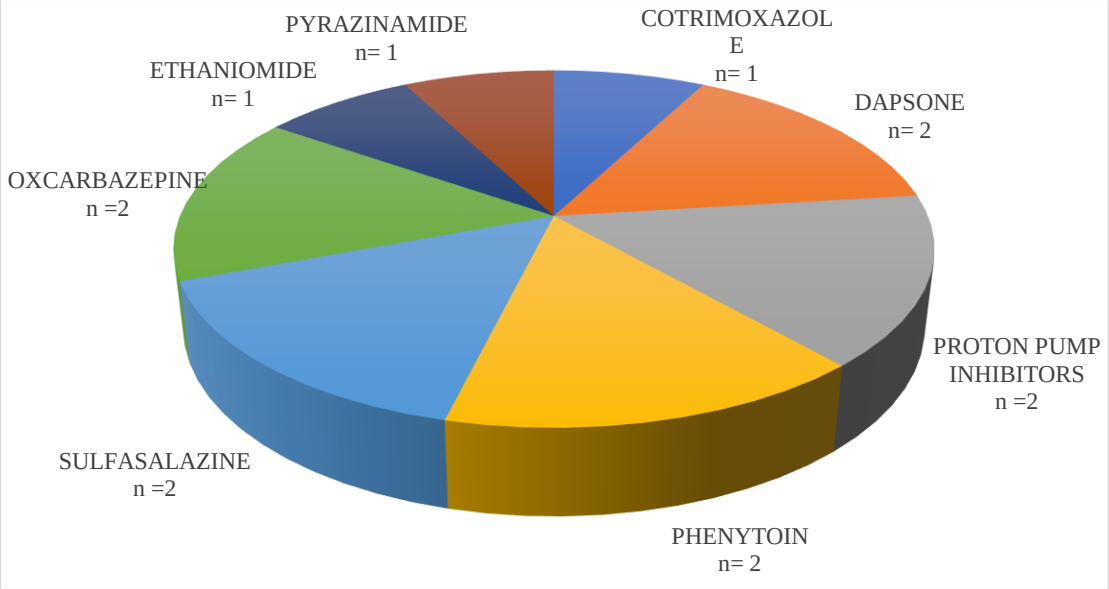


Figure 16 Drugs implicated in DRESS

Table 7 shows the latent period of all drugs implicated in each phenotype of CADR

Drug group	Drug	Mean latent period in phenotype of CADR
Antiepileptics	Phenytoin	MPE 11 ± 8.18
		DRESS 22 ± 12.16
		SJS/TEN 16
	Carbamazepine / oxcarbazepine	DRESS 11
		SJS/TEN 6
		AGEP 1
Antibiotics	Betalactams	MPE 8.5 ± 8.5
Sulfa drugs	Cotrimoxazole	MPE 21
		DRESS 35
	Dapsone	MPE 7
		DRESS 11
	Sulfasalazine	DRESS 30
Intravenous Contrast	Iodinated (Ioxehol/Iodoquinol)	MPE 2.4 ± 1.94

b. Drug probability scoring:

Naranjo's adverse reaction probability scale was used to determine drug causality among patients with drug-induced MPE and DRESS. The lowest score and highest score among MPE and DRESS were 2,4 and 8,9 respectively. The median scores for MPE and DRESS were 6 and 7 respectively. Figure 17 shows the box and whiskers plot of the Naranjo score of the cases recruited. ALDEN score was calculated for all SJS/TEN patients. Three out of 5 patients with SJS/TEN had an ALDEN score of 6, other 2 patients had scores of five and one each.

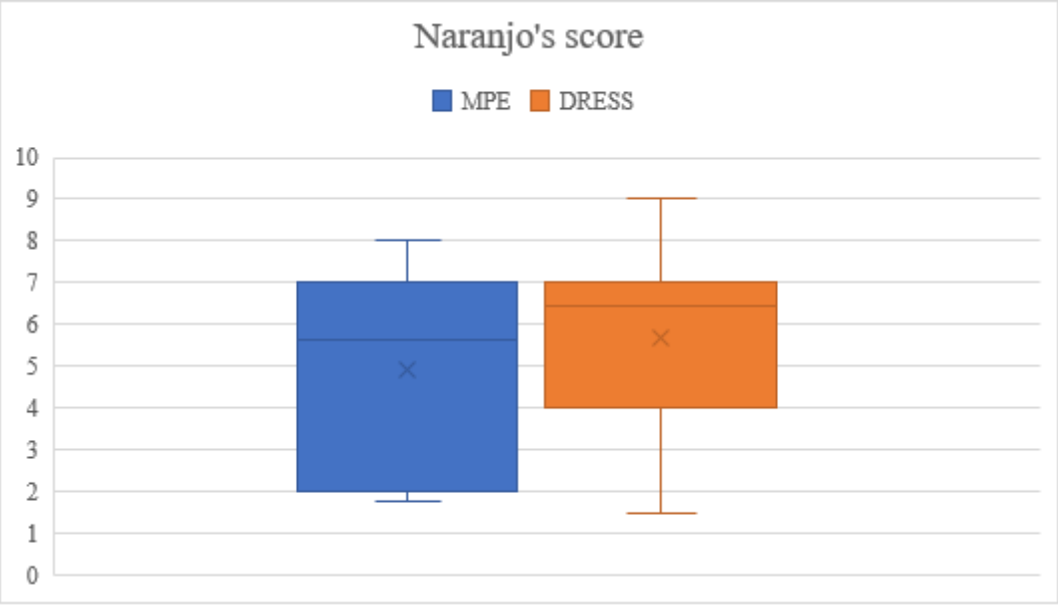


Figure 17 Naranjo's scoring in DRESS and drug induced MPE

c. Past history of drug reaction:

Four patients with CADR had a previous history of drug reactions. One patient had AGEP to carbamazepine (CBZ) with a past history of SJS/TEN to the same. Though the index patient had only a stat dose of CBZ, he developed the AGEP

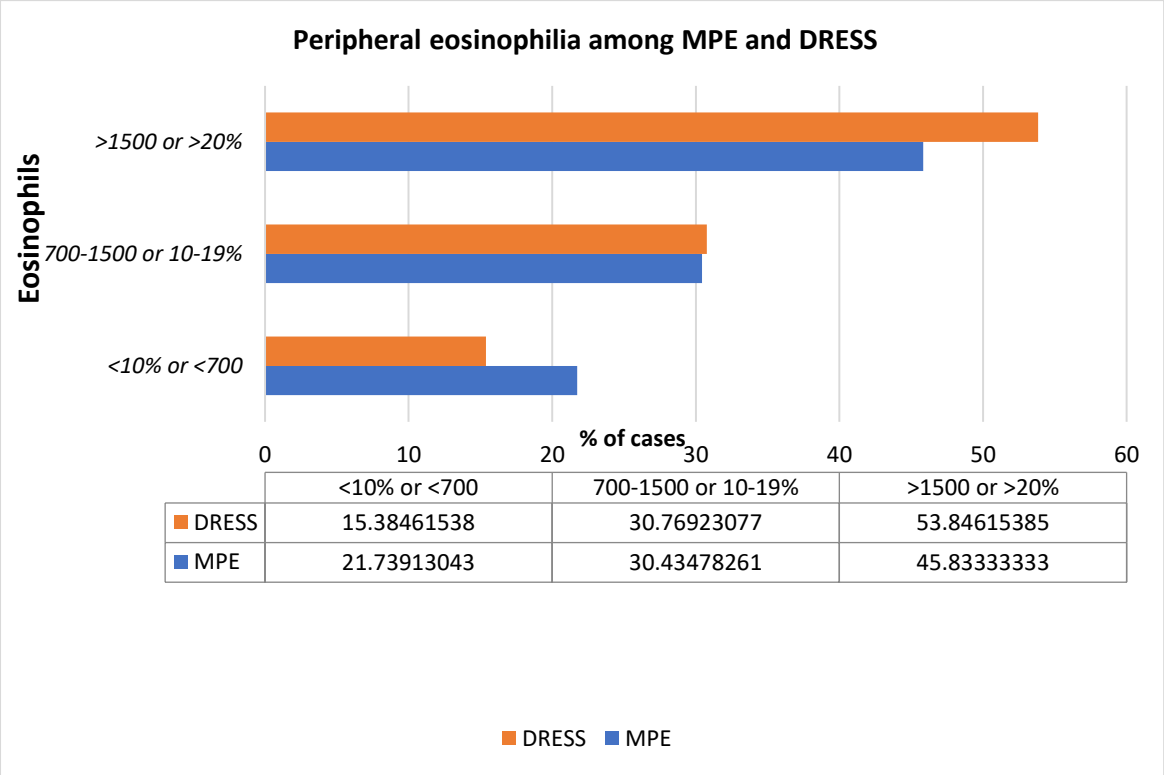
phenotype of drug hypersensitivity which was severe enough to warrant inpatient treatment with systemic steroids. Another patient had MPE to 2 different regimens of ART with lamivudine being present both times. Two patients with drug-induced MPE had a previous history of CADR to unrelated drugs.

8. Systemic involvement

a. Lymphadenopathy: Enlarged lymph nodes were present in 66.7% (9/13) of patients with DRESS against 12.5% of MPE patients (2/23) with p-value of <0.0001.

b. Hepatic dysfunction: It was seen in 75% (9/13) of patients with DRESS versus 25% (6/23) patients with MPE with a significant p-value of 0.017. Hepatic dysfunction most commonly encountered was transaminitis while few had elevated bilirubin and/or increased levels of alkaline phosphate. Low albumin levels (<3.5mg/dl) were seen in 58.3% (7/13) of patients with DRESS as compared to 33.3% (8/23) of patients with MPE with p-value of 0.30 which was not significant.

c. Peripheral eosinophilia: Peripheral eosinophilia of more than 1500 cells/cumm was slightly more in DRESS as compared to MPE with 53.8% (n= 7/13) and 45.8% (n= 13/23) respectively with p-value of 0.70. Eosinophilia was further categorized as absolute eosinophil count of more than 700-1499 cells/cumm or 10-19% was seen in 30.7 % (n= 4/13) in DRESS (percentages were used if WBC count was <4000 cells/cumm) and its distribution among MPE and DRESS is demonstrated in figure 18.



	<10% or <700	700-1500 or 10-19%	>1500 or >20%
DRESS	15.38461538	30.76923077	53.84615385
MPE	21.73913043	30.43478261	45.83333333

Figure 18 Peripheral eosinophilia among MPE and DRESS

d. Other haematological involvement: One patient with DRESS to dapsone had a leukemoid reaction (maximum counts 52900/cumm). One patient with DRESS to carbamazepine developed neutropenia requiring granulocyte colony-stimulating factor.

e. Gastrointestinal involvement: Two patients presented with persistent loose stools. Interestingly, both these patients had CADR to proton pump inhibitors (DRESS to pantoprazole and MPE to esomeprazole).

f. Respiratory involvement: One patient with DRESS to Dapsone was suspected to have Dapsone-induced pneumonitis/Hospital-acquired infection. He was also found to be HLAB13 positive.

g. **Renal involvement:** Two patients with DRESS and 2 patients with TEN had acute kidney injury. The patients who developed TEN had pre-existing chronic kidney disease. Two patients with drug-induced MPE to iodinated radiocontrast also had drug-induced kidney injury. Urine for eosinophils was positive in 8% (n= 2/25) patients with CADR; one patient had SJS/TEN to allopurinol and one had MPE to radiocontrast media-Iodixanol.

9. RegiSCAR scoring

All patients with RegiSCAR of ≥4 were classified as DRESS and cases with scores <4 were classified as MPE. RegiSCAR ≥ 4 was seen in 13 cases and >5 was seen in 6 cases. The average RegiSCAR score for DRESS was 5.3±0.7 and for MPE was 0.8±1.4. The lowest score assigned to a case was -1 and maximum score was 6. Figure 19 shows the distribution of RegiSCAR score among cases with DRESS and drug-induced MPE. Among patients with DRESS, the most common component of RegiSCAR score which was present was fever (12/13) seen in 92% of patients followed by "BSA>50%" seen in 69% of patients (9/13). The most common organ system positive in RegiSCAR scoring was liver involvement.

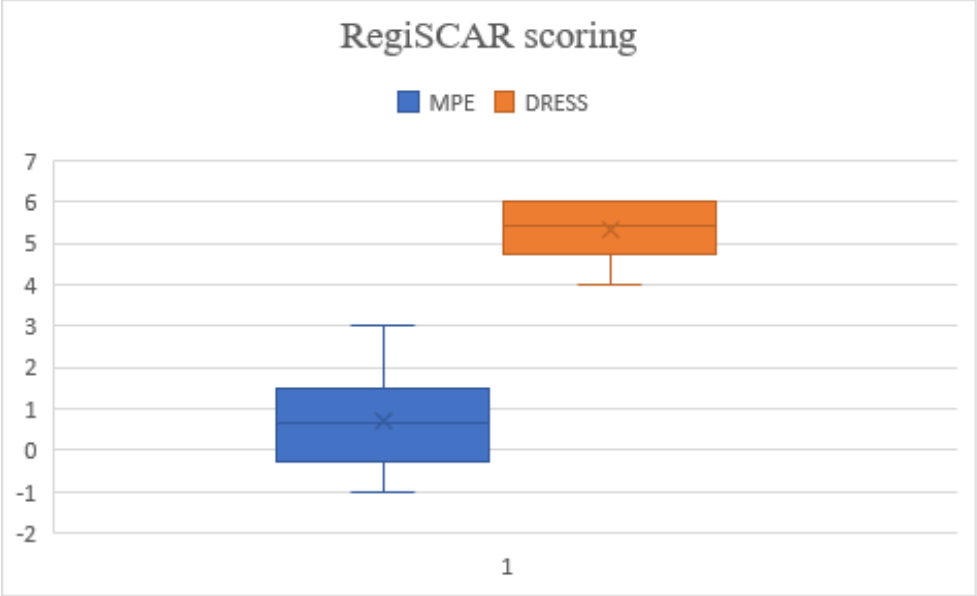


Figure 19 RegiSCAR scoring in DRESS and drug induced MPE

10. Controls- Patients with viral exanthem

There were 9 patients with viral exanthem who served as controls. Majority of the patients were males (8/9). The mean age among controls was 35.77 years. All these patients had a blanching erythematous rash; few (22%, n = 2) had the classical islands of sparing seen in dengue induced exanthem. Only 3 patients had pruritus, most patients' rash were asymptomatic. All patients had confirmed serology for dengue infection (NS1antigen or Dengue IgM or Dengue IgG positive).

11. Markers of Inflammation

a. Serum C- reactive protein

Serum C- reactive protein (CRP) levels were higher in patients with DRESS (median 24.20 with IQR 16.65- 53.12) as compared to patients with MPE (median 16.15, IQR 7.05- 29.22) and viral exanthem (median 11.2 IQR 5.74- 18.25), as depicted in figure 20.

However, the CRP levels were not significantly different among these subgroups (p-value 0.13).

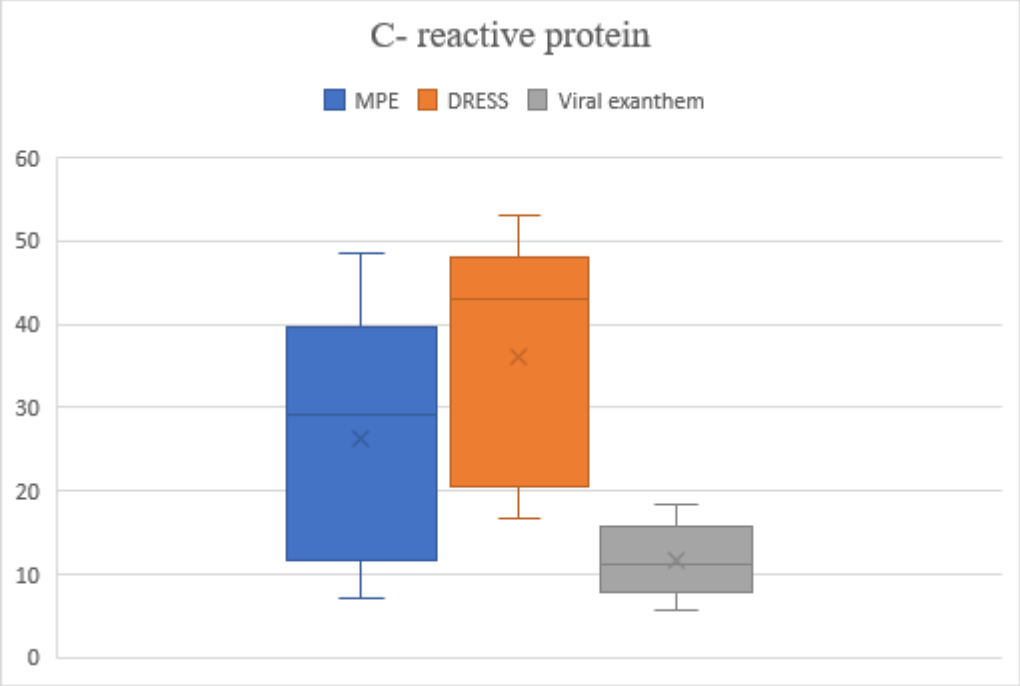


Figure 20 C-reactive protein levels in DRESS, drug induced MPE and viral exanthem patients

b. Glasgow prognostic score:

The maximum Glasgow Prognostic score (GPS) was 2 and the minimum was zero. The components of GPS include serum albumin and serum CRP. Serum albumin < 3.5gm/dl and CRP >10mg/dl is given a score of one for each component. A higher percentage of patients with SCARs had a score of 2 as compared to patients with MPE and viral exanthem (p-value <0.001). Figure 2.13 shows a comparison of GPS among MPE, DRESS, and viral exanthem.

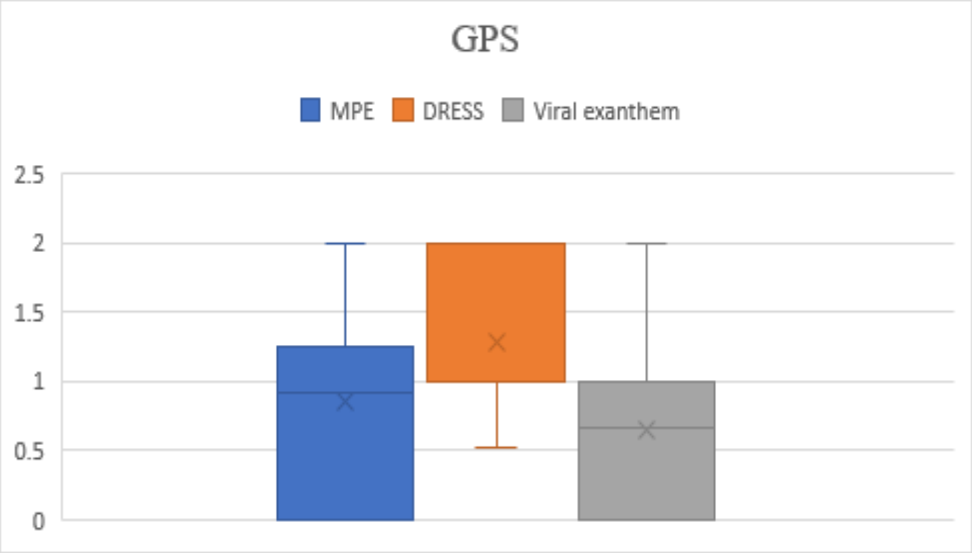


Figure 21 Glasgow prognostic scores in as quartiles in DRESS, drug induced MPE and viral exanthem

c. Systemic inflammatory response scoring:

Systemic inflammatory response syndrome (SIRS) score included one point each for WBC count <4000/uL or >12000/uL, pulse rate >90/min, body temperature >38℃ or <36°C and respiratory rate >20/min or $PaCO_2$ < 32 mmHg. SIRS score of ≥ 2 was considered worse prognosis and patients with CADR were classified accordingly. There were 71% of SCARs (15/21) and 43% of MPE (10/23) patients with SIRS score ≥ 2 with a p-value of 0.03.

d. Neutrophil -lymphocyte ratio:

The ratio between neutrophil count and lymphocyte count (NLR) was highest among patients with AGEP, consistent with neutrophilia that is seen in AGEP. One patient with AGEP had a normal NLR ratio as she presented 9 days after the acute fever and rash. NLR for SCARs (median 3.79 IQR 9.15-2.46) was similar to MPE (median 4.06 IQR 2.95-6.35). NLR in CADR was higher

compared to patients with viral exanthem (median 1.88 IQR 1.05- 4.18) but not statistically significant (p-value 0.25). The NLR distribution among recruited subjects is depicted in figure 2.15.

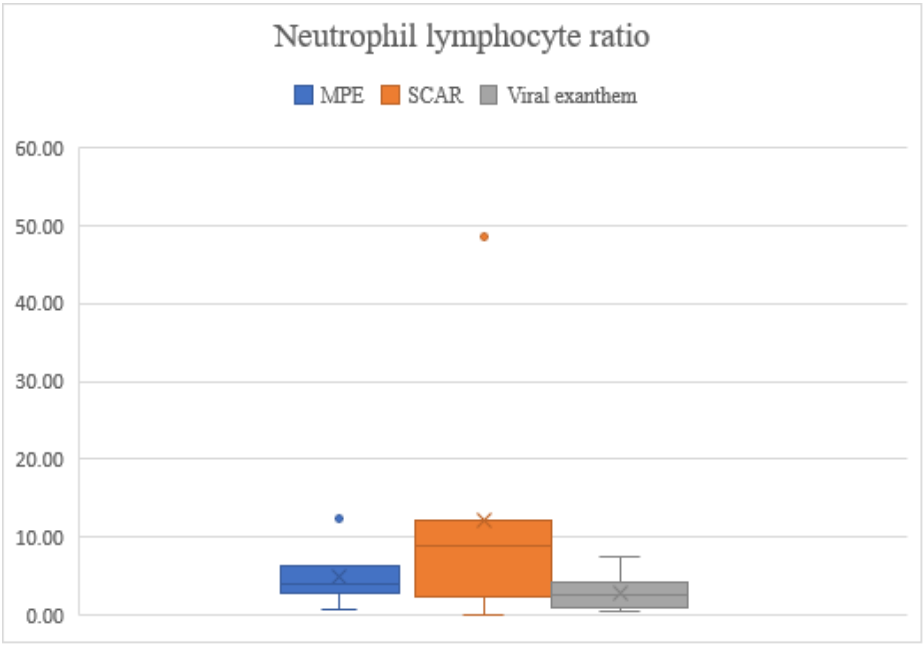


Figure 22 Neutrophil lymphocyte ratio in patients with drug-induced MPE, SCARs and viral exanthem

12. Histopathology

This was not performed routinely in all patients. It was done in 3 patients with MPE, 9 with DRESS, 2 with SJS/TEN and in all the three AGEP patients. The histopathological findings noted were spongiosis, the presence of necrotic keratinocyte, lymphocyte exocytosis, dermal eosinophils and interface change. Spongiosis was seen in 66% (6/9) DRESS, none of the patients with MPE had spongiosis. Necrotic keratinocytes were seen in 77% (7/9) DRESS as opposed to 33% (1/3) of MPE patients and interface changes in 55% (5/9) of DRESS versus 33% (1/3) in MPE. Basal cell vacuolation was seen in 66% in both DRESS and MPE patients and dermal eosinophils in 55% and 66% of DRESS

and MPE patients respectively. Interface dermatitis was encountered in 55% in DRESS and in 33% in MPE. All 3 patients with AGEP had spongiosis, necrotic keratinocyte and papillary edema and neutrophil infiltrate while only 2 patients had subcorneal vesicles. Two patients with TEN who underwent skin biopsy showed pan epidermal necrosis and only a focal area of dermal inflammation.

13. TARC levels

Serum TARC was performed in all subjects i.e., patients with CADR and viral exanthem. The median TARC value in CADR was 1201pg/ml (IQR 148.5- 2000) which was higher than in patients with viral exanthem was 792pg/ml (IQR 5- 792) with p-value of 0.056 with a trend towards significance. Among the CADR, serum TARC levels were higher in patients with SCARs with a median of 1349 pg/ml (IQR 200.5- 2000 pg/ml) as compared to patients with MPE with a median of 996.5 pg/ml (IQR 129.5- 1737 pg/ml) and viral exanthem 218pg/ml (IQR 5-792 pg/ml) as demonstrated in figure 2.17. However, the difference was not found to be statistically significant. (p-value 0.1086). Among MPE and DRESS the mean TARC value for MPE was 997pg/ml with 95% CI [655.233- 1338.76] and for DRESS was 1080pg/ml with 95% CI [300.36-1860.30]. The difference among the means of the two groups was not statically significant. There was no statistical correlation between TARC values in RegiSCAR score in patients with DRESS and MPE.

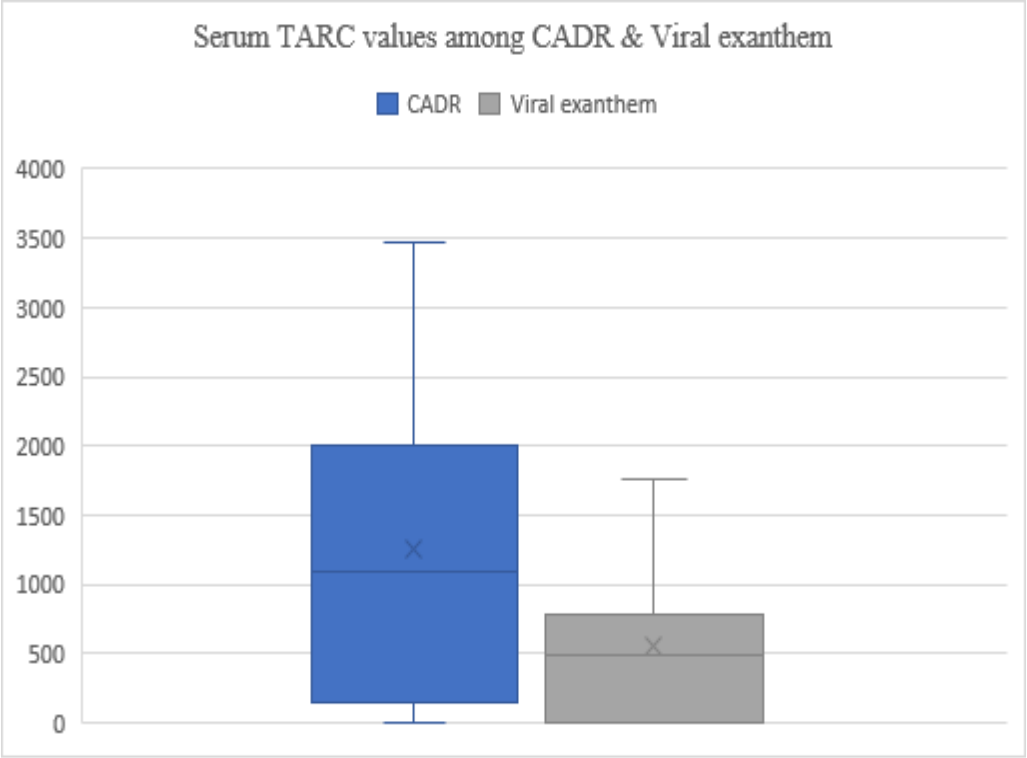


Figure 23 Comparison of serum TARC levels among patients with CADR and viral exanthem

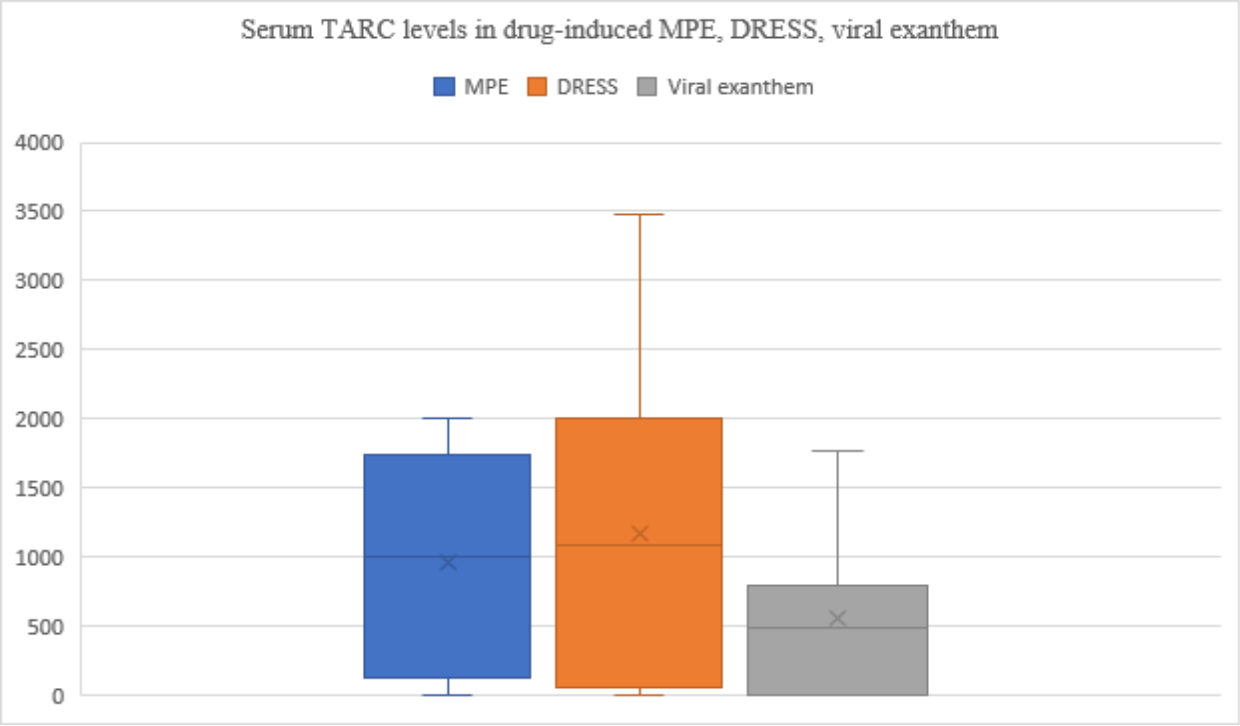


Figure 24 Comparison of serum TARC levels in patients with drug-induced MPE, DRESS and viral exanthem

14. Relationship between Serum TARC and peripheral eosinophilia

Higher peripheral eosinophilia positively correlated with increased levels of serum TARC with p-value of 0.004 by Pearson 2 tailed correlation. This positive correlation was seen in both the DRESS and MPE subgroup of patients as demonstrated in a scatter plot in figure 2.15.

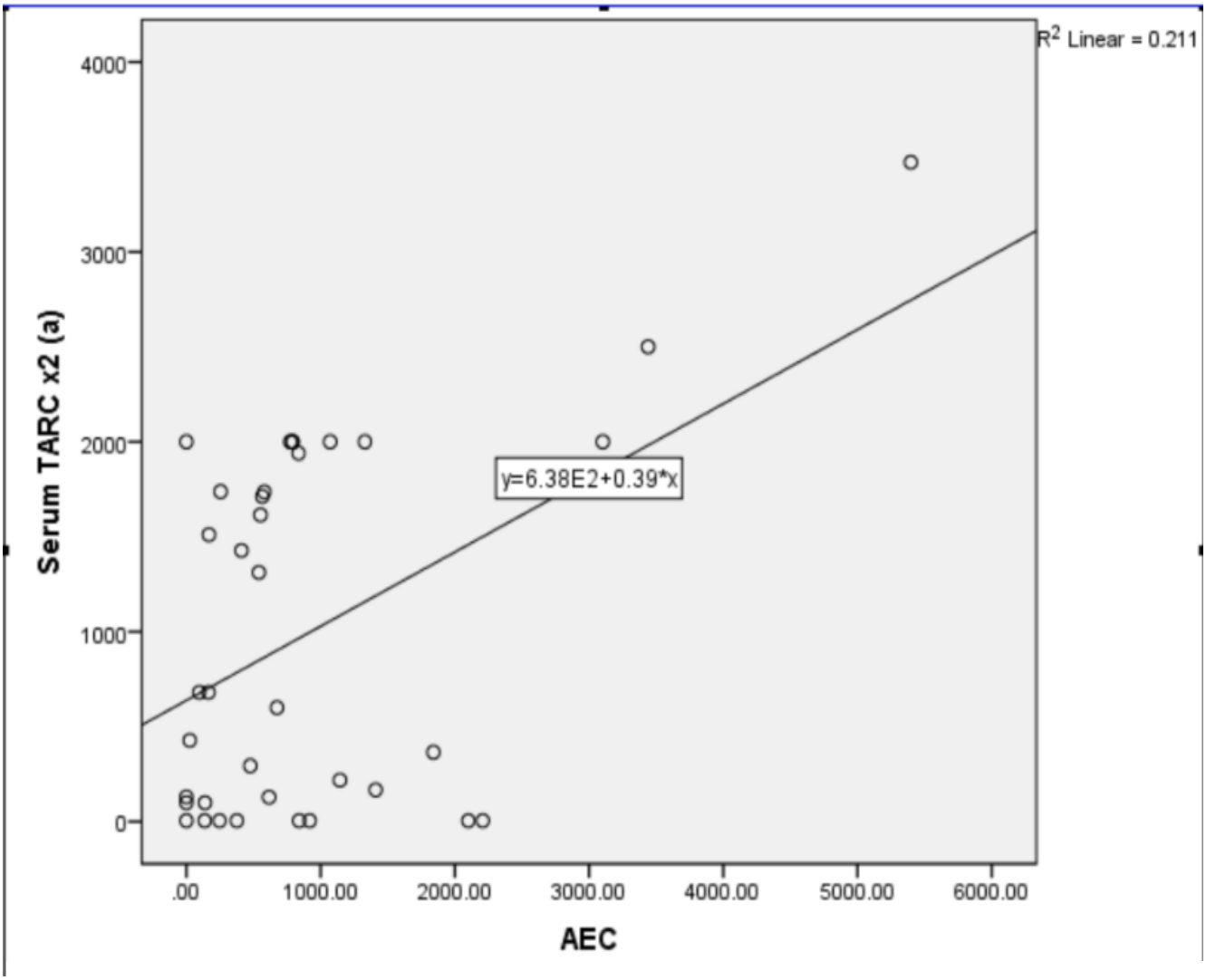


Figure 25 showing Absolute eosinophil count (AEC) in X-axis and Serum TARC in Y-axis in patients with DRESS and MPE

Clinical pictures

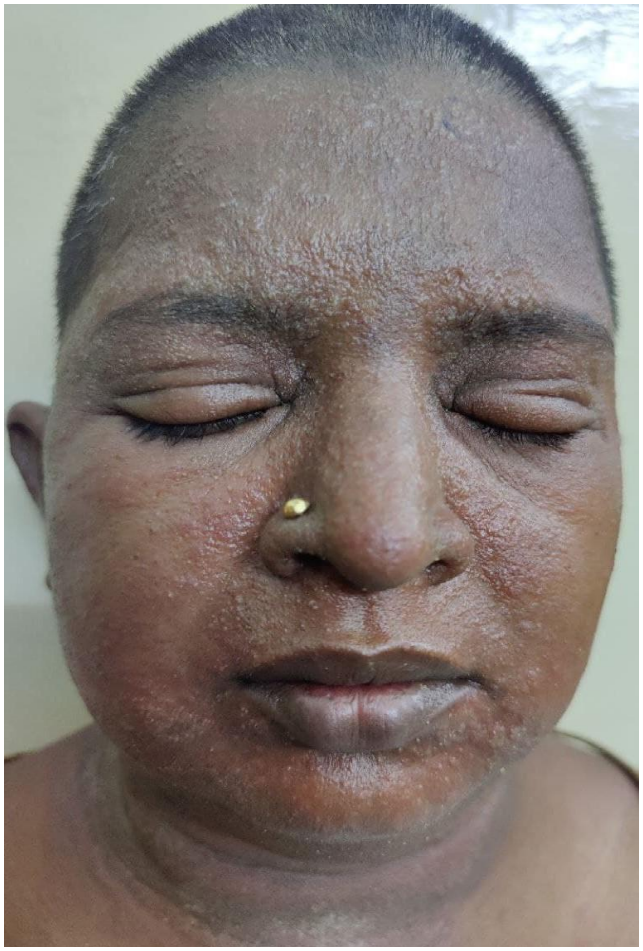


Figure 26 shows facial oedema and pustules in a patient with AGEP

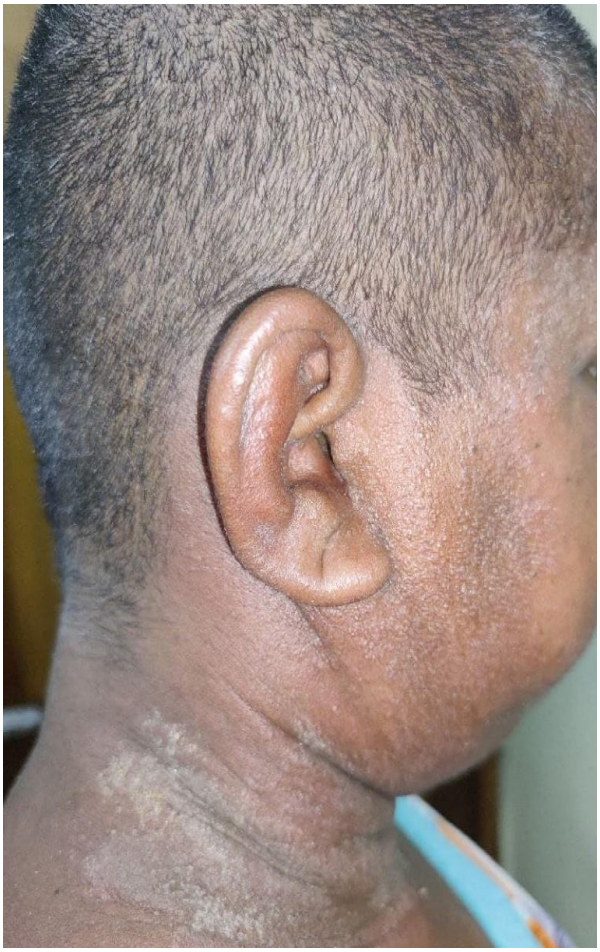


Figure 27 The same patient as in figure 27 with oedematous earlobe and desquamation

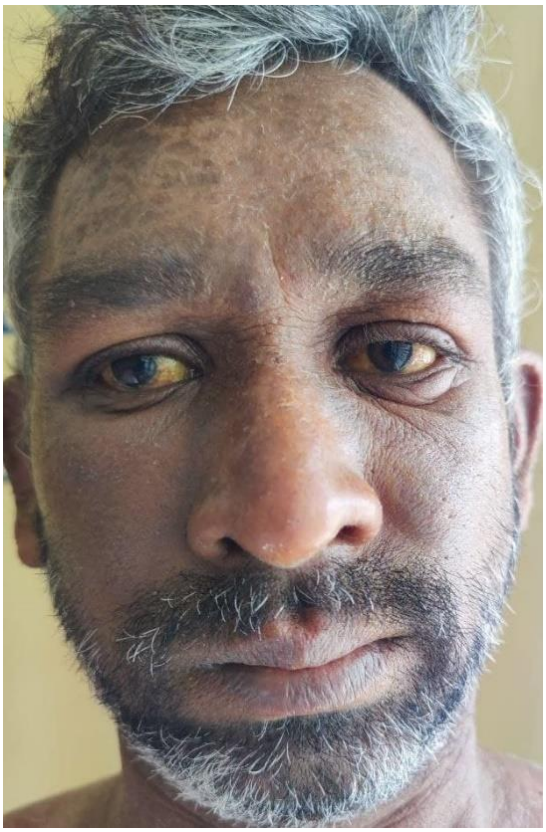


Figure 29 Facial edema in a patient with DRESS

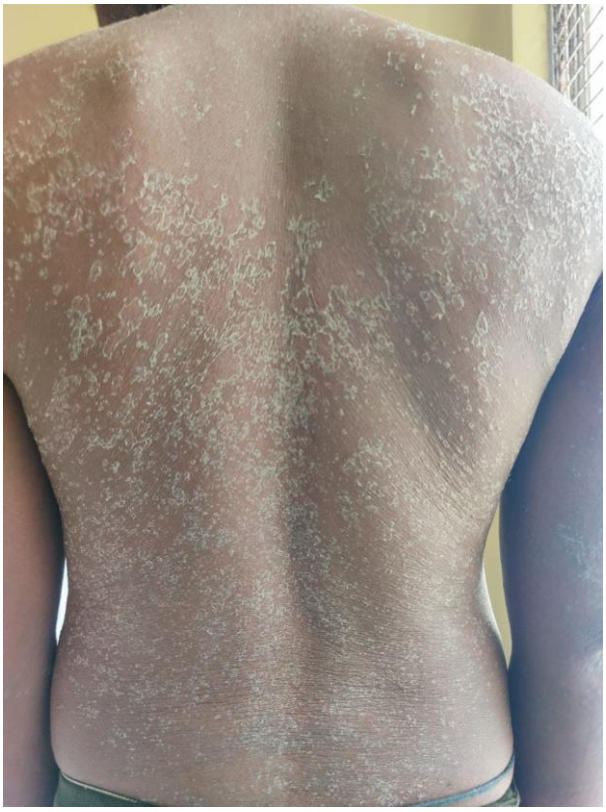


Figure 28 erythroderma with desquamation in DRESS, same patient as in figure 29

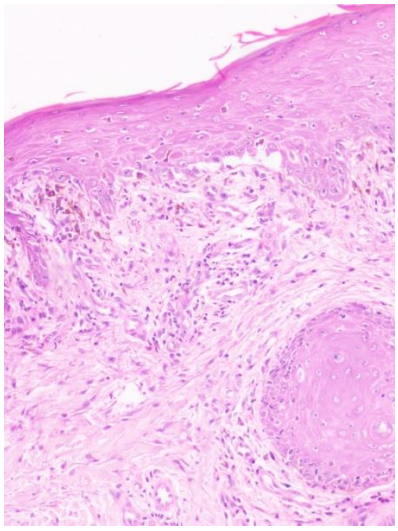


Figure 30 Figure 30 Photomicrograph showing section of skin with interface change, necrotic keratinocytes and superficial perivascular chronic inflammation including few eosinophils (H&Ex100) in a patient with DRESS

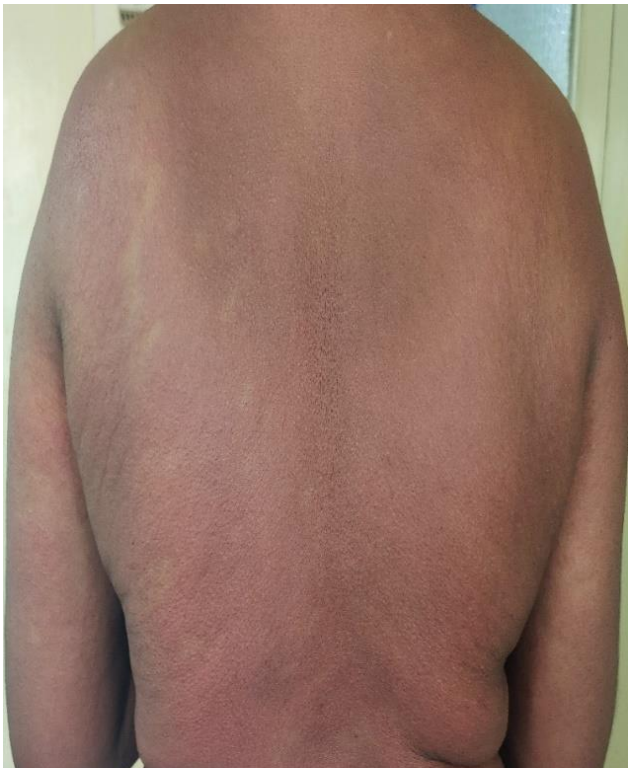


Figure 31 Back of a patient with drug induced MPE with diffuse erythematous maculopapular rash with few areas of sparing

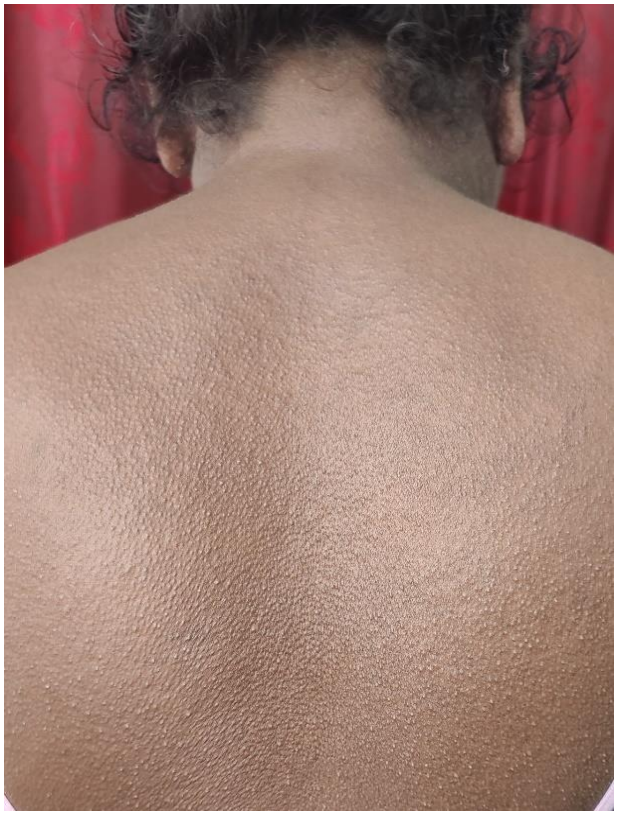


Figure 33 Drug induced MPE with papular rash

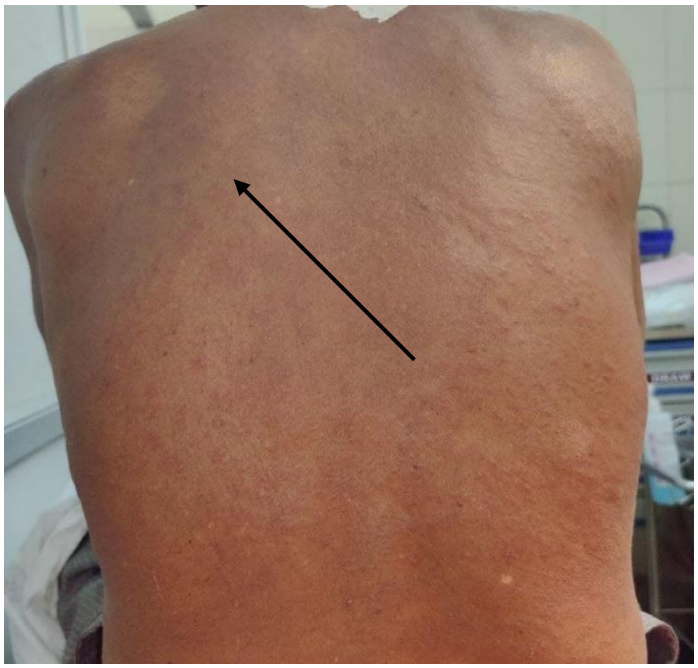


Figure 32 Arrow showing the sparing of leprous patch in a patient with DRESS

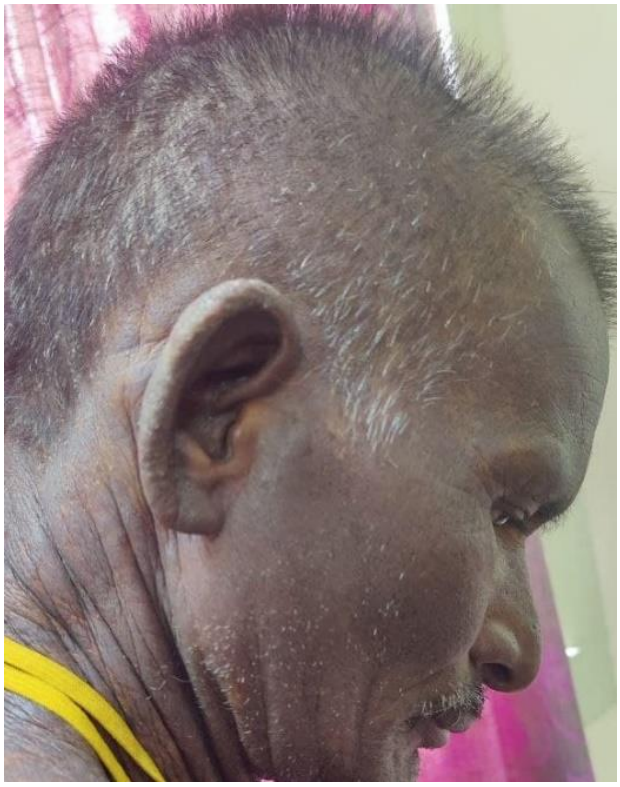


Figure 35 Diffuse alopecia in a patient with DRESS

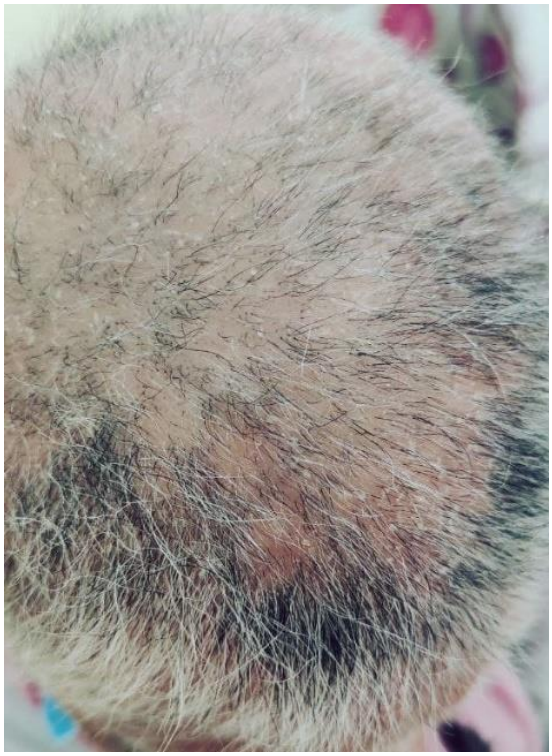


Figure 36 Diffuse alopecia and greying of hair in a patient with DRESS

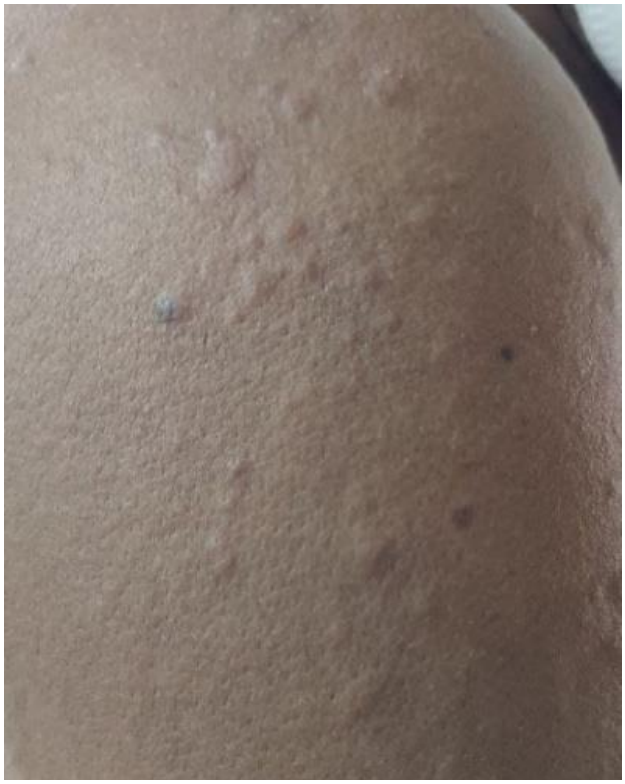


Figure 34 Urticated lesions in a patient with DRESS

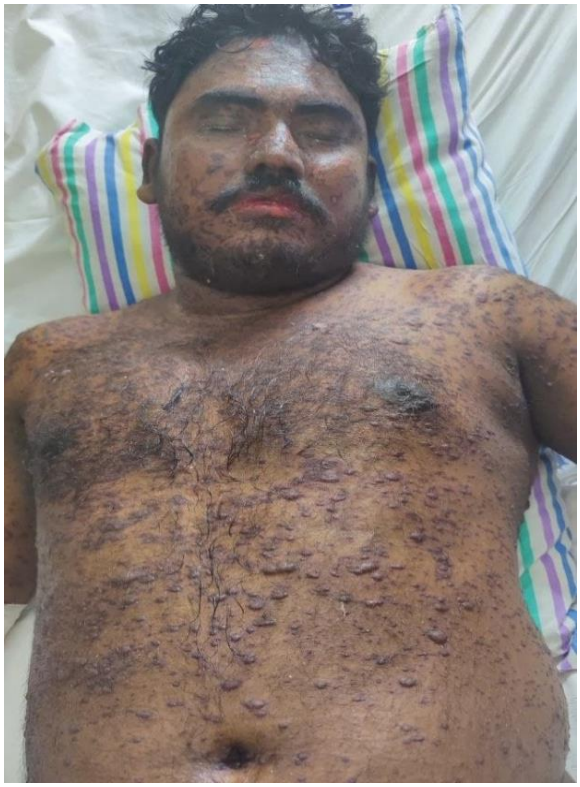


Figure 37 TEN to carbamazepine with vesicles and bullae with purpuric hue and mucosal erosions

Figure 38 with TEN with mucosal erosions and skin sloughing

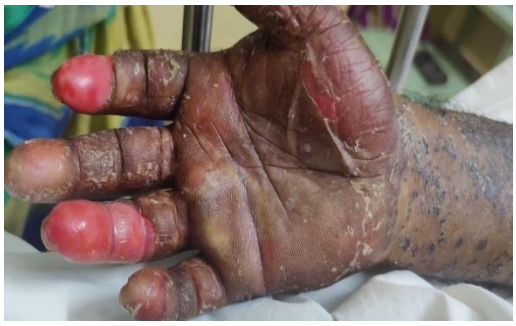


Figure 40 39 Involvement of palms in the same patient as in figure 37

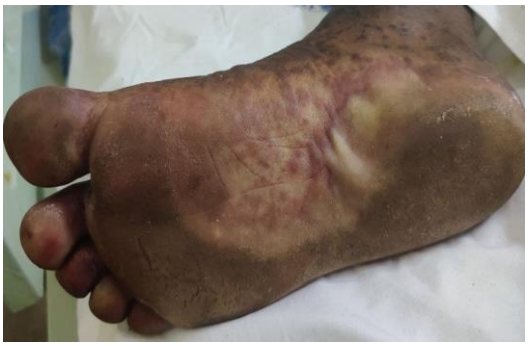


Figure 39 Involvement of soles in SJS/ TEN

Discussion

Cutaneous adverse drug reactions are among one of the most frequent ADRs (83). Drug induced MPE has been reported to represent the majority of CADR as seen in our study which resolves without any sequelae (83,84).

Drug reaction eosinophilia and systemic symptoms is a multisystem disorder which frequently presents with skin rash, fever, lymphadenopathy, eosinophilia and visceral involvement. Peripheral blood eosinophilia suggests a Th-2 type immune response (72). Serum TARC is a Th-2 chemokine that is elevated in DRESS. There are few studies that have demonstrated elevated TARC levels in DRESS as a diagnostic marker which correlates to blood eosinophil count and prognostic marker of severity of systemic inflammation (5,23,77,78). One Indian study has compared serum TARC levels in MPE with DRESS (RegiSCAR $\geq$ 2) and found higher TARC levels in patients with "possible", '"probable" and "definite" DRESS as compared to "no" DRESS (23). However, there are no studies to date to our knowledge that have compared DRESS with viral exanthem, which is a close differential and a diagnostic dilemma. We aimed to study the clinical profile of patients with CADR, to measure serum TARC in various CADRs, and compare TARC levels among DRESS, drug induced MPE and viral exanthem.

1. Demographic profile:

Demographic comparison of our study with various studies on CADR in India is shown in table 8 and demographical details of Indian and international studies on DRESS are in table 9. In our study, the number of SJS/TEN was much lower as compared to other studies. The possible explanation could be the exclusion of patients with malignancies

which is significantly associated with SJS/TEN(85). We had a low number of cases with AGEP which is consistent with all the studies quoted below.

i. **Age:** The maximum number of patients with CADR in our study were in the age group 18-40 years, similar to multiple Indian studies on CADR (83,84,86,87). The systematic review by Patel et al. (13) on Indian CADR which included all the above quoted studies suggests that high incidence in this young age group is probably because of higher percentage of Indian population in this age group. Patients with DRESS in our study had an average age of 41.38 years that was comparable to the previously published data on DRESS (23,27,34,36,38,88). There was no difference in age presentations of patients with MPE and SCAR in our study, contrary to previous data published where they found an earlier age of onset in DRESS as compared to drug-induced MPE (38,89).

ii. **Gender:** There was a greater number of males with DRESS in our study similar to previous publications (27,28,35). In our study, women with DRESS had a younger age of onset as compared to men (mean of 31.5 versus 49.8) consistent with studies published earlier (27,90). Maoz et al. suggested the plausible autoimmune stimulating effect of oestrogen in female sex leading to earlier onset in women than men and perhaps indicating female gender as a risk factor (13,90).

Table 8 Indian studies on cutaneous adverse reactions

Parameter	Sharma V K et al. (84)	Sushma et al. (91)	Pudukaran et al. (92)	Sasidharana pillai et al. (93)	Present study
Country	India	India	India	India	India
Study period	1991-1996	1994-2002	2001-2003	2011-2012	2019-2021
Study duration	6 years	9 years	2 years	1 year	3 years
Study design	Prospective study	Retrospective study	Prospective study	Prospective study	Prospective study
Place of study	North India	South India	South India	South India	India
Age	34.5	21-40	34.06+/- 30.12	46-60	41.16 ± 14.23
M: F	1.5:1	1.08:1	0.87:1	1.47:1	1: 1.03
CADR[*]	SJS/TEN - 57 [†]MPE- 173	MPE 144 SJS 75 TEN 21 DRESS 13 Erythroderma 14	SJS/TEN-17 AGEP-2 MPE-11	SJS/TEN 17 DRESS-7 AGEP-1 MPE-8	SJS/TEN-5 DRESS- 13 MPE- 23 AGEP- 3 VIRAL-11

[*] CADR: Cutaneous Adverse Drug Reaction

[†] MPE: Maculopapular eruption

2. Clinical features:

Clinical features that are seen in DRESS, as reported in various studies are shown in table 9. All studies quoted in table 9 classified RegiSCAR ≥ 4 as DRESS except for Choudhary et al.(23) who considered DRESS as RegiSCAR ≥ 2 and Avancini et al. (35) (DRESS as RegiSCAR >5). Original RegiSCAR validation scoring classifies DRESS as 2-3 = possible, 4- 5= probable, >5 = definite (30). Our study had similar findings to the landmark study by Kardaun et al. and other studies published subsequently with regards to presence of fever, lymphadenopathy, abnormal liver, and renal functions in DRESS syndrome (23,27,33,35).

i. **Fever:** Fever of more than 100.4˚C was the most commonly present variable in the RegiSCAR validation score for DRESS in our study. Most studies including our study reported fever in more than 90% of patients with DRESS (23,27,34–36).

ii. **Mucocutaneous features**: The commonest rash morphology in DRESS was a maculopapular (exanthematous) rash as reported previously (23,94,95). Facial oedema was significantly more in DRESS than in MPE as described by Bocquet et al. in 1996 and subsequently verified by many other studies (23,38,48,96). Infiltrated appearance, purpuric lesions were seen more frequently in DRESS than in MPE, and pustules were seen only in DRESS however the findings were not statically significant, similar to Momen et al. (38). Mucosal lesions were seen in 69.3% in DRESS in our study similar to Kardaun et al. where 56% of patients had mild mucosal lesions (27). All 3 patients with AGEP in our study had non-follicular sterile pustules with background erythema and edema as classically

described in AGEP by Roujeau et al.(97). All patients with SJS/TEN had atypical target lesions, purpuric lesions, erosions and, mucosal involvement as classically described (98). The most common mucosal involvement in SJS/TEN was oral erosions followed by ocular and genital involvement consistent with the initial description by Revuz et al(99) who had a case series of 87 patients with SJS/TEN.

iii. **Lymphadenopathy:** Lymphadenopathy was significantly more in DRESS as compared to MPE and this finding was consistent, published studies on DRESS from India and west.(23,27,33–36).

iv. **Atypical lymphocytes**: The percentage of patients with DRESS who had atypical lymphocytes was 25% which was similar to a previously published study on DRESS by Sasidharanpillai et al. (19.2%) in the Indian population (36).

v. **Hepatic involvement:** This was the most frequent systemic involvement in DRESS across all studies quoted in table 3.2 (23,27,33–36), with an elevation of alanine transaminase (AST or SGPT) being the most frequent finding (26).

vi. **Renal involvement:** This was the second most common systemic involvement seen in our patients with DRESS. This was similar to other studies quoted in table 3.2. Elderly age group, pre-existing renal disease and, allopurinol and well-known risk factors for renal injury in CADR, especially SJS/TEN (26,98,100)

vii. **Pulmonary involvement:** This was less frequently encountered in our patients(15%) with DRESS which was similar to other Indian studies (12%, 11.5%) (23,36). Kardaun et al. reported 32% of DRESS patients having lung involvement. A systematic review on pulmonary involvement in DRESS

published in 2019 stated lungs were less frequently involved in DRESS, nonetheless pulmonary involvement was associated with a worse clinical course and increased mortality (43). The most common involvement being pneumonitis followed by acute respiratory distress syndrome (ARDS). Minocycline and Abacavir are traditionally linked with DRESS associated pulmonary involvement (43). These drugs were not implicated in our set of patients.

Table 9 Comparison between demographic and clinical features of DRESS in various studies

Parameter	Kardaun et al. (27)	Hiransuthiku et al. (33)	Walsh S et al. (34)	Avancini et al. (35)	Sasidharanpillai et al. (36)	Choudhary et al. (23)	Present study
Country	Europe	Thailand	Europe	Latin America	India	India	India
Study period	2003-'09	2004-'14	2005-'11	2008-12	2010-2013	2021	2019-2021
Study design	Prospective	Retrospective	Prospective	Retrospective	Prospective	Prospective	Prospective
Subjects with DRESS	n= 117	n = 52	= 27	n= 27	n= 26	n= 25	n= 13
RegiSCAR score	≥ 4	> 5	≥ 4	> 5	≥ 4	≥ 2	≥ 4
Age in years	48 ± 32	33 ± 25	40	36 ± 16.4	37.7	43.16 ± 12.8	41.38 ± 15.91
M:F ratio	1: 0.80	1: 2.47	1: 0.58	1: 0.58	1: 0.8	1: 1.5	1:

							0.71
Drugs implicated	Carbamazepine, Allopurinol	Phenytoin	Phenytoin, Carbamazepine	Phenytoin	Phenytoin	Sulfasalazine	Phenytoin, Dapsone
Latent period(days)	17-31	9- 27	10-49	3-180	7-90	10-44 days	5-55 days
Fever	90%	78.8%	100%	96.2%	96.2%	100%	92%
Facial edema	76%	7.7%	85.1%	62.9%	96.2%	88%	69.2%
Mucosal lesions	56%	-	22%	-	73.07%	100%	69.3%
Lymphadenopathy	54%	50%	88%	62.9%	50%	76%	61.5%
Abnormal LFT	75%	94.2%	74%	85.1%	80.8%	80%	69.3%
Abnormal RFT	37%	15.4%	7%	33.3%	7.69%	32%	23%
Pulmonary involvement	32%	3.8%	-	3.7%	11.5%	12%	15.3%
Peripheral eosinophilia	95%	60%	92.5%	96.2%	34.6%	56%	84.6%
Atypical lymphocytes	68%	26.9%		62.9%	19.2%	-	25%
Thrombocytosis	19%	-	-	-	-	-	0

3. Drug details:

a. **Latent period:** The latent period in the DRESS group was much longer than MPE (p-value <0.0001) in our patient population which is consistent with both Indian and western studies published comparing the same (23,38,101). All 3 of our patients with AGEP in our study had an onset of rash in 1 day of intake of drug which was similar to the median duration of onset, published by Sidoroff et al. in a multinational case-control study (EuroSCAR) (15). Soria et al. classified DRESS into rapid onset group (≤15 days) and delayed onset (>15 days) (28). In our study, 15% (2/13) patients with DRESS had a rapid onset following exposure to the culprit drug. All patients with DRESS cases caused by antiepileptics (n=4) and Sulfasalazine (n=2) had a delayed onset similar to findings by Soria et al. (28).

b. **Drug Causality**: The Naranjo Adverse Drug Reaction Probability scale was used to assess the causality of CADRs and ALDEN was used specifically for SJS/TEN. Major causative drugs identified were antibiotics (34%) followed by antiepileptics (20.45%) which was similar to the systemic review published on Indian CADR with 45.46% and 14.57% (13) and Manriquez et al. of 50%, 19% respectively in each drug group. The most common among the antibiotic group was Betalactams consistent with the peer-reviewed article by Mockenhaupt (1). Antibiotics were implicated more commonly in MPE in contrast to anticonvulsants in SCARs (p-value 0.019) similar to previous studies (13,86,102). Anticonvulsants are the most common culprit drug in most of the

reported studies except in Choudhary et al. (23) where they found sulfasalazine as the most common implicated drug.

Features of drugs implicated in CADR are as follows: -

- **Dapsone:** There were 3 patients who had CADR to dapsone, 2 DRESS, and 1 had MPE. Out of the 3 of them, 2patients tested had HLA B*13:01 polymorphism. This polymorphism is reported to be present in 1-12% of the Indian population hence a genetic pre-screening prior to the institution of the drug could reduce the morbidity and mortality associated with DRESS to dapsone(103). One patient with DRESS having Hansen's disease had characteristic sparing of the rash over the leprous skin patches. Hyperbilirubinemia, transaminitis, and the lack of peripheral eosinophilia were seen in our patients as described in the literature (32).
- **Iodinated intravenous contrast media**: We had 5 cases of drug-induced MPE to iodinated contrast with RegiSCAR scores of 0-2. Out of these 5 patients, 3 patients had received prior contrast with no reactions. Three patients received Ioxehol and 2 received Iodixanol. History of atopy is a frequently reported risk factor(104) that was seen in only one patient. 60% of patients with MPE radiocontrast media had a cardiac disease which is a risk factor as reported previously (105).
- **Carbamazepine/oxcarbazepine**: Out of the 2 patients with SCAR to oxcarbazepine (1 DRESS, 1 AGEP) the patient with AGEP had a past history of SJS/TEN to carbamazepine. Both these patients were negative for HLAB15 consistent with the suggestion that screening HLAB15 only, prior

to administration of antiepileptics may not be useful in the Indian population (106,107).

- **Proton pump inhibitors** (PPIs): We had one patient with DRESS to esomeprazole and pantoprazole each. There are 21 published case reports of DRESS to PPIs (46,108). Both of our patients had a fever, rash eosinophilia, and loose stools. Stool examination and culture were negative for infective causes. The presence of gastrointestinal symptoms is similar to previously published literature (46). The patient with DRESS to esomeprazole was also on cotrimoxazole which was given for 70 days prior to eruption and discontinued one week before hospital admission for DRESS, hence the possibility of DRESS to cotrimoxazole could not be excluded. DRESS to PPIs could be confirmed by patch testing which was reported positive in multiple reports however, caution against a flare of DRESS should be kept in mind (108).
- **Sulfasalazine**: In patients with DRESS to sulfasalazine, the symptoms of DRESS persisted for a long duration following discontinuation of the drug(32). This was seen in our patient who presented to us with 7 months of DRESS related symptoms. Both patients (n=2) with DRESS to sulfasalazine had facial edema, purpuric lesions, and delayed onset of DRESS. Sulfasalazine induced DRESS is also known as ‘3 weeks sulfasalazine syndrome’ with latent period ranging from 1 week to 4 months(32,109). Sulfasalazine being a sulphonamide has metabolites having a half-life of up

to 100 hours resulting to prolonged exposure of the drug in the body of the patient even after discontinuation of the drug (110).

4. **Markers of inflammation**:

   a. **Glasgow prognostic scoring:** This scoring involves serum albumin and CRP levels in the blood. In our study the mean score for DRESS was 1.4 ± 0.5 and that for drug-induced MPE was 0.9 ± 0.7 which was significantly higher in patients with DRESS as compared to MPE as demonstrated in a previous study by Komatsu-Fujii et al. where they had a GPS score for DRESS (n = 10) verses MPE (n=16) as 1.7 ± 0.4 v/s 0.4 ± 0.5 (111). We also had significantly higher values of GPS in DRESS as compared to viral exanthem (p-value <0.001). A score of 2 (maximum score) was exclusively seen in patients with DRESS (not in MPE or viral exanthem)

   b. **Systemic inflammatory Response scoring (SIRS):** Systemic inflammatory response score in our study in DRESS versus MPE was 2.2 ± 1.4 versus 1.1 ± 0.9 which was significant (p-value 0.03), similar to previous publication which compared SIRS score (involving WBC count, body temperature, pulse rate but not respiratory rate) where their scores were 2.2 ± 0.6 in DRESS versus 0.5 ± 0.8 in MPE with p-value 0.002 (77).

   c. **C-reactive protein (CRP):** We did not find any statistically significant difference between CRP values in DRESS, MPE and viral exanthem. A 2017 published study from Japan by Komatsu Fujii et al. compared CRP values in

MPE(n=14) and DRESS (n=6) had similar findings as ours with no statistically significant difference in CRP values in MPE and DRESS (78). Choudhary et al. compared highly sensitive CRP (hsCRP) in MPE and DRESS and found a statistically significant difference, however they considered DRESS as RegiSCAR ≥ 2 and below that as MPE while we considered DRESS as RegiSCAR ≥ 4 and below that as MPE (23). Another retrospective study from Switzerland by Hubner et al. compared CRP values in patients with DRESS with RegiSCAR ≥ 2 and found elevated levels similar to Choudhary et al., Hubner et al. also found elevated procalcitonin levels in DRESS patients even in the absence of infection (23,52).

d. Neutrophil-lymphocyte ratio (NLR): Neutrophil- lymphocyte ratio were higher in our patients with DRESS as compared to MPE and viral exanthem however the differences were not statistically significant as found by Komatsu-Fuji et al. who compared 10 patients with DRESS and 16 patients with MPE and found a statistically significant difference with a p-value of 0.001 (111).

5. Histopathology:

This was done on a case-to-case basis according to the judgment of the treating dermatologist to differentiate from a connective tissue disorder, viral exanthem, etc. Findings by Ortonne et al. suggested the presence of more than one tissue reaction pattern was significantly associated with DRESS as compared to MPE or non-drug exanthem on histopathology and this was seen in 3 out of 9 patients of DRESS in

our study who underwent a skin biopsy (39). Literature shows that histopathology on SJS/TEN and AGEP are well defined; the same is not true for DRESS which has varied/polymorphous histopathological findings including but not limited to spongiotic dermatitis, erythema multiforme, features of SJS, etc. (39). Momen et al. found basal cell squamatization, interface inflammation, and epidermal necrotic keratinocytes more frequently in DRESS as compared to MPE with significant p-values (38). We also had higher percentages of patients with DRESS than MPE with interface changes (55% v/s 33%; n= 5/7, n= 1/3), epidermal necrotic keratinocytes (77% v/s 33%; n=7/9, n=1/3) but equal percentages of basal cell squamatization. Spongiosis was seen in DRESS (66%, n=6/9) and not in MPE similar to findings by Walsh et al. who looked at 27 patients with DRESS and 59% of their patients had spongiosis (34). DRESS is traditionally known to have dermal eosinophils, however, there was no difference in dermal eosinophils in DRESS and MPE in our study, similar to previous studies (8,11). Walsh et al. found dermal eosinophils in only 37% of patients with DRESS indicating that dermal eosinophilia is probably not a useful indicator to differentiate between MPE and DRESS (34). Two patients of ours with SJS/TEN who underwent a skin biopsy had pan epidermal necrosis with sparse inflammation as classically reported in the literature (98). Marked dermal edema and necrotic keratinocytes was seen in all 3 patients with AGEP with 2 patients having subcorneal vesicopustules as described in the literature (112).

6. **Serum TARC levels**:

Serum TARC levels were measured in cases with CADR and viral exanthem. Serum TARC levels were elevated in DRESS as compared to MPE similar to previous

studies; however, the difference was not statistically significant as had been seen in the other studies (5,23,76–78). The mean TARC value in DRESS in our study was similar to another Indian study by Choudhary et al. (1080pg/ml, 1216 pg/ml respectively), though the TARC kits used were different. However, all Japanese studies have very high TARC levels. Choudhary et al.(23) had very low TARC levels in MPE as compared to all other studies including ours, probably because they considered MPE as CADR with RegiSCAR of <2 while we considered MPE as RegiSCAR <4. Komatsu-Fijii et al. classified DRESS/DIHS according to Japanese criteria and Ogawa et al. used both RegiSCAR and Japanese consensus criteria(5,76–78). Our study is the first, to the best of our knowledge, to compare TARC values of viral exanthem with CADR, TARC levels were lower in patients with viral exanthem as compared to DRESS and MPE however the difference was not statistically significant (p value 0.10). Our study also looked at serum TARC values of SJS/TEN (mean 1293 ± 986 pg/ml) which was similar to previous studies by Ogawa et al. (1543 ± 2770pg/ml) and Wang et al. (580 pg/ml) (76,113). We also looked at serum TARC values in patients with AGEP however we had only 3 patients which is a small number to draw any significant conclusions. The comparison among various studies with TARC in CADR is listed in table 3.4.

Serum TARC levels correlated with absolute eosinophil count in patients with DRESS and MPE (correlation coefficient 0.45) which is consistent with findings by Komatsu-Fujii et al. (78).

Table 10 Comparing studies on TARC values in CADRs

Various studies	Year published	Country	Kit used	Numbers of CADRs recruited	TARC (pg/ml)			
					DRESS	MPE	SJS/TEN	AGEP
Komatsu-Fujii T et al. (78)	2017	Japan	‡CLEIA (Shionogi, Japan)	DRESS (6) SJS/TEN (5) MPE (14)	31713.8 ± 28310.7	5822.5 ± 9990.4	4702 ± 3582.1	-
Komatsu-Fujii T et al. (77)	2018	Japan	CLEIA (Shionogi Japan)	12- DRESS 18- MPE	32156 ± 22566	2033± 4548	-	-
Ogawa et al. (2014) (76)	2014	Japan	§ ELISA (R&D Systems U.S.A.)	30 - DRESS 15- SJS/TEN 17- MPE	**21023 ± 17040 ††7449 ± 12440	2142±3056	1543 ± 2770	-
Ogawa et al. (5)	2013	Japan	ELISA (R&D Systems U.S.A.)	8 -DRESS 7 - SJS/TEN 14- MPE	31259 ± 6374	2193± 1203	2198 ± 1203	-
Quaglino et al. (6)	2007	Italy	ELISA (R&D Systems, U.S.A.)	7- SJS/TEN	-	-	580	-
Choudhary et al. (23)	2021	India	ELISA (Ray Biotech, U.S.A.)	25- DRESS 25- MPE	1216.97 ± 737.10	160.59 ± 124.07	-	-
Wang et al. (113)	2014	China	ELISA (Ray Biotech, U.S.A.)	19- SJS/TEN 21- MPE	-	4440.4	2290.5	-
Present study		India, Bhutan	ELISA (Abcam, U.K.)	SJS/TEN-5 DRESS- 12 MPE- 24 AGEP- 3 VIRAL-11	1080.333 ± 1227.585	997 ± 809.3685	1293 ± 986.73	1566 ± 456.45

‡‡ CLEIA: - chemiluminescent enzyme immunoassay
§ ELISA- enzyme-linked immunosorbent assay
** With HHV-6 reactivation
†† Without HHV-6 reactivation

Conclusion

1. In this study, there were 23 patients with drug-induced MPE, 13 with DRESS, 5 with SJS/TEN and 3 with AGEP. Nine patients with viral exanthem served as controls.
2. The mean age group among patients CADR was 41.16± 14.23 years while most patients belonged to the age group of 18-40 years.
3. Gender distribution was similar in patients with DRESS with females having a younger age of onset (31.5 years) as compared to males (49.8 years).
4. The most common drugs implicated for MPE were antibiotics (9/23, 39%) and that for DRESS were antiepileptics (3/13, 23%).
5. The mean latent period in DRESS was 24.92 ±13.85 days. The mean latent period in drug-induced MPE was 12.3 ± 11.06. The latent period in DRESS was significantly longer than drug-induced MPE with a p-value <0.0001.
6. The two patients with DRESS to proton pump inhibitors (n=2) had gastrointestinal involvement.
7. Facial oedema was significantly associated with DRESS as compared to MPE with a p-value <0.001.
8. Lymphadenopathy was significantly associated with DRESS as compared to MPE with a p-value <0.0001.
9. Fever was seen in almost all patients with DRESS (12/13) as compared to only 22% of patients with MPE (5/23) with p-value of < 0.0001.
10. The most common systemic involvement among patients with DRESS was involvement of liver (69.3%).

11. Glasgow prognostic score in DRESS was significantly higher in DRESS (1.4 ± 0.5) v/s MPE (0.9 ± 0.7) and viral exanthem (0.6 ± 0.8) with p-value of <0.001.
12. Systemic Inflammatory response score of ≥ 2 was significantly more in patients with DRESS than MPE with a p-value of 0.03.
13. The median TARC value in DRESS (1080pg/ml, IQR 300.36-1860.30) was higher than MPE (996.5 pg/ml, IQR 129.5- 1737) and viral exanthem (792pg/ml, IQR 5- 792) but was not statistically significant.
14. There was a fair correlation between peripheral eosinophilia and TARC values in patients with MPE and DRESS with a correlation coefficient of 0.45 and p-value of 0.004.

Limitations

1. We had less number of patients in our study. Studies with a greater number of patients will be required to draw meaningful conclusions on serum TARC levels in SCARs especially in DRESS.
2. Serum TARC values have been demonstrated to be significantly higher in DRESS with viral reactivation (76). Markers for viral reactivation were not measured in our study.

Recommendations

Multicentric studies with larger sample size should be done to validate the utility of serum TARC levels to differentiate drug induced MPE and DRESS and to determine a cut-off value to differentiate DRESS from MPE.

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Annexures

Annexure 1 – Institutional review board approval (IRB)

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

January 21, 2020.

Dr. Lydia Sharon K,
PG Registrar,
Department of Dermatology - 2,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant New Proposal:**
Estimation of serum thymus and activation regulated chemokine (TARC) in drug induced eruptions and severe cutaneous adverse reactions (SCAR's).
Lydia Sharon K, PG registrar, DVL, Dr. Dincy Peter, DVL-2, , Dr. Leni George, Dr. Mahabal Gauri Dinesh, Dr. Priya Sara Kuryan, Dr. Susanne Pulimood, DVL-2, Dr. B. Antonisamy, Biostatistics, Dr. Pamela Christudoss, Clinical Biochemistry, Mrs. S Vanitha, Clinical Biochemistry.

Ref: IRB Min. No. 12355 [OBSERVE] dated 05.11.2019.

Dear Dr. Lydia Sharon K,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Ref: IRB Min. No. 12355 [OBSERVE] dated 05.11.2019

Dear Dr. Lydia Sharon K.

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Estimation of serum thymus and activation regulated chemokine (TARC) in drug induced eruptions and severe cutaneous adverse reactions (SCAR's)" on November 05th 2019.

The Committee reviewed the following documents:

1. IRB application format
2. Consent form and information sheet (English, Tamil, hindi, Bengali, Telugu, Malayalam)
3. Cvs of Drs. Susanne Alexander, Pamela.
4. No. of documents 1- 3

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on November 05th 2019 in the New IRB Room, Christian Medical College, Vellore 632 004.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. B. J. Prashantham	MA (Counseling Psychology), MA(Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Ms. Grace Rebekha	M.Sc. (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. John Jude Prakash	MBBS, MD	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Rekha Pai	BSc, MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Premila Abraham	M.Sc, Ph.D	Professor, Department of Biochemistry, CMC,	Internal Clinician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL	Sr. Legal Officer, Vellore	External Legal Expert
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Joe Varghese	MBBS, MD Biochemistry	Professor, Department of Biochemistry	Internal Clinician
Dr. Jayaprakash Muliyil	MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prabhadham, M.A., M.A., Dr Min (Clinical)
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Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Sathish Kumar	MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MD, DNB, PhD	Professor, Endocrinology, CMC, Vellore	Internal, Clinician
Mrs. Sophia V	M.Sc Nursing	Addl. Deputy Dean CMC, Vellore	Internal, Nurse
Mrs. Nirmala Margaret	MSc Nursing	Addl. Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "Estimation of serum thymus and activation regulated chemokine (TARC) in drug induced exanthem and severe cutaneous adverse reactions (SCAR's)." on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

The Institutional Ethics Committee wants to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Policy.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 2,47,340/- INR (Rupees,Two Lakh Forty Seven Thousand Three Hundred and Forty only) will Be granted for 19 months.

Yours sincerely,

Dr Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min. No. 12355 [OBSERVE] dated 05.11.2019

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

ANNEXURE- II- patient information sheet

Title of Research Project: A study of serum TARC in drug induced reactions

CHRISTIAN MEDICAL COLLEGE, VELLORE - DEPARTMENT OF DERMATOLOGY
INFORMATION SHEET

Explanation of the purpose of research?
Drug induced rashes are very common and usually occur within a few weeks of starting new medications. While majority of these are not severe and resolve in a few weeks with supportive management, a small proportion can evolve into life threatening disease. Identifying the patients who are at risk of progressing into a severe disease early would help the doctor to manage the patient aggressively with systemic and topical treatment in an in-patient set up, thus potentially reducing the death rate. TARC is a molecule which was identified as a mediator responsible for the skin manifestations in drug induced rashes. This study will help us to show the relationship between TARC and the different types of drug rashes. This may help us to recommend TARC as a predictor of severe drug induced rashes in patients who present early in the course of the illness.

What will you have to do if you participate in his study?
If you agree to participate in this study once you have been diagnosed to have drug rash, you will be requested to allow a doctor to take a detailed history and examination. You are also required to give two samples of 3 ml blood sample for the measurement of serum TARC

Can you withdraw from this study after it starts?
Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in anyway.

What will happen if you develop any study related injury?
We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study these will be treated at no cost to you.

Will you have to pay for the blood test?
The test serum TARC levels will be done for you free of cost.

Will your personal details be kept confidential?
The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study without your additional permission should you decide to participate in this study.

If you have any query, contact Dr. Lydia at (0416 3072054/8360628774) or email to lydia.sharon.kati@gmail.com

ANNEXURE -III – Informed consent form

Informed Consent form to participate in a research study

Study Title: A study to measure serum TARC in drug induced rash

Study Number: _____

Subject's Initials: _____

Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

(vi) I give consent to store my samples for future analysis [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:
Or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness:
_____

Date: _____/_____/_____

Name & Address of the Witness: _____

ANNEXURE -IV – Data collection proforma

A study of serum TARC in drug induced rash

1. Date: 2. Serial no:

3. Name: 4. Hospital no:

5. Age:

6. Sex: M /F

7. Occupation:

8. Address:

9. State:

10. Contact number:

11. Presenting complaints:

12. Day since the onset of the first skin lesion -

13. Duration of cutaneous symptoms -

	Symptom	Yes	No	Duration
a	Itching			
b	Burning sensation			
c	Conjunctival lesions			
d	Oral mucosal lesions			
e	Genital mucosal lesions			
f	Others			

14. Duration of Systemic complaints:

	Symptoms	Yes	No	Duration
a	Fever			
b	Cough			
c	Breathlessness			
d	Jaundice			
e	Arthralgia			
f	Swelling of face /hands and feet			

15. Drug/drugs implicated-
16. Indication for the initiation of these new drug/drugs -
17. Type of the implicated drug – anticonvulsants / antibiotics / analgesics / antiretroviral / antituberculous

Serial number	Medication	Initiation date	Date of stoppage	Duration	Half life

18. Concurrent drugs:

Serial number	Drug	Duration	Other comments

19. Previous history of drug reaction: yes/no
20. If yes, then details:

Serial number	Drug name	Type of reaction	Date of previous reaction

21. Drug timeline -

Drug	-5	-4	-3	-2	-1	Day 0	+1	+2	+3
1.									
2.									
3.									
4.									

22. Is the patient on oral steroids? Yes / No
23. If yes, duration:

24. Indication:

25. Other co-morbidities-

26. Personal history:

Alcohol, if yes: duration_____ (in years) and amount_____ (in ml)

Clinical Features:

27. Fever:

28. Heart rate:

29. Respiratory rate:

30. Blood pressure:

31. Lymphadenopathy:

32. Respiratory system:

33. Gastrointestinal system:

34. Type of lesion: Blanching erythema / macular / papular / maculopapular / purpuric / erythema multiforme-like (targetoid) / vesicles / pustules / bullae / erosions

35. Body surface area:

36. Scaling : Yes / No

37. Palms and soles : yes / no

38. If yes, describe:

39. Face involvement : yes / no

40. If yes, describe

41. Mucosal involvement: yes / no

42. If yes, describe:

43. Eyes: yes / no

44. Oral cavity yes/no

45. Genitalia yes/no

46. Nail changes: yes / no

47. If yes, describe

48. Hair and scalp : yes / no

49. If yes, describe:

50. Others:

s.no	Investigations	Day no. _
51.	Hemoglobin	
52.	Platelets	
53.	Total counts	
54.	Neutrophil count	
55.	Lymphocyte count	
56.	Eosinophil count	
57.	Serum albumin	
58.	Liver function test	
59.	Urine for eosinophils	
60.	Serum IgE	
61.	Serum C-reactive protein	
62.	Serum creatinine	
63.	Serum urea	
64.	Serum bicarbonate	
65.	Chest X ray findings	
66.	HIV	
67.	Serum TARC x 2	

68. RegiSCAR score:
69. GPS score:
70. SIRS score:
71. ALDEN: (only for SJS/TEN)
72. SCORTEN: (only for SJS/TEN)
73. Histopathology findings with date
74. EuroSCAR score for AGEP
75. Naranjo’s score

ANNEXURE -V – NARANJO'S algorithm

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

ANNEXURE -VI – ALDEN SCORING

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	−3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely −1	>56 Days	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present	
	Excluded −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar[c] drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative −2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case–control studies[d]	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case–control studies[d]	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[e]	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score	−1
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	
Final score −12 to 10			

ANNEXURE VII – DRESS RegiSCAR INCLUSION CRITERIA

Hospitalization

Reaction suspected to be drug related

Acute skin rash*

Fever above 38°C *

Enlarged lymph nodes at at least two sites*

Involvement of at least one internal organ*

Blood count abnormalities

- Lymphocytes above or below the laboratory limits*
- Eosinophils above the laboratory limits (in percentage or absolute count)*
- Platelets below the laboratory limits*

**Three or more required*

ANNEXURE -VIII – DRESS VALIDATION SCORE RegiSCAR

RegiSCAR scoring for DRESS				
Score	-1	0	1	2
Fever≥ 38.5^{O} C	No / U	Yes		
Enlarged lymph nodes		No/U	Yes	
Eosinophilia		No / U	>0.7x10^{9}L	>1.5x10^{9}L
Eosinophils if leukocytes <4.0 x 10^{9}/L			10%-19.9%	>20%
Atypical lymphocytes		No / U	Yes	
Skin involvement		No / U	>50%	
Skin rash extent (% body surface area)				
Skin rash suggesting DRESS	No	U	Yes	
Biopsy suggesting DRESS	No	No / U		
Organ involvement (2 or more involved score: 2)				
Liver		No / U	Yes	
Kidney		No / U	Yes	
Muscle/heart		No / U	yes	
Pancreas		No / U	Yes	
Other organs		No / U	Yes	
Resolution ≥ 15 days	No/U	Yes		
Evaluation of other potential causes:			Yes	

Antinuclear antibody, Blood culture Serology HAV / HBV / HCV Chlamydi Mycoplasma If none positive and ≥ 3 of above negati				
TOTAL <2 excluded; 2-3 possible; 4-5 probable; >6 definite				

ANNEXURE IX - BOCQUET criteria for DRESS

Drug Rash with Eosinophilia and Systemic Symptoms: Proposed Criteria of Diagnosis*

Criterion
1. Cutaneous drug eruption
2. Hematologic abnormalities: Eosinophilia ≥1.5 10^9/L or presence of atypical lymphocytes
3. Systemic involvement: Adenopathies ≥2 cm in diameter or hepatitis (liver transaminases values ≥2 N) or interstitial nephritis or interstitial pneumonitis or carditis

*The proposed classification is based on 3 criteria. A person shall be said to have "DRESS" if 3 criteria are present.

ANNEXURE X – J-SCAR criteria for DRESS/DIHS

SCAR-J diagnostic criteria for DRESS/DIHS

1. Maculopapular rash developing > 3 weeks after starting therapy with a limited number of drugs

2. Persistent clinical findings after drug withdrawal

3. Fever (> 38°C)

4. Hepatic abnormalities (TGP > 100 U/L)

5. Leukocyte abnormalities (at least one present)
   a. Leukocytosis (> 11.000/mm3)
   b. Atypical lymphocytosis (>5%)
   c. Eosinophilia (>1.500/mm3)

6. HHV-6 reactivation

The diagnosis is confirmed by the presence of the seven criteria (typical DIHS) or of the first five criteria (atypical DIHS).
* This can be replaced by other organ involvement such as renal involvement.
+ Reactivation is detected from second to third week after symptoms onset, through IgG anti-HHV-6 titers elevation.

ANNEXURE -XI – DRESS VALIDATION- AGEP- EUROSCAR

Table 1: AGEP validation score of EuroSCAR study group

Variable	Score	Variable	Score
Morphology		Course	
Pustules		Mucosal involvement	
Typical*	+2	Yes	−2
Compatible**	+1	No	0
Insufficient***	0	Acute onset (<10d)	
Erythema		Yes	0
Typical	+2	No	-2
Compatible	+1	Resolution <15 days	
Insufficient	0	Yes	0
Distribution		No	−4
Typical	+2	Fever >38.75°C	
Compatible	+1	Yes	+1
Insufficient	0	No	0
Postpustular desquamation		PMNs >7000/mm^3	
Yes	+1	Yes	+1
No/insufficient	0	No	0
		Histology	
		Other diseases	−10
		Not representative/No histology	0
		Exocytosis of PMN	+1
		Subcorneal and/or intraepidermal nonspongiform or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustule (s) without papillary edema	+2
		Spongiform subcorneal and/or intraepidermal pustule (s) with papillary edema	+3

Interpretation: 0=no AGEP, 1-4=Possible AGEP, 5-7=Probable AGEP, and 8-12=Definite AGEP, *Typical: typical morphology, **Compatible: not typical, but not suggestive of other disease, and ***Insufficient: lesions cannot be judged, AGEP=Acute generalized exanthematous pustulosis, PMN=Polymorphonuclear neutrophils, NOS=Not otherwise specified

ANNEXURE -XII– Glasgow prognostic score

Uses serum albumin and C- reactive protein (CRP)

GPS score	0	1	2
Cut – off value	Alb>= 3.5mg/dl and CRP <=1.0gm/d	Alb< 3.5mg/dl or CRP >1.0gm/d	Alb< 3.5mg/dl and CRP >1.0gm

ANNEXURE XIII – SIRS SCORE

Uses Body temperature, pulse rate, respiratory rate, WBC counts

SIRS score	+1	+1	+1	+1
Cut off values	WBC counts > 12,000 Or <4000/uL	BT >38° C Or <36° C	PR > 90/mi	RR>20/min or PaCO2<32mmHg

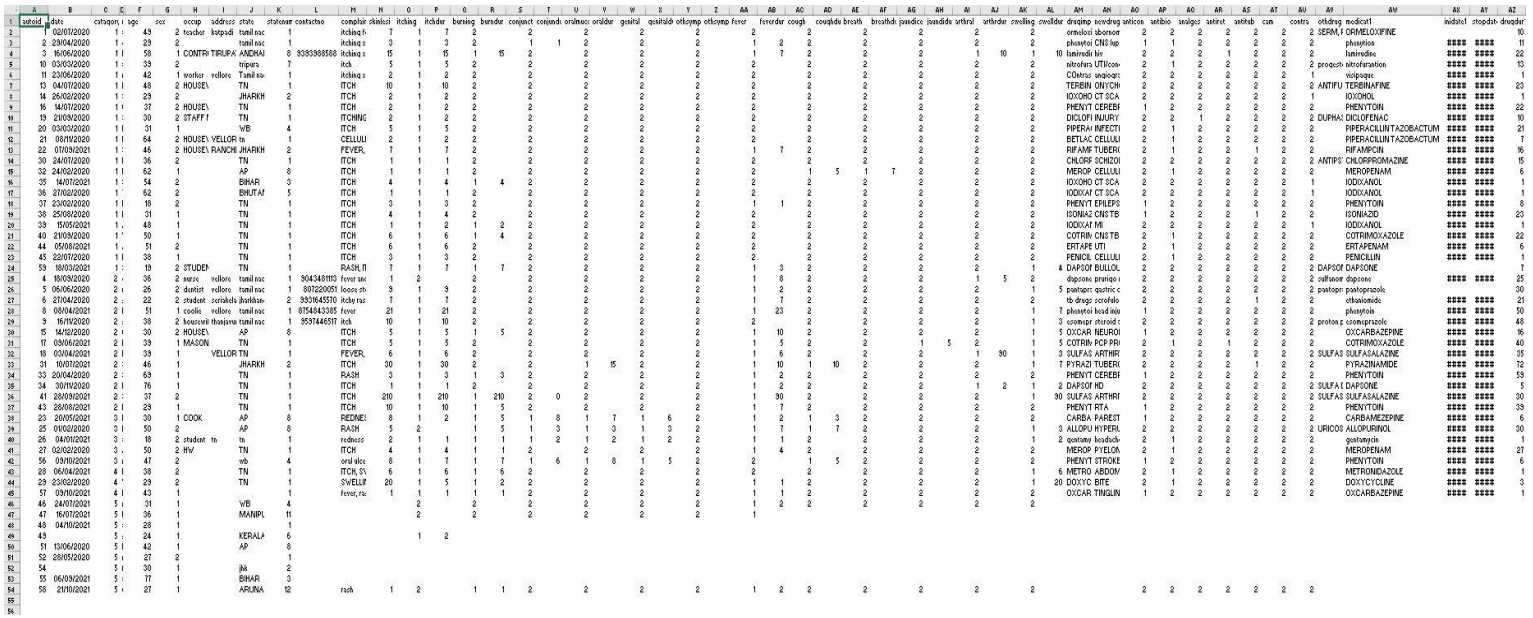
Score of >= 2 classified as SIRS

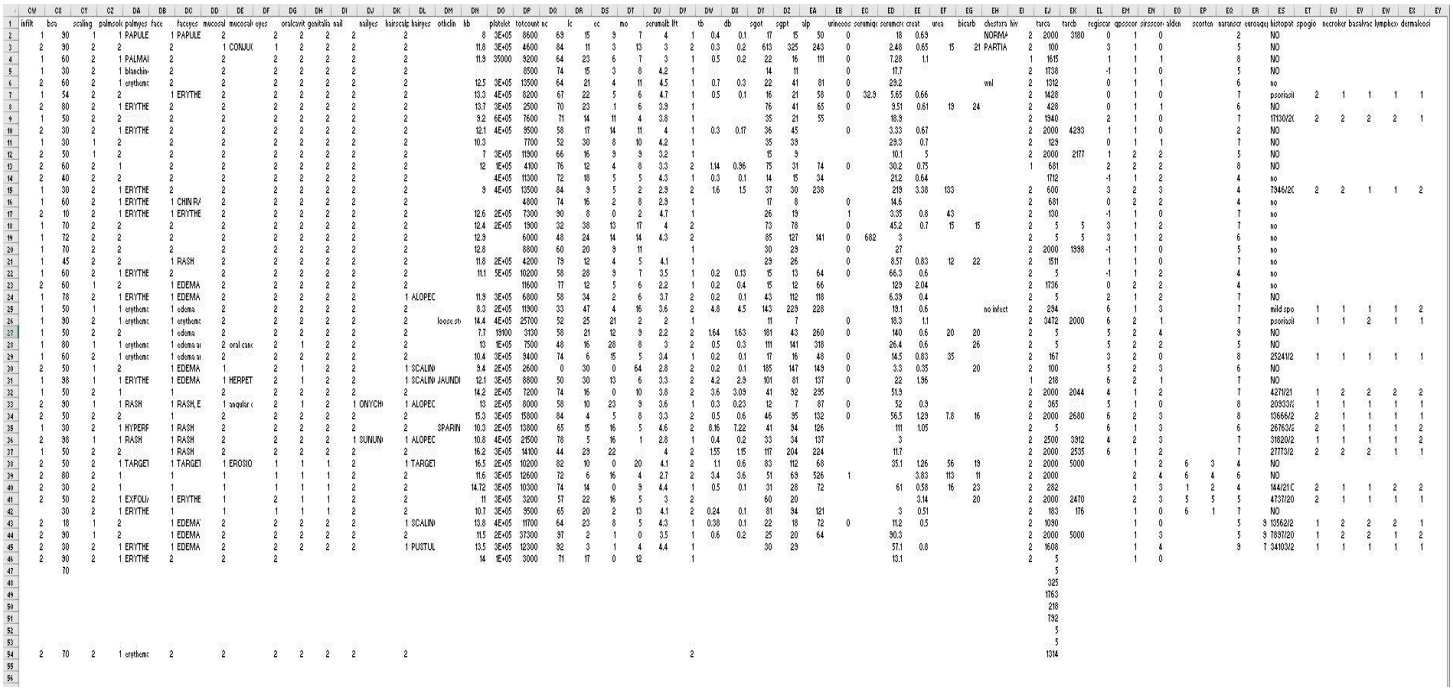
ANNEXURE XIV- SCORTEN

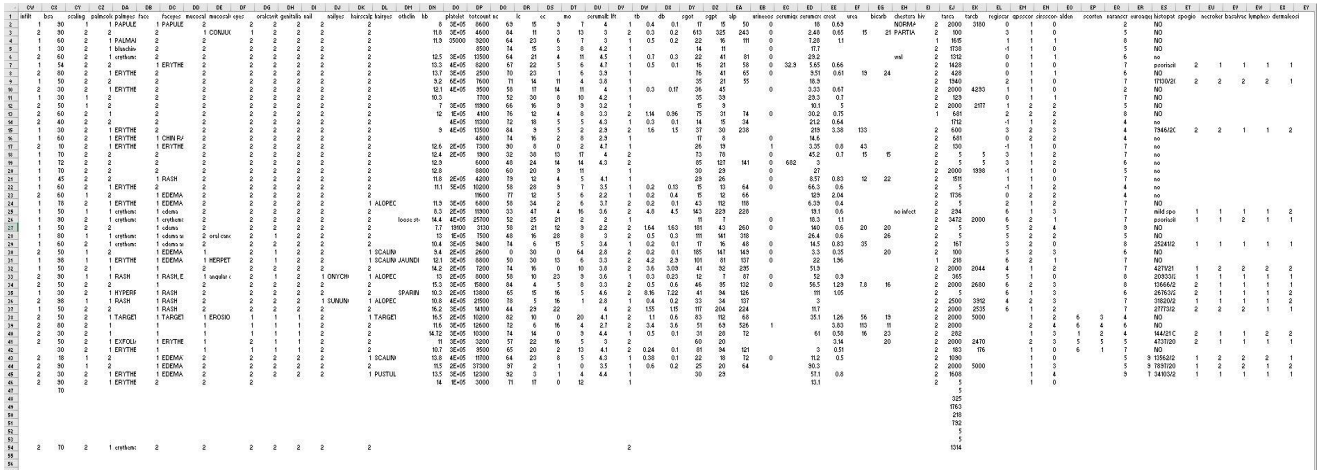
SCORTEN; TEN-specific severity-of-illness scoring system with respective mortality rates

SCORTEN variables	
Extent of epidermal detachment - >10%	
Age - ≥40 years	
Heart rate - ≥120/min	
Bicarbonate - <20 mmol/L	
Serum urea nitrogen - >28 mg/dl	
Glucose - >252 mg/dl	
History of malignancy	
SCORTEN value	**Predicted mortality rate (%)**
0-1	3.2
2	12.1
3	35.3
4	58.3
5 or more	>90

APPENDIX XIII- DATASHEET







autoid	Auto id number	<IDNUM>	
date	Date	<dd/mm/yyyy>	
catagory	cat	# 1=MPE, 2=DRESS, 3=SJS, 4=AGEP 5=VIRAL	
name	Name	_____	
hospno	Hospital number	_____	
age	Age	###	
sex	Sex	# 1=Male, 2=Female	
occup	Occupation	_____	
address	Address	_____	
state	State	_____	
STATENUM	STATE IN NUMBER	## 1=TN, 2=JHARKHAND, 3=BIHAR, 4=WB, 5=BHUTAN, 6=KERALA, 7=TRIPURA, 8=AP, 9=TELANGANA, 10=KARNATAKA, 11=MANIPUR,	
contactno	Contact number	##########	
complain	Presenting complaints	_____	
skinlesi	Day since the onset of the first skin lesion	###	
	DURATION OF CUTANEOUS SYMPTOMS		
ITCHING	Itching	# (1=Yes, 2=No)	
itchdur	Itching duration	### days	
burning	Burning sensation	# (1=Yes, 2=No)	
burndur	Burning sensation duration	### days	
conjunct	Conjunctival lesions	# (1=Yes, 2=No)	
conjundur	Conjunctival lesions duration	### days	
oralmuco	Oral mucosal lesions	# (1=Yes, 2=No)	
oraldur	Oral mucosal lesions duration	### days	
genital	Genital mucosal lesions	# (1=Yes, 2=No)	
genitaldur	Genital mucosal lesions duration	### days	
othsymp	Other cutaneous symptoms	# (1=Yes, 2=No)	
othsympdur	Other cutaneous symptoms duration	### days	
	DURATION OF SYSTEMIC COMPLAINTS		
fever	Fever	# (1=Yes, 2=No)	
feverdur	Fever duration	### days	
cough	Cough	# (1=Yes, 2=No)	
coughdur	Cough duration	### days	

breathdur	Breathlessness duration	### days
jaundice	Jaundice	# (1=Yes, 2=No)
jaundidur	Jaundice duration	### days
arthral	Arthralgia	# (1=Yes, 2=No)
arthrdur	Arthralgia duration	### days
swelling	Swelling of face hands and feet	# (1=Yes, 2=No)
swelldur	Swelling of face hands and feet duration	### days
drugimpli	Drug / drugs implicated	_____
newdrug	Indication for the initiation of these new drug	_____

Type of the implicated drug

anticon	Anticonvulsants	# (1=Yes, 2=No)
antibio	Antibiotics	# (1=Yes, 2=No)
analges	Analgesics	# (1=Yes, 2=No)
antiret	Antiretroviral	# (1=Yes, 2=No)
antitub	Antituberculous	# (1=Yes, 2=No)
cam	CAM	# (1=Yes, 2=No)

<

contra	Contrast	# (1=Yes, 2=No)
othdrug	Other drugs	_____
medicat1	Medication 1	_____
inidate1	Initiation date 1	<dd/mm/yyyy>
stopdate1	Date of stoppage 1	<dd/mm/yyyy>
drugdur1	Duration 1	#####
halflife1	Half life 1	#######.##
medicat2	Medication 2	_____
inidate2	Initiation date 2	<dd/mm/yyyy>
stopdate2	Date of stoppage 2	<dd/mm/yyyy>
drugdur2	Duration 2	#####
halflife2	Half life 2	#######.##

CONCURRENT DRUGS

condrug1	Drug (concurrent drug) 1	_____
cdrugdur	Drug duration (concurrent drug) 1	####
conothcom1	Other comments (concurrent drug) 1	_____

condrug2	Drug (concurrent drug) 2	_____
cdrugdur2	Drug duration (concurrent drug) 2	###
conothcom2	Other comments (concurrent drug) 2	_____
condrug3	Drug (concurrent drug) 3	_____
cdrugdur3	Drug duration (concurrent drug) 3	###
conothcom3	Other comments (concurrent drug) 3	_____
prevdrug	Previous history of drug reaction	# (1=Yes, 2=No)
prevdrug1	Previous drug name 1	_____
prevreac1	Previous drug type of reaction 1	_____
prevdate1	Date of previous reaction 1	<dd/mm/yyyy>
prevdrug2	Previous drug name 2	_____
prevreac2	Previous drug type of reaction 2	_____
prevdate2	Date of previous reaction 2	<dd/mm/yyyy>
oralster	Is the patient on oral steroids	# (1=Yes, 2=No)
steroidyes	If oral steroid yes, duration	### days

indicat	Indication	_____
comorbid	Other comorbidities	_____
alcohol	Alcohol	# (1=Yes, 2=No)
alcohdur	If alcohol yes, duration (years)	##
alcoholml	Alcohol amount	#### ml
	CLINICAL FEATURES	
fevert	Fever temp	###.##
hr	Heart rate	###
respirate	Respiratory rate	###
sysbp	Systolic bp	###
diasbp	Diastolic bp	###
lymphad	Lymphadenopathy	# (1=Yes, 2=No)
resisyst	Respiratory system	_____
gastrosyst	Gastrointestinal system	_____
blaneryt	Blanching erythema	# (1=Yes, 2=No)

Macular	Macular	#	(1=Yes, 2=No)
Papular	Papular	#	(1=Yes, 2=No)
maculpap	Maculopapular	#	(1=Yes, 2=No)
purpuric	Purpuric	#	(1=Yes, 2=No)
erytmult	Erythema multiforme-like	#	(1=Yes, 2=No)
Vesicles	Vesicles	#	(1=Yes, 2=No)
Pustules	Pustules	#	(1=Yes, 2=No)
Bullae	Bullae	#	(1=Yes, 2=No)
Erosions	Erosions	#	(1=Yes, 2=No)
exfoliat	Exfoliation	#	(1=Yes, 2=No)
infilt	Infiltration	#	(1=Yes, 2=No)
bsa	Body surface area	###	
scaling	Scaling	#	(1=Yes, 2=No)
palmsole	Palms and soles	#	(1=Yes, 2=No)
palmyes	If palms and soles yes, describe	_____	
face	Face involvement	#	(1=Yes, 2=No)
faceyes	If face involvement yes, describe	_____	
mucosal	Mucosal involvement	#	(1=Yes, 2=No)
mucosalyes	If mucosal involvement, describe	_____	
eyes	Eyes	#	(1=Yes, 2=No)
oralcavit	Oral cavity	#	(1=Yes, 2=No)
genitalia	Genitalia	#	(1=Yes, 2=No)
nail	Nail changes	#	(1=Yes, 2=No)
nailyes	If nail changes yes, describe	_____	
hairscalp	Hair and scalp	#	(1=Yes, 2=No)
hairyes	If hair and scalp yes, describe	_____	
othclin	Other clinical features	_____	
	INVESTIGATIONS		
hb	Hemoglobin	##.##	
platelet	Platelets	########	
totcount	Total counts	#####	
nc	Neutrophil count	###	
lc	Lymphocyte count	###	

ec	Eosinophil count	###
mo	Monocyte count	###
serumalb	Serum albumin	#.#
lft	Liver function test	# 1=Normal, 2=Abnormal
TB	TB	###.##
DB	DB	###.##
SGOT	SGOT	####.##
SGPT	SGPT	####.##
ALP	ALP	###.##
urineeos	Urine for eosinophils	###
serumige	Serum IgE	#####.##
serumcreac	Serum C-reactive	###.##
creat	Serum Creatinine	##.##
urea	Serum Urea	###.##
bicarb	Serum bicarbonate	###.##
chestxray	Chest X ray findings	
hiv	HIV	# 1=Positive, 2=Negative

tarc-a	Serum TARC x2 (a)	######.###
tarc-b	Serum TARC x2 (b)	######.###
regiscar	RegiSCAR score	##
gpsscore	GPS score	#
SIRSscore	SIRS score	#
alden	ALDEN (only for SJS/TEN)	##
scorten	SCORTEN (only for SJS/TEN)	##
naranscr	Naranjo score	##
euroagep	EuroSCAR AGEP	##
HISTOPATH	HISTO DONE OR NOT	
SPOGIO	SPONGIOSIS	# 1= YES, 2=NO
NECROKERA	NECROTIC KERATINOCYTES	# 1= YES, 2=NO
BASALVAC	BASAL CELL VACULATION	# 1= YES, 2=NO
LYMPHEXO	LYMPHOCYTE EXOCYTOSIS	# 1= YES, 2=NO
DERMALEOSI	DERMAL EOSINOPHILS	# 1= YES, 2=NO