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CUTANEOUS ADVERSE DRUG REACTIONS TO SYSTEMIC THERAPY: PATTERNS, CAUSALITY, AND PREVENTABILITY IN 138 PATIENTS FROM A TERTIARY HOSPITAL IN WESTERN INDIA

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Abstract:
Background: Cutaneous Adverse Drug Reactions is a frequent cause of dermatology consultations, the patient presentation can range from mild eruptions to severe life threatening reactions such as Stevens-Johnson syndrome(SJS) and Toxic Epidermal Necrolysis(TEN). Therefore, continous monitoring of CADRs is important to improve patient safety.
Objective: To evaluate the patterns, causality, severity and preventability of CADRs in patients presenting to a Tertiary care Hospital in Western India.
Methods: An observational cross-sectional study was conducted over 18months (July 2019 - January 2021) among 138 patients with mucocutaneous ADRs. Causality was assessed using WHO-UMC scale, severity with the Modified Hartwig and Siegel scale, and preventability with the Schumock and Thornton scale. Data were analysed descriptively.
Results: The most common CADR was Fixed Drug eruption(30.43%), followed by urticaria(28.26%). Antibiotics and NSAIDs were the most frequently implicated drug groups. Most reactions were of moderate severity(92.02%). Twenty cases were classified as definitely preventable, and one as probably preventable. One mortality was reported in a case of SJS-TEN secondary to Levetiracetam.

Conclusion: CADRs are common and often associated with irrational drug use, particularly antibiotics and NSAIDs. Most reactions were preventable or of moderate severity, highlighting the need for enhanced pharmacovigilance, patient education, and rational prescribing to reduce CADR-related morbidity and mortality.

Keywords: Cutaneous adverse drug reactions, fixed drug eruption, urticaria, Stevens-Johnson syndrome, pharmacovigilance, preventability.

Introduction: Cutaneous adverse drug reactions (CADRs) are “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts risk from future administration and warrants prevention, specific treatment, alteration of the dosage regimen, or withdrawal of the product”. They can vary from mild, as in maculopapular rashes, to

severe and life-threatening, as with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)[1]. The severity of cutaneous reactions varies from mild, maculopapular rashes to the more severe, life-threatening manifestations, like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). It is essential to document and publish emerging trends in drugs associated with CADR for various reasons [2]. It aids doctors in the early recognition and removal of offending agents, thereby preventing subsequent morbidity and mortality. Identifying high-risk drugs may help guide better prescribing practices [3]. Post-market, including published data, can uncover new or infrequent CADRs not discovered in clinical trials. Knowledge of high-risk drugs can determine medical therapy, which may be significant in cases of cross-reacting drugs or known allergies [3]. This information is critical for preventative approaches, education, and enhancement of the patient's overall care that ultimately decreases the consequences of drug-related hospitalisations and economic burden. Lastly, knowledge of the current trends in CADR-inducing drugs will assist in the management and timely resolution of medicolegal issues arising from Adverse drug reactions.[4]

Materials and Methods

The first patient was enrolled after obtaining permission from the Institutional Ethics Committee for Human Research - PG Research (IECHR-PGR) to conduct this study. All patients with suspected mucocutaneous adverse drug reactions (ADRs), of any age and sex, who presented to the outpatient department and inpatient wards of the Department of Dermatology, Venereology & Leprosy, as well as other inpatient wards and ICUs of Shri Sayaji General Hospital, affiliated with Medical College, Baroda, were included in the study. The type of study was observational cross-sectional.

The patients' signs and symptoms were assessed using the WHO-UMC causality assessment scale to determine the causal association between the drug(s) and the reaction. Patients with skin and/or mucosal manifestations of suspected ADRs due to systemic drug administration (enteral or parenteral) and categorised as '*Definite*', '*Probable*', or '*Possible*' based on WHO-UMC Causality Assessment Criteria, were included in the study [5]. Only patients who were willing to sign the consent form were enrolled. Patients classified as 'Unlikely' on the WHO-UMC Causality Assessment Criteria, those with suspected cutaneous ADRs due to topically administered drugs, were excluded from the study. Patients with Acneform eruptions due to oral or intravenous steroids were also excluded due to the benign nature of the skin lesions.

A detailed medical history was recorded, and a cutaneous examination was conducted using a pre-set detailed proforma. The study duration was 18 months (July 2019 to January 2021). Relevant investigations, including blood tests, radiological imaging, and/or skin biopsies, were performed wherever clinically indicated to confirm the diagnosis and manage patients. Confirmed drug reactions were reported to the Regional Pharmacovigilance Centre.

The severity of the drug reactions was assessed using the ADR Severity Assessment Scale (Modified Hartwig and Siegel) [6]. Preventability was evaluated using the Schumock and Thornton scale, which classifies ADRs as definitely preventable, probably preventable, or not preventable.[7] Photographs of the rashes were taken with written consent from the patients. Patients were not intentionally rechallenged with the suspected offending drugs due to ethical concerns and the non-interventional nature of the study.

A total of 138 patients meeting the inclusion criteria were enrolled. Patients were managed according to their specific conditions. Data were recorded in Microsoft Excel 2017, independently verified by two volunteers, and analysed.

Ethics Approval and Consent to Participate:

Ethics approval was obtained from the Institutional Ethics Committee for Human Research - PG Research (IECHR-PGR), Medical College. The study protocol was approved by the Institutional

Ethics Committee for Human Research - PG Research (IECHR-PGR), Medical College Baroda, Vadodara, India. Written informed consent was obtained from all participants before enrolment.

Consent for Publication:

Written informed consent for publication of anonymized clinical data and photographs was obtained from the patients.

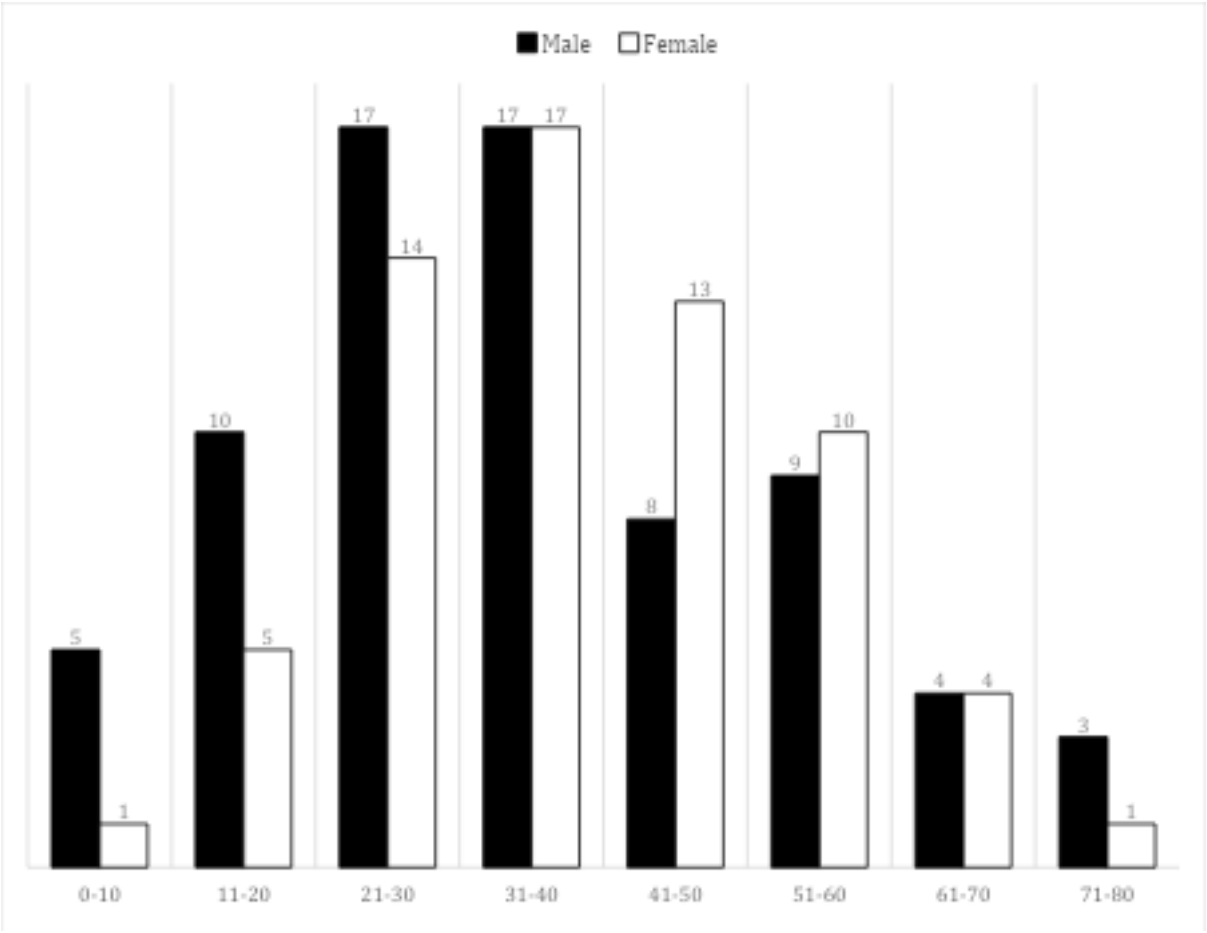
Availability of Data and Materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results:

A total of 138 patients were included in the study. The age and sex distribution of the patients is shown in Figure 1. The majority of patients were between the ages of 21-40 years (47.1%). There was a slight preponderance of males **(52.89%)** vs females (**47.11%**).

Figure 1: Gender and Age Distribution of Subjects:



31% (n=43) of patients consumed the drug either on their own or purchased it directly from a pharmacist, 57% (n=79) consumed the drug on the prescription of an allopathic doctor, 12% (n=16) consumed it on the prescription of an alternative medicine practitioner.

Figure 2 shows the clinical indications for the drugs taken by the patients in the study. The most common indication was musculoskeletal pain in 23 patients (16.66%), followed by diarrhoea in 17 (12.31%).

Figure 2

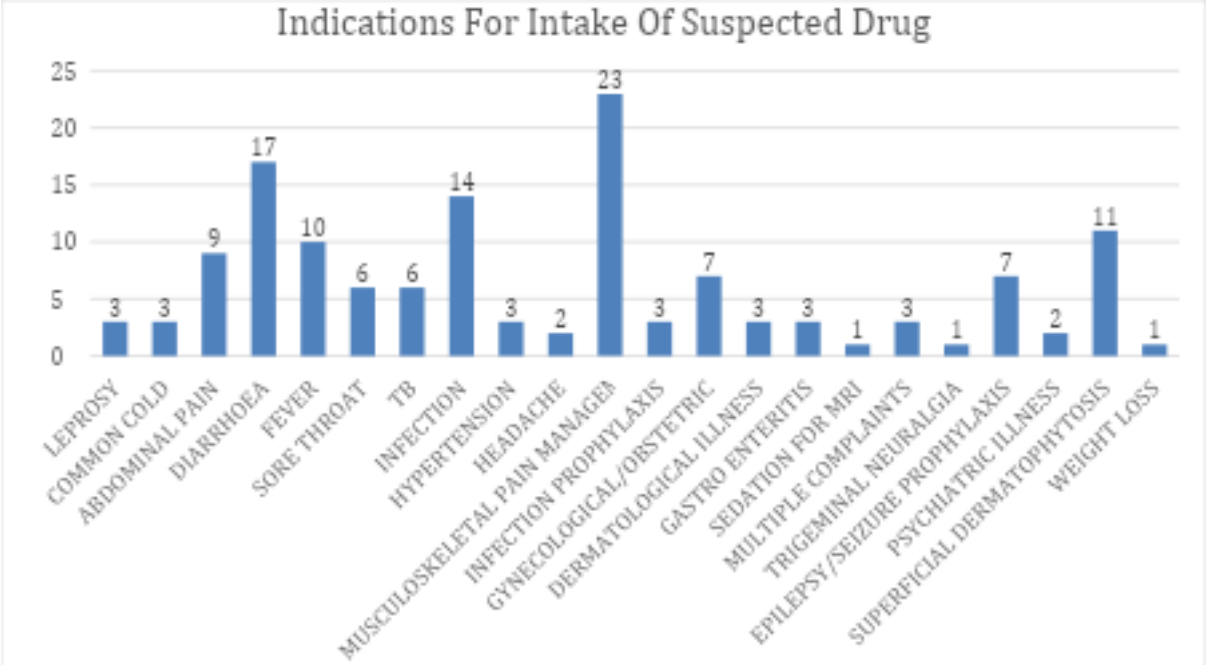


Table 1 shows the distribution of various types of CADR in patients in the study, along with a comparison to similar studies. The most common CADR pattern seen in our study was Fixed Drug Eruption (30.43%), followed by urticaria (28.26%).

Table 1

Provisional diagnosis	**Present study**	**Iftikhar et al [7]**	**Sharma et al [8]**	**Thakkar et al [9]**
DRESS SYNDROME	5 (3.62%)	10 (3.98%)	-	2 (1.17%)
FDE	42 (30.43%)	12 (4.78%)	50 (33.33%)	37 (21.64%)
SJS-TEN	9 (6.52%)	29 (11.55%)	6 (4%)	6 (3.51%)
ANGIOEDEMA	12 (8.70%)	-	1 (0.66%)	5 (2.92%)
URTICARIA	39 (28.26%)	31 (12.35%)	26 (17.33%)	37 (21.64%)
PHOTO SENSITIVITY	2 (1.45%)	-	5 (3.33%)	2 (1.17%%)
MACULO PAPULAR RASH	16 (11.59%)	120 (48%)	20 (13.33%)	41 (23.98%)
URTICARIA WITH ANGIOEDEMA	5 (3.62%)	-	-	8 (4.68%)
ERYTHRODERMA	2 (1.45%)	-	4 (2.66%)	2 (1.17%)
ERYTHEMA MULTIFORME	2 (1.45%)	29 (11.55%)	15 (10%)	10 (5.85%)
ECZEMATOUS ERUPTION	1 (0.72%)	2 (0.79%)	-	-
AGEP	(0.72%)	-	-	-
LICHENOID ERUPTION	1 (0.72%)	2 (0.39%)	-	1 (0.58%)
MUCO CUTANEOUS ULCERATION	1 (0.72%)	1 (0.39%)	-	3 (1.75%)
OTHERS	-	16 (6.37%)	23 (15.33%)	18 (10.46%)
Total	**138**	**251**	**150**	**172**

Based on the Modified Hartwig and Siegel severity assessment scale, 8 (5.79%) were classified as mild reaction, 127 (92.02%) as Moderate reaction, and 3 (2.17%) as a severe reaction. 3.62% (n=5) of cases could be classified as "*Certain*" as per the WHO UMC Causality assessment, without re-challenge, as they had records of a history of drug reaction to a particular group of drugs and yet

consumed the probable offending drug again at the time of presentation to us. 8% (n=11) patients were labelled as "*Unclassifiable*" due to unknown drug intake 20 ADR were classified as "Definitely preventable" and 1 as "*Probably Preventable*" per the Schumock and Thornton Scale. Among the "*Definitely Preventable*", one involved an incorrect drug dosage prescribed to the patient, while 19 had a history of similar drug reaction in the past. 16 patients (11.59%) had to be admitted in the Dermatology ward for further management, while the remaining 122 (88.41%) were managed on an outpatient basis. Among the ones admitted to in patient department for further treatment, there was 1 death of a patient of SJS-TEN secondary to Levetiracetam, due to secondary infection and sepsis developing as a complication. 122 patients presented within 7 days of development of ADR, among which 16 presented within 24 hours, in our study. 6 patients presented at least a month after development of ADR, due to delay in diagnosis or referral.

Distribution of patients on the basis of time duration, between the suspected drug intake and the onset of 1st clinical complaint is shown in Table 2. The mean duration of onset of skin lesions after the intake of suspected drug in DRESS syndrome was the longest, at 44 days, while the shortest mean duration was seen in Urticaria at 2.6 hours. The mean duration of development of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome) was 36.2 days.

Table 2

Provisional Diagnosis	**<1 Hour**	**1-12 Hours**	**13-24 Hours**	**1-3 Days**	**4-7 Days**	**7-28 Days**	**29-365 Days**	**>1 Year**	**Total**
FDE	1	17	14	5	3	2	-	-	42
URTICARIA	3	17	7	10	1	1	-	-	39
MACULO PAPULAR RASH	-	6	3	3	1	2	1	-	16
ANGIOEDEMA	2	4	1	1	-	2	-	2	12
STEVEN JOHNSON SYNDROME-TOXIC EPIDERMAL NECROLYSIS (SJS-TEN)	-	-	1	-	4	4	-	-	9
DRESS SYNDROME	-	-	-	-	-	-	5	-	5
URTICARIA WITH ANGIOEDEMA	-	-	2	-	1	2	-	-	5
PHOTOSENSITIVITY	-	-	-	-	1	1	-	-	2
ERYTHRODERMA	-	-	-	-	1	-	1	-	2
ERYTHEMA MULTIFORME	-	-	-	1	1	-	-	-	2
ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)	-	-	1	-	-	-	-	-	1
ECZEMATOUS ERUPTION	-	1	-	-	-	-	-	-	1
LICHENOID ERUPTION	-	-	-	-	-	1	-	-	1
MUCO CUTANEOUS ULCERATION	-	-	-	-	1	-	-	-	1
Total	**6**	**45**	**29**	**20**	**14**	**22**	**7**	**2**	**138**

Discussion:

Fixed Drug Eruption (FDE) was the most common ADR occurring among the patients. Among patients with FDE, Genital mucosa was involved in 16.66% (n=7), oral mucosa in 33.33% (n=14), and 3 patients had involvement of both genital and oral mucosa. 26.19% (n=11) of the patients had a past history of FDE at the same site as the time during presentation in our study. The list of drugs causing FDE in our study is presented in Table 3:

Table 3:

Suspected Drug	**No. (%)**
Ofloxacin	6 (9.52%)
Fluconazole	4 (9.52%)
Ciprofloxacin	4 (7.14%)
Norfloxacin	3 (4.76%)
Metronidazole	2 (4.76%)
Doxycycline	2 (4.76%)
Diclofenac	2 (4.76%)
Paracetamol	2 (2.38%)
Aceclofenac	2 (4.76%)
Cotrimoxazole	1 (2.38%)
Sodium Valproate	1 (2.38%)
Metronidazole	1 (2.38%)
Amoxicillin+Clavulanic Acid	1 (2.38%)
Nimesulide	1 (2.38%)
Terbinafine	1 (2.38%)
Cefoperazone+Sulbactum	1 (2.38%)
Cyclobenzaprine	1 (2.38%)
Ayurvedic Powder	1 (2.38%)
Ibuprufen	1 (2.38%)
Unknown Drug	5 (11.90%)
Grand Total	**42 (100.00%)**

The case of FDE due to Ayurvedic powder (Ashwagandha) was similar to a case reported by V. Sehgal et al [(10)]. Another rare case was development of FDE to Cyclobenzaprine, a Tricyclic anti-depressant with muscle relaxant properties, prescribed to a patient of muscle pain with concomitant depression. There is no published literature of FDE to Cyclobenzaprine. Flouroquinolones formed the largest group of drugs causing FDE in our study (n=13, 30.95%). 11 of them took the drug over the counter for diarrhoea, which is an irrational use [(11)] and can be considered as a potential point of legislative action to reduce the incidence of Fixed drug eruptions among the general public.

Out of the 56 patients in our study had drug induced Urticarial syndrome, 39 (69.64%) had only Urticaria, 12 (21.43%) had only Angioedema, and 5 (8.93%) had Urticaria with Angioedema. Among patients with only angioedema, 2 patients had Losartan induced angioedema, which was a rare finding, as angiotensin receptor blockers are generally considered safe in that regard except for a few case reports [(12)]. One of the two developed the ADR 1 year after continuous use of Losartan. The others were due to Paracetamol (n=3), Diclofenac (n=3), and 1 each due to Fluconazole, Itraconazole, Vancomycin and Midazolam. Due to polypharmacy, it was difficult to pinpoint a specific drug to be the cause of the urticarial rash. The groups of suspected drugs causing urticarial rash in our study are mentioned in Table 3. Among NSAIDS, Paracetamol (n=11) was the most common drug suspected to be causing urticarial rash, while Diclofenac (n=6) was the 2nd most common. Notable mention was Nitrofurantoin as no published literature mentions it to be causing urticaria. Five patients developed Urticaria with angioedema. Four of them we caused by the following: 1st line Anti Tubercular drugs, Cefixime, Norethisterone and Amoxicillin, while the cause in one of them remained to be identified.

Table 4: Suspected drugs causing urticaria (n=39)

1. Antibacterial	33 (44.00%)
Penicillin group	11 (14.66%)
Cephalosporins	8 (10.66%)
Fluoroquinolones	5 (6.66%)
Tetracyclines	4 (5.33%)
Miscellaneous	5 (6.66%)
Metronidazole	2 (2.66%)
Amikacin	1 (1.33%)
Nitrofurantoin	1 (1.33%)
Tazobactum	1 (1.33%)
2. NSAIDS	22 (29.33%)
Paracetamol	11 (14.66%)
Diclofenac	6 (8.00%)
Ibuprofen	4 (5.33%)
Aceclofenac	1 (1.33%)
3. Anti-Hypertensives	5 (6.67%)
Angiotensin Receptor Blockers	2 (2.66%)
ACE Inhibitors	1 (1.33%)
Calcium Channel Blockers	1 (1.33%)
Clonidine	1 (1.33%)
4. Antispasmodics	5 (6.67%)
Dicyclomine	5 (6.67%)
5. Anti-Epileptics	1 (1.33%)
Phenytoin	1 (1.33%)
6. Others	9 (12.00%)
Flavoxate	2 (2.66%)
Calcium gluconate	2 (2.66%)
Theophylline	1 (1.33%)
Etophylline	1 (1.33%)
Bisacodyl	1 (1.33%)
Domperidone	1 (1.33%)
Phenylephrine	1 (1.33%)
Total	75 (100%)

A total of 9 patients were diagnosed with SJS-TEN spectrum, with a different drug to be the cause in 8 of them, while 1 consumed an unknown drug. The incriminating drugs were: Ofloxacin, Phenytoin, Rifampicin, Levetiracetam, Aceclofenac, Oxcarbamezapine, Diclofenac, and a notable mention of Itraconazole [13]. Mean body surface area involvement at the time of presentation was 24 %. Among

the five patients diagnosed as DRESS syndrome, two were attributable to Dapsone, one to Isoniazid & Carbamezapine each, and one remarkably to a rare cause, Phenobarbitone [14]. All were admitted and were given intravenous steroids for their management for a mean duration of 7.4 days, followed by extended duration of oral steroids after discharge. 35 drugs were suspected to be the cause of maculo-papular rash in 16 patients, with antibiotics forming the largest group, and Levofloxacin (n=4) being the most common among them.

Table 5: Suspected drugs causing Maculo Papular rash in our study: (n=16)

Anti-Bacterial	20	(55.56%)
2nd line Anti-Tubercular drugs	9	(25.71%)
FQs	4	(11.42%)
Cephalosporins	3	(8.57%)
Aminoglycosides	2	(5.71%)
Ivermectin	2	(5.71%)
NSAIDs	4	(11.11%)
Aceclofenac	3	(8.57%)
Ibuprofen	1	(2.85%)
Anti-Epileptics	2	(5.56%)
Lamotrigine	1	(2.85%)
Carbamazepine	1	(2.85%)
Anti-Retrovirals	3	(8.33%)
NNRTIs	2	(5.71%)
NRTIs	1	(2.85%)
Others	6	(16.67%)
Mebeverine	2	(5.56%)
Chlordiazepoxide	1	(2.85%)
Ondansetron	1	(2.85%)
Unknown	2	(5.71%)
Total	35	(100%)

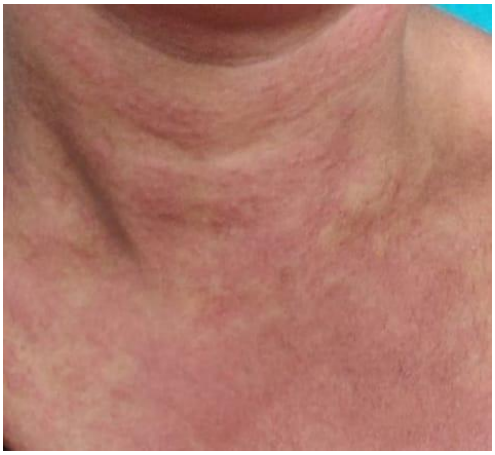


Image 1: MP rash due to Ibuprofen

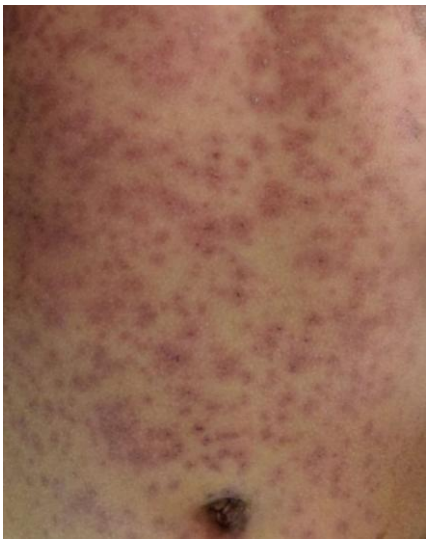


Image 2: SJS due to Aceclofenac

The only overdose related cutaneous CADR in our study was due to methotrexate. The ingested dose was 70 mg over a week, and presented with ulceration over the existing psoriatic plaques and oral mucosa. The patient's leucocyte count at the time of presentation was 320 / mL, and he was immediately admitted in the intensive care unit and appropriate treatment given. The only case of Lichenoid eruption was due to first line Anti Tubercular therapy initiation, consisting of Rifampicin, Isoniazid, Ethambutol and Pyrazinamide. The causative drug in the single case of AGEP remained unknown as the patient took loose medications from an alternative medicine practitioner without any packaging, for fever.

Conclusion: This study characterized the spectrum of cutaneous adverse drug reactions (CADRs) in the observed patient population. Fixed Drug Eruption and Urticaria were identified as the most common CADR patterns, frequently associated with antibiotics and NSAIDs. While most reactions were mild to moderate in severity, the occurrence of severe and preventable cases highlights the critical need for ongoing pharmacovigilance and careful prescribing practices to minimize the impact of CADRs.

Limitations: This study was conducted at a single tertiary care centre, which may limit the generalizability of the findings to other geographic regions or healthcare settings. Additionally, the reliance on patient-reported drug histories in some cases where case files were not available, introduces the possibility of recall bias, particularly in cases where multiple drugs were consumed simultaneously. The exclusion of reactions to topical agents; and the non-performance of drug rechallenge due to ethical constraints may have led to underestimation or misclassification of certain CADRs. Furthermore, the observational design restricts the ability to establish definitive causality.

Competing Interests:
The authors declare that they have no competing interests.

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Authors' Contributions:
Dr. Ankush Anil Ajbani: Data collection,Conceptualization, study design, supervision, critical revision of the manuscript.
Dr. Nipul Vara: Patient management, manuscript drafting.

Dr. Hiral Shah: Data interpretation, literature review, manuscript editing.
Trivedi Rudra Pankajkumar: Data entry, statistical analysis, preparation of figures and tables, manuscript drafting.
All authors have read and approved the final version of the manuscript and agree to be accountable for its contents.

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