ORIGINAL ARTICLE

# A Cross Sectional Study of Cutaneous Adverse Drug Reactions in a Tertiary Health Centre

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## ABSTRACT

**Introduction:** Cutaneous Adverse Drug Reactions (CADRs) range from being self-limiting (maculopapular rash, urticaria) to life-threatening (Stevens-Johnson syndrome/toxic epidermal necrolysis, DRESS). Common causes include penicillins, sulfonamides, anticonvulsants and NSAIDs. With the constant introduction of new drugs into the market, the varied presentations of CADRs in every community requires periodic evaluation because early identification of severe CADR significantly reduces morbidity and mortality. Thus, it is necessary for all practicing physicians, not just Dermatologists, to be well-versed in recognizing CADRs. **Materials and Methods:** A descriptive cross-sectional study was carried out within the Dermatology department at a tertiary care hospital over 6 months including 50 patients. The objective was to examine morphological patterns of drug eruption in outpatients, inpatients and referrals; to identify culprit drug(s) by Naranjo scale and also the treatment response. **Results:** Mean age of presentation was 38.42 years. Most common CADRs were acneiform eruption (14%), fixed drug eruption (14%), urticaria (14%) and SJS/TEN (8%). The most frequently implicated drug category was antibiotics (22%), with analgesics (16%) and antiepileptics (10%) coming next. Mean latency from drug intake to development of rash was 17 days. Severe CADRs were observed in 20% cases. Drug withdrawal was implemented in all cases except for ATT-induced acneiform eruptions. Most patients responded to antihistamines and corticosteroids. **Conclusion:** Physicians need high index of suspicion for diagnosing the frequently overlooked CADRs. The changing trends of drug use require periodic study to assess the ADR spectrum. Few unusual presentations like topical gatifloxacin-induced TEN and cilnidipine in acute generalised exanthematous pustulosis etc., in this study aid in adding to the existing literature.

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**Keywords:** cutaneous adverse drug reaction, ADR, naranjo scale, fixed drug eruption, toxic epidermal necrolysis

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## INTRODUCTION

The World Health Organization describes an adverse drug reaction (ADR) as any harmful and unintended response to a medication, occurring at standard doses typically used for disease prevention, diagnosis, treatment, or the alteration of physiological functions in humans [1]. As a common preventable public health problem, ADRs represent a significant yet often underrecognized and overlooked public health issue, being one of the top preventable causes of mortality and morbidity globally. Cutaneous manifestations occur in roughly 10–30% of ADRs, of which only 2-3% are noted in inpatients [2].

CADRs are a significant clinical entity in Dermatology and described as any unwelcome alteration in the structure or function of the skin and its appendages or mucous membranes, encompassing all adverse events connected to drug eruptions, regardless of their cause [3].

The incidence of CADRs is 1-3% in high-income countries while higher in low- and middle-income nations (2-5%) [4]. However, it is challenging to ascertain the true frequency because many mild/transient reactions go unrecorded. Contrarily, viral exanthems are sometimes misidentified as morbilliform eruptions and herpes labialis is occasionally mistaken for bullous fixed drug eruption. The most common causes include penicillins, sulfonamides, anticonvulsants, NSAID and fluoroquinolones.

Genetic determined variations in metabolism of drugs, atopy, comorbidities, viral infections, immune status,

and simultaneous use of other medications can all influence the presentation of CADRs. The pathogenesis is complex and involves several factors such as drug class, HLA subtypes, T-cell receptor clonotypes, and viruses.

CADRs can be nonimmunological (predictable, more common) and immunological. Immunological CADR (IM-CADR) have an unpredictable presentation and account for 20% of CADRs [5]. They arise from allergic sensitization to a medication following prior exposure to the same or a chemically related drug. The first episode of reaction takes a few days to weeks to manifest; the subsequent reactions develop within few hours to days and very small dose far below the therapeutic level is sufficient to cause it.

CADRs can be as simple or complex. Simple CADRs are common, limited to the skin and have a benign course. Clinical patterns include maculopapular exanthem, fixed drug eruption (FDE), urticaria and angioedema, erythema multiforme, lichenoid eruption, acneiform eruption, photosensitivity, pigmentary changes, psoriasiform rash, pityriasis rosea like rash, bullous eruptions etc.

Complex CADRs in the form of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS) and erythroderma could be severe, life-threatening and may also affect multiple organ systems. These conditions are collectively referred to as 'severe cutaneous adverse reactions' (SCAR) is preferred for such conditions [6]

CADRs can mimic any inflammatory dermatoses. As there are no reliable and validated laboratory investigations, strong clinical suspicion and proper history-taking are essential. The testing methods that may be used sometimes comprise skin prick testing, epicutaneous patch test, and intradermal tests.

Due to the availability of over-the-counter medicines, the concomitant intake of several medications and self-medication, the prevalence of CADRs is steadily rising. This along with the constant introduction of novel compounds and shifting trends in medication use are responsible for the variations in clinical patterns and drugs that induce different reactions. More importantly, the morbidity and mortality of severe CADRs is very high and requires early identification.

Therefore, we undertook this study with the aim of illustrating the current trend of CADR in South Indian demography, so that not just Dermatologists but all healthcare professionals can gain a better understanding of CADRs and become more acquainted with it.

## MATERIALS AND METHODS

A descriptive cross-sectional study was conducted in the department of Dermatology in a tertiary care teaching institution over a period of 6 months from July 2023 to December 2023, under Pharmacovigilance Programme of India, following approval from Institutional Ethics committee (056/03/2023/PG/SRB/SMCH). It comprised 50 patients of both sexes and aged above 18 years, including outpatient, inpatient and referral cases.

Patients who were unable to recall the correct name of their medication, blamed indigenous (ayurvedic, siddha and homeopathic) medicines of unknown composition, declined consent, in whom viral exanthems as a possibility could not be ruled out or rated as having only a 'possible' drug rash (on Naranjo scale) were all excluded. Also, drug toxicity, overdose, drug-drug interactions, intolerance, and pharmacological side effects of a drug, were not included in this study.

A comprehensive history was documented, including the details on drug intake, skin rash, the time interval between drug consumption and cutaneous reaction, dosage, duration, indication, drug class, improvement in rash upon discontinuation of the medication, and any related systemic symptoms. Furthermore, a general examination was carried out, along with a detailed examination of the skin and mucosal surfaces focusing on the distribution, morphology and pattern of drug eruption. In addition, history of drug use, details of related allergies, comorbidities and family history were noted. Relevant hematological, microbiological and biochemical investigations were carried out in severe cases and histopathological examination of biopsy specimen was undertaken if required.

The Naranjo algorithm was used to analyse causality, categorizing CADRs as definite, possible, and probable. The offending agent was identified by examining the timeline from drug introduction to symptom onset. In cases where multiple drugs were suspected to be responsible, the most likely culprit drug was identified and withdrawn. After treatment and recover, all patients were educated about ADR and to stay vigilant in the future and given a list of medications that could cause reactions. Upon completion of the study, the data were examined, and inferences were formulated utilizing SPSS software.

The list of abbreviations in this article is as follows: 1. ADR (Adverse Drug Reaction), 2. AGEP (Acute Generalized Exanthematous Pustulosis), 3. ATT (Anti-Tubercular Treatment), 4. CADR (Cutaneous Adverse Drug Reaction), 5. DIHS (Drug-Induced Hypersensitivity Syndrome), 6. DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), 7. FDE (Fixed Drug Eruption), 8. G-CSF (Granulocyte-Colony Stimulating Factor), 9. IM-CADR (Immunological CADR), 10. MB-MDT

(Multi-Drug Therapy for Multibacillary Leprosy), 11. NSAID (Non-Steroidal Anti-Inflammatory Drug), 12. OTC (Over-the-Counter), 13. PR-like Drug Eruption (Pityriasis Rosea-like Drug Eruption), 14. SCADR (Severe Cutaneous Adverse Drug Reaction), 15. SCAR (Severe Cutaneous Adverse Reaction), 16. SDRIFE (Symmetrical Drug-Related Intertriginous and Flexural Exanthema), 17. SJS/TEN (Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis).

## RESULTS

Over a 6-month period, sixty-one cases were newly detected and suspected of CADR among 13,028 patients consulting Dermatology department. Eleven cases were excluded due to the following reasons- inability to recall the precise name of the ingested drug, attributing issues to indigenous medicine or declining to give consent. The final assessment took into account the remaining 50 patients, thereby rendering a prevalence of 0.38%.

The mean age in this study was found to be 38.42 years and range was 19 to 72 years. Majority (50%) of CADRs were noted in young adults (15-39 years) followed by middle aged adults of 40-59 years (38%) and old adults of 60-79 years (12%). Men (54%) were more affected than women. Average age among male patients was 37.40 years, and among female patients was 39.60 years. The male-to-female ratio was 1.17:1.

The majority of incriminated drugs (82%) were prescribed by physicians. Additionally, CADRs encountered because of over-the-counter (OTC) medications encompassed acneiform eruption, urticaria, FDE, TEN and Pityriasis rosea-like drug eruption (PR-like drug eruption). Almost 60% of patients had pruritis as a predominant complaint which accompanied the rash.
The most prevalent causative drug category was antibiotics (22%) including azithromycin, ciprofloxacin and cefotaxime as the most frequent causes. The second most common was analgesics (18%) with acetaminophen

**Table I- Type of CADR with the corresponding causative drugs**

| CADR | Causative Drug | Category of the Causative Drug | Number of Patients with the CADR | Percentage of Patients with the CADR |
|---|---|---|---|---|
| Acneiform eruption | Lorazepam<br>ATT(Isoniazid)<br>Betamethasone<br>Clobetasol propionate<br>Prednisolone(3) | Anxiolytic(1)<br>ATT(1)<br>Corticosteroid(5)- topical, oral | 7 | 14.0 |
| AGEP | Amoxicillin<br>Cilnidipine | Antibiotic(1)<br>Calcium channel blocker(1) | 2 | 4.0 |
| Angioedema | Enalapril<br>G-CSF | ACE Inhibitor(1)<br>Antiemetic(1) | 3 | 6.0 |
| Dapsone hypersensitivity syndrome | Ondansetron<br>Dapsone | G-CSF(1)<br>Antileprosy agent(1) | 1 | 2.0 |
| Erythema multiforme | Acetaminophen<br>Tinidazole | Analgesic(1)<br>Antiprotozoal(1) | 3 | 6.0 |
| Exfoliative dermatitis | ATT<br>ATT(Ethambutol)<br>Vincristine<br>MB-MDT(Rifampicine) | ATT(1)<br>ATT(1)<br>Chemotherapeutic agent(1)<br>Antileprosy agent(1) | 3 | 6.0 |
| FDE | Diclofenac sodium<br>Nimesulide<br>Ceftriaxone<br>Ciprofloxacin<br>Cetirizine<br>Azacytidine<br>Metronidazole | Analgesic(2)<br>Antibiotic(2)<br>Antihistamine(1)<br>Antiprotozoal(1)<br>Chemotherapeutic agent(1) | 7 | 14.0 |
| Heparin induced skin necrosis | Heparin | Anticoagulant(1) | 1 | 2.0 |
| Lichenoid drug eruption | Phenytoin<br>ATT(Isoniazid) | Antiepileptic(1)<br>ATT(1) | 3 | 6.0 |
| Maculopapular exanthem | Cyclosporine<br>Ciprofloxacin | Immunosuppresant(1)<br>Antibiotic(1) | 3 | 6.0 |
| PR-like drug eruption | Phenytoin(2)<br>Terbinafine | Antiepileptic(2)<br>Antifungal(1) | 2 | 4.0 |
| Psoriasiform dermatitis | Omeprazole<br>Carbamazepine | Proton pump inhibitor(1)<br>Antiepileptic(1) | 1 | 2.0 |
| SJS/TEN | Azithromycin<br>Cotrimoxazole<br>Gatifloxacin | Antibiotic(3)<br>Antiepileptic(1) | 4 | 8.0 |
| SDRIFE | Carbamazepine<br>Ceftriaxone | Antibiotic(1) | 1 | 2.0 |
| Urticaria | Aceclofenac<br>Acetaminophen(3)<br>Aspirin<br>Cefotaxime | Analgesic(5)<br>Antibiotic(1)<br>Anticoagulant(1) | 7 | 14.0 |
| Vasculitis | Rivaroxaban<br>Azithromycin<br>Methotrexate | Antibiotic(1)<br>Chemotherapeutic agent(1) | 2 | 4.0 |
| Total | | | 50 | 100.0 |

being the most frequent, and third most common category of drug was antiepileptic agents (10%) with phenytoin being the most frequent drug. Polypharmacy was seen in 34% of patients and antibiotics and analgesics were commonly used together.

The most frequently observed cutaneous adverse drug reactions were acneiform eruptions (14%), FDE (14%), urticaria (14%) and SJS/TEN (8%). Table I shows Type of CADR with the corresponding causative drugs.

The mean latency period from time of intake of drug to the development of drug rash was found to be 17 days. The shortest reaction time was 6 hours, observed in a patient who presented with urticaria following intake of acetaminophen for fever while the longest reaction time extended to 4 months in 2 patients (exfoliative dermatitis by anti-tubercular treatment or ATT for ileocaecal TB and acneiform eruption by prednisolone for acute lymphoblastic leukemia). The Naranjo scale was employed to assess causality [7]. Patients with definite causality were 12% and probable causality were 88%.

Fourteen percent of patients gave similar history of skin lesions upon taking same drug in the past. No patient had a documented history of previous drug reaction to a different drug group. Three patients were found to have personal history of atopy. No significant link to underlying comorbidities was identified. Majority of the drugs were administered orally (n=41, 82%) followed by injectable (n=6, 12%) and topical (n=3, 6%).

The most commonly involved site was the upper trunk and least common was conjunctiva. Mucosal involvement was seen in 16% of cases. Skin biopsy showed correlation with clinical findings in TEN, AGEP, SDRIFE, vasculitis and lichenoid drug eruption. The clinical presentation of AGEP in a postnatal mother caused by amoxicillin is depicted in Figure 1, while erythroderma in a case due to vincristine is shown in Figure 2. A case of heparin-induced skin necrosis is shown in Figure 3; Baboon syndrome in a patient triggered by ceftriaxone is shown in Figure 4; and TEN in a case where gatifloxacin was implicated is illustrated in Figure 5.

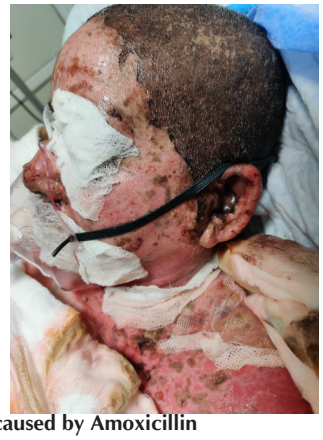

**Figure 1: AGEP caused by Amoxicillin**

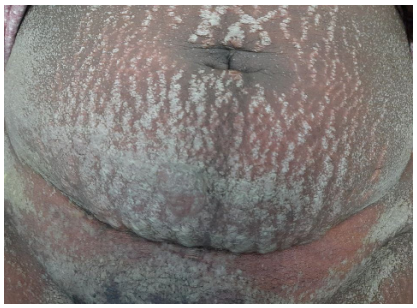

**Figure 2: Erythroderma by Vincristine**

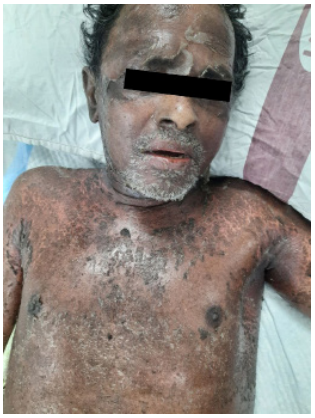

**Figure 3: Heparin-induced skin necrosis**

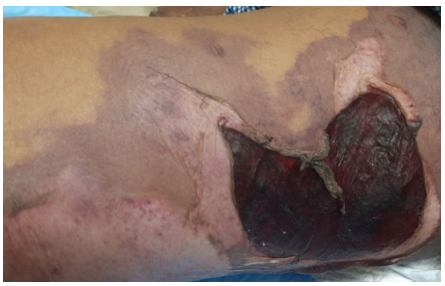

**Figure 4: SDRIFE by Ceftriaxone**

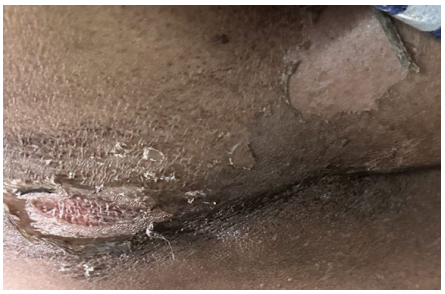

**Figure 5: STEN caused by Gatifloxacin**

Clinical criteria were used in diagnosing and scoring AGEP [8], TEN [9] and DIHS [10]. All patients with severe CADR (SCADR) underwent skin biopsy, complete hemogram, urine analysis, blood sugar levels, liver function test, kidney function test, serum electrolytes, serology, pus culture and sensitivity, chest x-ray and ECG in order to rule out systemic involvement. The SCORTEN criteria was applied to assess prognosis in TEN patients [11]. Among the ten SCADR patients, three had deranged renal function test, four had deranged liver function test, two had low hemoglobin, three had leucocytosis and two had deranged electrolyte which

normalised post-treatment. Table II shows distribution of SCADRs in the study population.

Around 36% were inpatients. Twelve patients (24%) were admitted directly under Dermatology department for neccessary further management of the CADR- lichenoid drug eruption (2%), SJS/TEN (8%), exfoliative dermatitis (6%), angioedema (2%), vasculitis (2%), dapsone hypersensitivity syndrome (2%) and Baboon syndrome (2%). Six patients (12%) were already admitted patients under other specialities and developed cutaneous ADRs during the course of admission- AGEP (2%), heparin-induced skin necrosis (2%), urticaria (2%), FDE (4%), erythema multiforme (2%).

**Table II - Distribution of SCADRs in the study population**

| SCADR | Drug | Category of Drug | Number of Patients | Percentage of Patients (%) |
|---|---|---|---|---|
| AGEP | Amoxicillin Azithromycin | Antibiotic | 1 | 2.0 |
| SJS/TEN | Cotrimoxazole<br>Gatifloxacin | Antibiotic(3)<br>Antiepileptic(1) | 4 | 8.0 |
| Exfoliative dermatitis | Carbamazepine<br>ATT (Ethambutol)<br>MB-MDT (Rifampicin)<br>Vincristine | ATT(1)<br>Chemotherapeutic agent(1)<br>Antileprosy agent in MB-MDT(1) | 3 | 6.0 |
| Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) | Ceftriaxone | Antibiotic | 1 | 2.0 |
| Dapsone hypersensitivity syndrome | Dapsone | Antileprosy agent in MB-MDT | 1 | 2.0 |
| Total cases | | | 10 | 20 |

Only one patient succumbed to the illness and had suffered heparin-induced skin necrosis. He also had acute decompensated heart failure, chronic pulmonary embolism, deep vein thrombosis, diabetes mellitus and alcoholism. Therefore, co-morbidity greatly influenced the unfavourable outcome in this case.

Withdrawal of causative drug was implemented in all cases except those with acneiform eruption induced by ATT. Most patients showed improvement with antihistamines, topical and oral corticosteroids. Inpatients were treated with intravenous corticosteroids. Cyclosporine was administered to two patients with TEN. In patients with TEN, AGEP and Exfoliative dermatitis, additionally antibiotics to counter secondary infection, analgesics, anti-inflammatory and anti-pyretic drugs, fluid replacement along with protein and nutritional supplementation was done. Sterile banana leaf dressing for wound care and eye care with steroid eye drops, saline flushes, preservative-free artificial tears was undertaken in TEN patients.

## DISCUSSION

The CADR prevalence of 0.38% in this study is comparable to a systematic review from India [12] and other studies abroad which showed a range between 0.36% and 12.2% [13-16]. Cutaneous drug reaction comprised 1.38% of all referrals to Dermatology department of a university hospital in Denmark and 1.5% of all dermatology consultations seen at a Tunisian medical facility [2,14].

In our study, males were more affected than females which was similar to other studies [2,14,17-19], though some studies reported a female preponderance [14,20-22].

Our study shows maximum number of CADRs reported 15-39 years of age (50%) followed by 40-59 years (38%). This is comparable to studies by Sushma et al and Jha et al [2,23]. The most common CADR developing within the first 24 hours of drug intake were angioedema and urticaria. FDE, urticaria, and maculopapular rash developed within a week. Oral route of drug ingestion (82%) was most frequent. These findings align with the study conducted by Modi et al [17]. Complex CADRs are depicted in Figures 1-5.

A history of previous drug eruption was recorded in 14% patients, a figure slightly lower than that reported by Saha et al [24]. Our study showed a personal and/or familial background of atopy in 6% as compared to 21% patients reported by by Al-Raaei et al [25]. Mucosal involvement was demonstrated in 27.52% cases by Jha et al. whilst it was 16% in this study [2].

The predominant CADRs were FDE (14%), urticaria (14%) and acneiform eruption (14%). Al-Raaie et al. noted urticaria, while Pudukadan et al. identified fixed drug eruption as the chief CADRs, respectively [20,25]. Other studies found exanthematous drug eruption to be the most frequent [2,18,24,26-28].

These variations among results may be due to the distinctions in drug usage patterns, drug reaction rates, and pharmacogenetic characteristics of the population under study [25,27].

Our study revealed antibiotics to be the most frequently implicated drug group, followed by NSAIDs and antiepileptics. This pattern is similar to few other studies [2,17,18,29]. Al-Raaie et al. reported NSAIDs, Noel et al. and Murthy et al. identified antiepileptics as the most prevalent culprit medications [25,27,30].

Among antibiotics, macrolides and fluoroquinolones topped the list in our research, in contrast to

cephalosporins as noted by Jha et al. [2]; fluroquinolones and penicillins were implicated by Sushma et al [23].

The Hartwig Scale classifies adverse drug reactions into 7 severity levels [31]. Levels 1 and 2 are considered mild, levels 3 and 4 are categorized as moderate, and levels 5, 6 and 7 are designated as severe. Mild ADRs are self-limiting and capable of resolving over time without therapy. Moderate ADRs necessitate treatment or extend the hospital stay by at least one day. ADRs that are life-threatening, result in permanent harm, or lead to death are labelled as severe ADRs. According to this, 12% had severe drug reaction in our study which is lower than that identified in a systematic review by Patel et al. [12] and other recent Indian studies [30, 32].

SCADRs made up 20% of the total CADRs, which is greater than that detected by Jha et al. (4.65%) and lower compared to those noted by Saha et al. (32.04%) and Sasidharan Pillai et al. (13.20%) [2,24,33]. SJS-TEN emerged as the most frequent SCADR (8%), which is consistent with previous research [18,19]

Antibiotics (cotrimoxazole, gatifloxacin, azithromycin) most commonly caused SJS/TEN in our study followed by carbamazepine. This finding does not align with the study by Choon et al., in which carbamazepine and allopurinol are the main culprits.[18].

The offending agent was promptly discontinued in all the cases upon ADR identification.

Drug rechallenge was not done in our study participants. The relatively short study duration and small sample size could be few limitations of the study. The Schumock and Thornton's criteria and WHO causality assessment for CADR prevention may be included in forthcoming extensive multicentric research.

## CONCLUSION

A wide range of CADRs was noted in our study and the major cause was identified as antibiotics. Physicians commonly encounter them in daily practice and should have a comprehensive understanding of the clinical spectrum for ensuring prompt diagnosis and effective management. Hitherto lesser reported CADRs in our study like gatifloxacin eye drops induced TEN, cilnidipine-induced AGEP, nimesulide causing FDE, rivaroxaban-induced urticaria and terbinafine causing PR-like drug eruption should alert the prescribing physician to be always vigilant. As there is no gold standard investigation, maintain a heightened level of clinical vigilance is crucial. Patient education is also pertinent to prevent re-administration of the suspected class of drug, to refrain from self-administering medications and from re-administering the offending medication(s) in the future.

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