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STUDY OF CLINICAL AND HISTOPATHOLOGICAL PATTERN, SEVERITY, CAUSALITY AND COST ANALYSIS IN HOSPITALISED PATIENTS WITH CUTANEOUS ADVERSE DRUG REACTIONS IN A TERTIARY CARE HOSPITAL

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Keywords:

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ABSTRACT: Objectives: To assess clinical and histopathological patterns, causative drugs, causality, severity and cost of treating Cutaneous Adverse Drug Reactions (CADRs) among patients admitted in tertiary care teaching hospital. **Methods:** In a prospective hospital-based study over a period of one year (June 2015- June 2016), CADRs of patients admitted to the dermatology department were recorded. The data was subjected to descriptive analysis. **Results:** Of the total 39 cases, 24 (61.54%) were male and 15 (38.46%) were female. Maximum patients (48.7%) belonged to 21 - 40 years age group. On causality analysis, 23 cases (58.33%) were of probable type whereas 16 (41.02%) of possible type. Steven Johnson syndrome (46.15%), maculopapular drug rash (20.51%) and drug reaction with eosinophilia and systemic symptoms (15.38%) were common CADRs. There were total 55drugs which could account for observed CADRs mostly belonging to anti-epileptic (32.72%), anti-microbial (29.09 %) and NSAIDs (21.81%) classes. The most frequent offending drug was phenytoin (18.18%) followed by paracetamol (10.91%) and carbamazepine (7.27%). Maximum CADRs were of severe type (66.67%) but no mortality was observed. In all the cases where histopathological examination was done initial diagnosis made after clinical examination did not change. The average cost of hospitalization per day was Rs 535.95. **Conclusion:** In our study the CADRs patterns found were similar to that seen in previous studies but most common causative class responsible was antiepileptics. Knowledge about the varied clinical presentations and the common putative drugs for CADRs will enable physicians in early diagnosis, prompt treatment and reduce economic burden.

INTRODUCTION: Adverse drug reactions (ADRs) are considered as major concerns in terms of patient's safety and the quality of medical care. ADRs are responsible for additional cost, increased length of hospital stay, poor treatment outcome and reduced compliance for the patients [1, 2]. Skin is the major target organ for ADR. Cutaneous adverse drug reaction (CADR) is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and includes all adverse events related to drug eruption, regardless of etiology. CADRs are common among adverse drug reactions which account for patients' suffering, hospitalization and economic burden, and may sometimes be fatal [3, 4].

The incidence and clinical pattern of drug eruption depends on the choice and frequency with which

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different drugs are used. Studies have found the overall incidence of CADRs in developed countries between 1 to 3 %, but the incidence in developing countries is slightly higher between 2% and 5% [5]. The clinical spectrum of CADRs is very wide, the common CADRs are maculopapular rash, urticaria, fixed drug eruption (FDE), angioedema, and contact dermatitis. Although the majority of CADRs are mild with self-limiting course, few such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia are severe and potentially fatal [6].

Numbers of drugs have been reported to induce these skin reactions, particularly antimicrobials, anticonvulsants and nonsteroidal anti-inflammatory drugs. It is necessary that the physicians should have adequate knowledge about the CADRs of drugs that may help them in selecting safer drugs. The cost of ADRs to societyand healthcare systems with limited medical resources is remarkable but studies analysing cost of CADRs are scarce. The pattern of clinical presentation and drugs responsible for them also keep changing every year because of inflow of new drugs, changing prescription pattern, increased use of drugs for treatment of diseases, drug interactions, growing tendency indiscriminate self-medication in the population and lack of ADR reporting culture [7, 8]. Knowledge of drugs that can cause CADRs can help physicians in early diagnosis, prompt treatment and therefore can be helpful to society at-large. Keeping these observations in the background, the present study was undertaken to assess the causality, clinical pattern, causative drugs, cost, severity and histopathological patterns of CADRs among patients admitted in tertiary care teaching hospital.

MATERIAL AND METHODS: Present study was a single centre, prospective, cross-sectional observational study conducted in the Department of Dermatology and Venereology of a KEM hospital, Mumbai. Study was conducted over the period of one year from June 2015 - June 2016 after institutional ethics committee permission. After obtaining written informed consent, patients of either sex of all age group who developed suspected CADRs admitted or referred from other wards in skin ward were included in the study. Patients with reactions where the drugs taken were not known or unclear drug history, patients who complain of only symptoms *e.g.* Itching, without visible skin lesions, CADRs due to drug abuse and errors in drug administration, those whose lesions were turned out to be disease related on close examination *e.g.* Viral exanthemas, rash due to rickettsial infection, collagen vascular disease *etc*. Subjects who had consumed indigenous treatments (ayurvedic, homeopathic *etc*.) were excluded from the study.

A thorough clinical evaluation was done with the help of expert dermatologists to assess the pattern, extent and severity of the reactions. For each patient, a detailed history was elicited regarding drug, route of administration, temporal correlation to drug intake and onset of symptoms, improvement of lesions after dechallenge, previous allergic history, *etc.* and records available with the patients were scrutinized to collect all relevant data. The causal relationship with the offending / suspected drug(s) was established (as certain, probable, possible, unlikely, conditional or unclassifiable) as per the WHO-UMC (Uppsala Monitoring Centre) causality assessment scale [9]. Re-challenge test to confirm the causative drug was not done due to ethical considerations. Severity of ADRs was graded as per scale developed by Hartwig *et al*., as mild, moderate and severe [10]. In addition, histopathology reports were obtained from the patients in whom biopsy was done by treating dermatologist.

The costs were calculated from the patients' perspective. Drugs that were provided from the hospital pharmacy and investigations which were free of charge were not considered in the cost calculations. The expenses incurred due to investigations carried out outside the hospital or drugs purchased from outside and cost of travel were included in direct cost. Loss of wages of patient and relatives during the period of hospitalisation of was considered as indirect cost.

Statistical Analysis: Collected data was analysed using descriptive statistics. All the documented data were analyzed for type of CADR, gender and age prevalence, common clinical pattern of the lesion, causality, severity, common drug and drug class involved and relationship between above factors. The results are depicted in the form of

tables and graphs. Statistical analysis was done using Microsoft Excel 2013 and SPSS version 23.

RESULTS: Total of 525 patients was admitted to the Department of Dermatology during the study period *i.e.* from June 2015 to July 2016, of which 47 patients were diagnosed as cutaneous ADRs. Hence 8.9% of the hospitalized patients in the Department of Dermatology were admitted due to cutaneous ADRs. Eight cases were excluded from further analysis as 2 refused to give consent, 1 case was diagnosed as having lupus erythematosus, 4 patients gave incomplete history, and 1 patient gave history of consumption of Ayurvedic medication regularly. The remaining 39 were included in the final evaluation giving prevalence of 7.4%. Of the total 39 cases, 24 (61.54%) were males and 15 (38.46 %) were females. The male to female ratio was 1:0.63. Maximum number of cases (19) were seen in the age group 21 - 40 years followed by the age group 41 - 60 years (12). After causality assessment, 23 cases (58.98 %) were found to be of probable type and remaining 16 cases (41.02%) were assessed to be of possible type. Details of the clinical pattern of CADRs are presented in **Fig. 1.** The most common reaction pattern encountered in IPD patients was Steven Johnson syndrome (18, 46.15 %) followed by Maculopapular drug rash (8, 20.51%) and drug reaction with eosinophilia and systemic syndrome (6, 15.38%). During the study period 16 (53.3%) patients were on single drug, rest were taking multiple drugs.

There were total 55 drugs responsible for CADRs belonging to mainly three major classes, *viz* Anti-epileptic (32.72%), anti-microbial (29.09%) and NSAIDs (21.81%). The most frequent offending drug responsible for CADRs was Phenytoin (18.18%) followed by paracetamol (10.91%) and Carbamazepine (7.27%). The details of causative drugs with gender distribution and clinical patterns are presented in **Table 1** and **Table 2.**

TABLE 1: COMMON CAUSATIVE DRUGS FOR CADRs (%), n=55

Causative drug	Male (%)	Female (%)	Total (%)
Phenytoin	4 (7.27)	6 (10.91)	10 (18.18)
Paracetamol	5 (9.09)	1 (1.82)	6 (10.91)
Carbamazepine	2 (3.64)	2 (3.64)	4 (7.27)
Indomethacin	2 (3.64)	1 (1.82)	3 (5.45)
Ofloxacin	0 (0)	3 (5.45)	3 (5.45)
Cotrimoxazole	2 (3.64)	0 (0)	2 (3.64)
Diclofenac	0 (0)	2 (3.64)	2 (3.64)
Ibuprofen	1 (1.82)	1 (1.82)	2 (3.64)
Lamotrigene	0 (0)	2 (3.64)	2 (3.64)
Amoxicillin +Clavulanic acid	1 (1.82)	1 (1.82)	2 (3.64)
Sulfasalazine	2 (3.64)	0 (0)	2 (3.64)
Other drugs *	13 (23.64)	4 (7.27)	17 (30.91)
Total	32 (58.18)	23 (41.82)	55 (100)

* Other drugs (n = 1) included

TABLE 2: COMMON CAUSATIVE DRUGS AND CLINICAL PATTERN OF CADRs (%), (n = 55)

Causative Drugs	SJS	MPR	DRESS	FDE	PS	AE	Total
Phenytoin	5 (9.09)	4 (7.27)	1 (1.82)	-	-	-	10 (18.18)
Paracetamol	3 (5.45)	-	-	-	1 (1.82)	2 (3.64)	6 (10.91)
Carbamazepine	1 (1.82)	1 (1.82)	2 (3.64)	-	-	-	4 (7.27)
Indomethacin	1 (1.82)	-	2 (3.64)	-	-	-	3 (5.45)
Ofloxacin	3 (5.45)	-	-	-	-	-	3 (5.45)
Cotrimoxazole	2 (3.64)	-	-	-	-	-	2 (3.64)
Diclofenac	2 (3.64)	-	-	-	-	-	2 (3.64)
Lamotrigine	2 (3.64)	-	-	-	-	-	2 (3.64)
Ibuprofen	1 (1.82)	-	1 (1.82)	-	-	-	2 (3.64)
Amoxicillin + Clavulanic acid	-	2 (3.64)	-	-	-	-	2 (3.64)
Sulfasalazine	-	-	-	1 (1.82)	1 (1.82)	-	2 (3.64)
*Others drugs	7 (12.73)	3 (5.45)	3 (5.45)	3 (5.45)	1 (1.82)	-	17 (30.91)
Total drugs	27 (49.09)	10 (18.18)	9 (16.36)	4 (7.27)	3 (5.45)	2 (3.64)	55 (100)

* Other drugs (n = 1)

AE: Angioedema, DRESS: Drug reaction with eosinophilia and systemic symptoms, FDE: Fixed drug eruption, MP Rash: Maculopapular rash, PSR: Photosensitivity reaction, SJS: Steven johnson syndrome.

The severity of reactions was graded as mild, moderate, and severe using Hartwig's scale. Out of 39 cases, 26 belonged to severe grade (66.67%) while remaining 13 were of moderate grade (33.33%). There was no mortality observed. Most of the CADRs caused by Antiepileptics and NSAIDs belonged to severe category. **Fig. 2** in this figure total number is 39 and not 55 because few patients were taking multiple drugs belonging to same class (*e.g.* antitubercular, antiepileptic drugs).

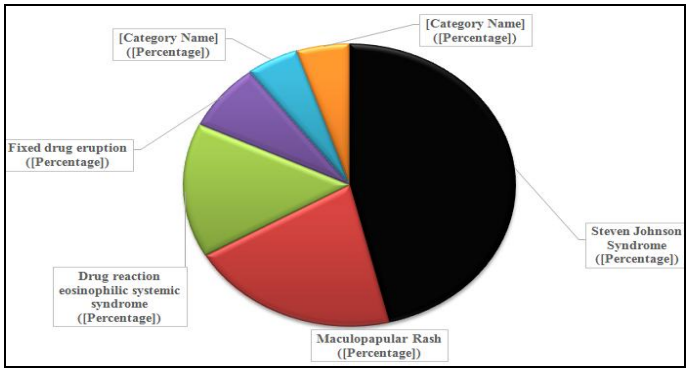

FIG. 1: CLINICAL PATTERN OF CADRs

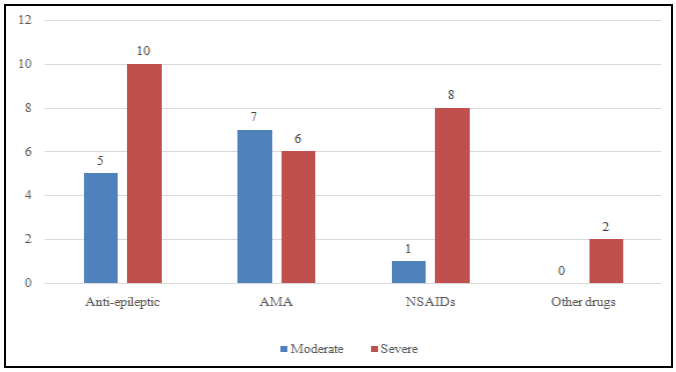

FIG. 2: DRUG CLASS AND SEVERITY OF REACTIONS (n = 39)

Histopathological examination is done to confirm the clinical diagnosis by dermatologists for CADRs. In this study histopathology reports for 29 cases of CADRs were available which were analysed.In all the cases examined, the diagnosis made initially after clinical examination remained same after histopathological examinations. The common features and patterns observed are presented below in tabular form in **Table 3** and **Fig. 3a - 3e** [11].

TABLE 3: COMMON FEATURES OF CADRs SEEN ON HISTOPATHOLOGICAL EXAMINATIONS

Clinical pattern	SJS (13)	MP (7)	DRESS (6)	PSR (2)	FDE (1)
Superficial perivascular lymphocytic lymphocyte, eosinophil	13	7	6	2	1
Keratinocyte necrosis	13		3	2	1
Basal layer degeneration	13	7	-	-	1
Sub epidermal spilt	13	-	-	-	-
Papillary dermal spongiosis	11	6	-	-	-
Pigment incontinence	11		-	-	1
Parakeratosis	5	5	2	1	-
Epidermal acanthosis with spongiosis	-	5	6	2	-
Lymphocytic exocytosis	-	5	5	-	-
RBC extravasation	-	7	6	-	-
Focal interphase change	-	-	4	2	-

DRESS: Drug reaction with eosinophilia and systemic symptoms, FDE: Fixed drug eruption, MP Rash: Maculopapular rash, PSR: Photosensitivity reaction, SJS: Steven johnson syndrome.

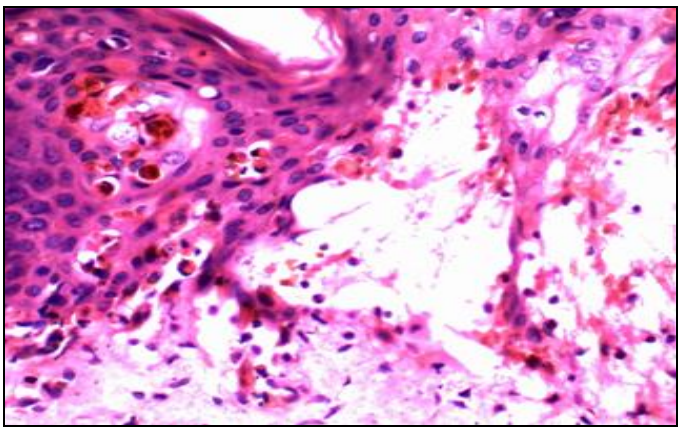

FIG. 3A: STEVEN JOHNSON SYNDROME (40X)

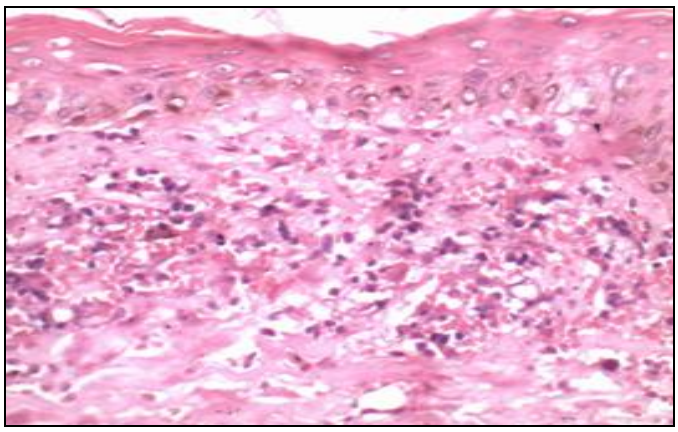

FIG. 3B: MACULOPAPULAR DRUG RASH (40X)

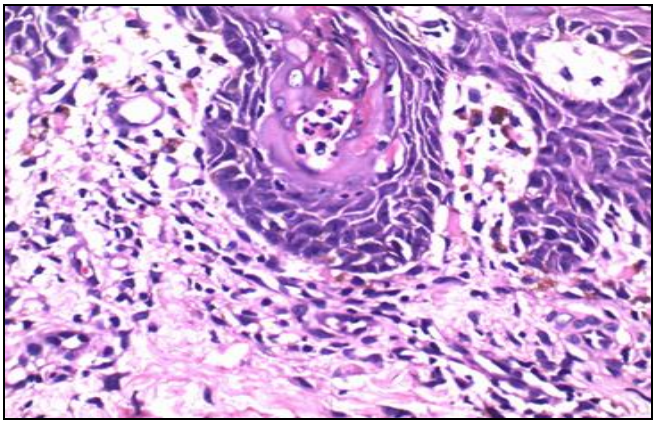

FIG. 3C: DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (40X)

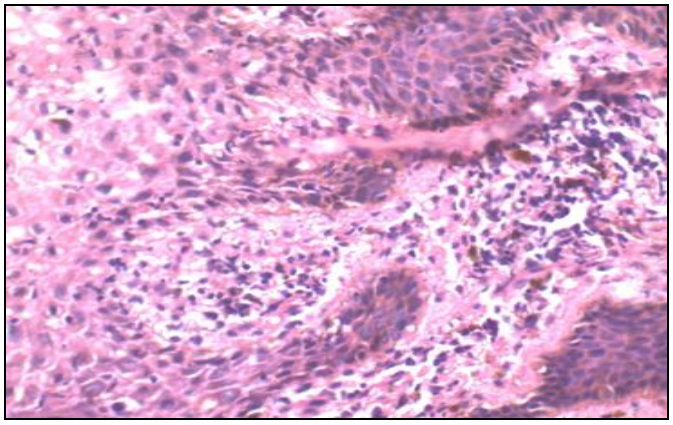

FIG. 3D: PHOTO SENSITIVITY REACTION (40X)

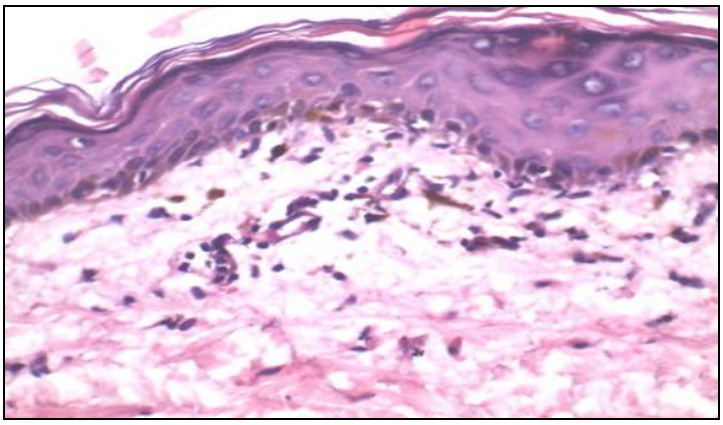

FIG. 3E: FIX DRUG ERUPTION (40X)

Total cost borne by all patients was Rs. 2,58,327, so the average cost of hospitalization was Rs. 6,623.77 (Rs 2,58,327/39 cases) which is further divided into average direct cost (Rs. 3,528.64) and average indirect cost (Rs 3,096.92).

Total hospitalisation days were 482 for 39 cases, hence the average cost of hospitalization per day was Rs 535.95. Other details of the cost segregation under various headings are represented in **Table 4**.

TABLE 4: COST ANALYSIS OF CADRs

	Cost head (in Rs)	Mean	S.D.	Minimum	Maximum
A	Investigations	930.13	1393.35	80	6135
B	Drugs	1844.31	2018.94	0	11000
	Medical cost (A+B)	2549.62	3161.87	180	17135
C	Travel	761.90	1123.93	0	5200
D	Direct (A+B+C)	3528.64	3997.07	180	18135
E	Indirect	3096.92	4632.46	0	26000
	Total (D+E)	6623.77	6949.91	455	29535

DISCUSSION: Regular studies on CADRs in each region are important to document the changes in the clinical patterns and to have knowledge regarding the culprit drugs which will help clinicians to anticipate and modify the prescription pattern. The present study in which we evaluated 39 hospitalized patients of CADRs, showed the clinical patterns, causative drugs / classes *etc.* similar to previous studies conducted in other regions of India. The proportion of patients of CADRs among all patients hospitalized in Dermatology department observed in our study was 8.9%. It was similar to that seen in study by Noel *et al*., but higher as compared to studies conducted outside India [12]. Reports for incidence of CADRs in male and female population are conflicting. Female preponderance was found in a study conducted by Mokhtari *et al*., in Iran [13]. Most of the studies conducted in India for inpatient and outpatient set up have shown male to be affected more than

female. In our study the male to female ratio was 1:0.63 and most of the patients belonged to age group of 21 to 40 years which is in accordance with another study conducted in inpatient and severe CADRs patients that also reported similar observations [12, 13]. The age group of 21 - 40 years coincides with the higher Indian population in this age group.

Different scales / algorithms are used for assessment of ADRs which includes Naranjo algorithm, WHO scale, French algorithm, RUCAM algorithm, and Hartwig scale. We have used WHO Scale for assessing causality of CADRs as it simple and widely used scale. Treating physicians at our hospital rarely carry re-challenge test for the confirmation of CADR. It has to be done with great caution and only if extremely necessary, because re challenge test may cause severe or even fatal reactions. Most of the CADRs in our study were designated as probable (53.33%) or possible (43.67%). Study by Noel *et al.,* like ours which included inpatients and used WHO scale for causality assessment reported 80% probable and 18% possible reactions [12].

Previous studies conducted in inpatient have classified CADRs in various ways. In our study SJS was most common CADR observed followed by MP and TEN similar to that reported by Sharma *et al*.,[13] However Noel *et al.,* reported most common type of CADR as MP followed by SJS and FDE for inpatients [12]. A study conducted in Iran by Mokhtari *et al.,* showed that the primary CADRs for which most patients admitted was maculopapular rash, however after the final diagnosis, the most prevalent clinical pattern was SJS followed by exanthematous drug eruptions and TEN [14]. This variation in clinical pattern of CADRs could be due to different patterns of drug usage and different ethnic group characteristics within as well as outside the country.

Among the etiological drugs, antiepileptics, mainly phenytoin and carbamazepine were responsible for the majority (33%) of the CADRs. The next major group of drugs implicated was antimicrobial agents (29%), mainly cotrimoxazole and ofloxacin followed by NSAIDs (22%), mainly paracetamol. Last two classes of drugs *i.e.* antimicrobials and $NSAID_S$ are commonly available over the counter drugs. Phenytoin, the commonly prescribed antileptic in our country was the culprit for maximum cases of SJS and MP. Paracetamol, cotrimoxazole and ofloxacin were also involved in maximum cases of SJS. Previous Indian study in hospitalised patients have shown antimicrobial *viz*. cephalosporins and fluoroquinolones (45%) whereas study conducted in Iran showed anticonvulsant drugs (52%) *viz* lamotrigine, carbamazepine to be the major causative agents for CADRs in hospitalised patients [12, 13, 14].

Most of the reactions for which patients admitted were of severe category (66.67%). Cases, the suspected drug was withdrawn and the patients were treated symptomatically and closely monitored till discharge.

In the clinical practice most of the time diagnosis of CADR is based on clinical presentation and history. Because of the wide spectrum of clinical presentations, drug eruptions are biopsied often for histopathology mostly to exclude differential diagnosis. The histopathologic patterns of cutaneous drug eruptions, is commonly associated with combination of different patterns in a single specimen. But it's importance is limited by vagueness in description and overlapping histopathological findings in different patterns of CADRs. In the study conducted by Cupolilo *et al*., involving both indoor and outdoor patients, the most frequent histopathological pattern was vacuolar interface dermatitis (41.9%). However clinical pattern seen in their study was mainly papular scaly eczema and erythema multiforme with most frequently involved drug being captopril [15]. A study conducted by Weyers *et al*., in which authors examined 300 consecutive cases [16] and a study conducted by Weinborn *et al.,* in which authors examined 106 slides [17] retrospectively, authors concluded that there was marked overlap of histological features. Thus it is often difficult to attach individual cases to one of the set of patterns. Our study also showed overlap of histopathological findings, thus making it difficult to assign a unique finding to one clinical pattern.

In addition to mortality and morbidity risks, CADRs also constitute a sizeable healthcare cost. The average cost of hospitalization incurred for CADRs in this study was Rs 535.95 per patient per

day. These findings are similar to the previous study conducted by Lee *et al.,* in Singapore[18]. However in a study conducted by Shah *et al* the average cost for CADRs for hospitalized patients was Rs. 264. [19] The difference may be attributed to prices of drug, investigations, wages, types & severity of reactions included in the study. In our study higher average cost incurred by hospitalized patients could be mainly due to the purchase of medicines from private pharmacy as many of the drugs were not available in the hospital pharmacy (where drugs are provided free of cost) and also as a result of loss of daily wages of participant/caretaker for longer period.

Limitations of the Study: The study was conducted in a single centre for the period of only one year which resulted in smaller sample size. 'Re-challenge' was not done due to ethical consideration which may result in overestimation of drug reactions. Follow up and monitoring of the patients was not done. Few patients were taking multiple drugs, so it was difficult to assign causality. Majority of patients visiting government run hospital belong to relatively poor socio-economic status and prescription pattern is also different than private health care set up mainly due to cost factor, so it may difficult to extrapolate findings. Due to same reasons, CADRs due to newer and expensive drugs was limited. Preventability and cost borne by hospital was not assessed.

CONCLUSION: In our study, most common type of CADRs found were similar to that seen in previous studies (Steven Johnson syndrome and Maculopapular rash). The most common causative class of drug found to be responsible was antiepileptics while it was antimicrobials in most of the other studies. The initial diagnosis of CADRs done after clinical examination remained same after histopathological examinations. Knowledge about the varied clinical presentations and the common putative drugs for CADRs will enable physicians to recognise, diagnose and institute timely measures, such as withdrawal of drugs, specific treatments and specialised care. It will also help in reducing the cost of treatment.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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