

# Comparison of Clinico-Epidemiological Features of Cutaneous Adverse Drug Reactions

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## ABSTRACT

### BACKGROUND

Cutaneous adverse drug reactions are an important group of disorders which pose considerable amount of diagnostic and therapeutic challenges. The incidence of CADR is estimated to be 1 - 2 % in the general population. We wanted to compare the clinico-epidemiological features of cutaneous adverse drug reactions in children and adults.

### METHODS

The study sample comprised of two hundred and twenty patients of CADR over a period of one and a half years. Patients were assessed using the WHO based algorithm of causality assessment of adverse drug reactions.

### RESULTS

222 rashes were seen in 220 patients and 315 drugs were implicated. The incidence of CADR among dermatology patients was 10.18 per thousand patients. The incidence of CADR among adults and children was 10.15 and 10.34 per thousand patients respectively. Out of the two hundred and twenty cases, thirty five (15.9 %) were in the paediatric age group (< 18 years of age). The most common cutaneous adverse drug reaction seen in our patients was maculopapular rash which was seen in 22 % patients. Antimicrobials were found to be the most common cause of CADR in both adults and children, while drugs acting on the central nervous system were a close second. When rashes were taken individually, antimicrobials were the most common cause of maculopapular reactions, urticaria and toxic epidermal necrolysis in both children and adults. Acneiform eruptions were caused by steroids in 82 % of cases. Although fixed drug eruptions were most commonly caused by antimicrobials in adults (especially quinolones and nitroimidazoles), NSAIDs particularly nimesulide was also implicated in a substantial number of cases.

### CONCLUSIONS

Newer antibiotics like cephalosporins are being used more often and thus a higher number of adverse drug reactions are seen with them. Therefore it would be useful for every individual institution to maintain a drug reaction registry.

### KEYWORDS

Cutaneous Adverse Drug Reaction, Maculopapular Reactions, Urticaria, Toxic Epidermal Necrolysis

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*DOI: 10.18410/jebmh/2020/527*

*How to Cite This Article:*

*Rao MM, Reddy KR, Sravan C.  
Comparison of clinic – epidemiological  
features of cutaneous adverse drug  
reactions. J Evid Based Med Healthc  
2020; 7(44), 2550-2556. DOI:  
10.18410/jebmh/2020/527*

*Submission 12-07-2020,*

*Peer Review 24-07-2020,*

*Acceptance 28-09-2020,*

*Published 02-11-2020.*

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**BACKGROUND**

With an increase in the number of drugs, adverse drug reactions have become very common in recent times. Among them cutaneous reactions have been steadily gaining importance and constitute a major proportion of all the adverse drug reactions. Innumerable epidemiological and clinical studies have highlighted the various aspects of this disorder. A large amount of data on cutaneous adverse drug reactions is being constantly updated.

In spite of a large number of studies and case reports, the incidence of undesirable Cutaneous Adverse Drug Reactions (CADRs) is, at best, an approximation. In a large percentage of ambulatory patients the CADRs are mild and transient, and therefore go unnoticed by the patient and physicians. On the other hand, cutaneous symptoms of diseases that may appear to have a temporal relationship to drug therapy are often erroneously classified as drug eruptions.<sup>1</sup>

With the introduction of newer drugs, and increase in number of HIV positive patients, the scenario of CADRs is rapidly changing. The importance of factors affecting CADRs like age, intercurrent infections, genetic predisposition and many others are coming into limelight. Newer insights are developing in understanding the relationship between drugs and rash. Thus it has become imperative to know the new trends in cutaneous adverse drug reactions.<sup>2</sup>

Few prospective studies have been done in the Indian population with regards to causative drugs and appearance / type of rash.<sup>3</sup> Furthermore, there is a paucity of studies comparing paediatric and adult population with regards to cutaneous adverse drug reactions.

This study was thus undertaken to evaluate the various patterns of cutaneous drug reactions, compare drug reactions in children and adults, and to study the distribution and frequency of drug eruptions in relation to sex, route of administration, associated infections and other diseases.

**METHODS**

All patients attending the Department of Dermatology, suspected of having a cutaneous adverse drug reaction (CADR) were evaluated. All the various departments of the hospital were informed about the study not only at the beginning of the study but also at regular intervals thereafter to ensure that all cutaneous adverse drug reactions were referred to our department.

**Inclusion Criteria**

A causality assessment of suspected CADR based on the WHO algorithm was used, and only those with "certain", "probable", and "possible" association were included in the study.<sup>4</sup>

**Exclusion Criteria**

Drug eruptions to topical medications were not evaluated.

Those falling into the category of "unlikely", "conditional / unclassifiable", according to the causality-based algorithm were not included in the study.<sup>4</sup>

A stepwise approach was taken to evaluate the patients. This included an exhaustive history and clinical examination. An accurate drug history was obtained. Names of all the drugs and the duration of intake were noted. Attention was also paid to the sequence of events, to rule out other diseases mimicking drug rash. The underlying disease for which drug were taken was also noted. History of any previous drug allergies in self and family members, were also noted. All patients were counselled and advised HIV testing. However, the test was done only in those patients who gave consent for testing. CD4 counts were not done as a routine. However, if a patient had a test report of CD4 counts the same was noted. In systems review, specific attention was given to history of UTI (Urinary Tract Infection), URTI (Upper Respiratory Tract Infection) or other intercurrent infection.

A meticulous and thorough clinical examination was done, which was supervised by a senior dermatologist. Attention was paid to the site, nature and extent of rash, pattern of rash as to whether it was generalized, localized, flexural or sun exposed. Distribution of rash was noted. Any special or unusual finding was noted. Colour of rash and secondary changes (like necrosis or blistering) were documented. On general examination in addition to the general condition of the patient, attention was paid to the presence of features like lymphadenopathy, icterus and pyrexia. Routine investigations such as total count were done in all patients that were included. (special investigations were done in certain individuals based on the rash category). Based on the clinical and laboratory findings the rash was categorized into one of the various morphological types.

**Patch Testing**

Patch testing was done in cases of suspected fixed drug eruptions and maculopapular reactions. The drugs to be tested were diluted by mixing with white petrolatum jelly. White petrolatum jelly was chosen as the vehicle because most of the drugs are either easily dissolved or evenly distributed in this medium, as well as chances of reactions to petrolatum are also very less. The drugs were thoroughly mixed with petrolatum to prepare the antigen. The concentration of the drug to be tested in this study was 10 %. Upper back was chosen in case of maculopapular eruptions; while an old healed lesion of a fixed drug eruption preferably over trunk or limbs was chosen. Flexures, palms, soles and face were avoided. Two patches were put over two FDE (Fixed Drug Eruption) lesions, one containing the drug and one with plain white petrolatum jelly as a control, to rule out any irritation to the vehicle. The pastes were placed over the site and covered with a blotting paper, which was then covered with a piece of gauze and held in place with a micro pore tape. The patients were instructed to keep the patches in place for 48 hours and not to wet the patches till the final reading was taken. Advice was given to avoid friction, scratching of site or strenuous exercises causing

sweating. A second reading was taken the next day (at 72 hours). Any evidence of erythema, oedema or blistering, itching or irritation was noted and taken as positive, after comparing it with the control site for lack of symptoms / signs. The patient was blinded as to the nature of patches to avoid bias.<sup>5</sup>

### Prick Testing

For prick tests the drugs were diluted to 10 % in normal saline. A drop of solution was placed over the medial aspect of forearm and a superficial prick was given using a lancet. Both a positive control (histamine) and a negative control (saline) were also used alongside. It was read after 15 minutes. Appearance of wheal twice or more the size of histamine wheal, with saline being negative were taken as positive results.<sup>5</sup>

### Statistical Analysis

Statistical analyses were performed using Microsoft Access and the Statistical Package for Social Sciences (SPSS) version 11.0.

Comparisons were made after categorizing the data. The sample data was expressed using descriptive statistics such as mean, standard deviation, percentage, etc. the comparison between groups was carried out by chi-square test / Fisher's exact test for categorical variables.

## RESULTS

In a total of 220 cases, the incidence of CADR in the patients seen in the Department of Dermatology was 10.18 per thousand patients. The total number of adults (> 18 yrs. of age) registered in Dermatology OPD were 18,229. There were 185 adult patients with CADR in the study. Thus the incidence of CADR among adults was 10.15 per thousand patients. The total number of children (0 – 18 yrs. of age) registered in Dermatology OPD between June 2004 and Dec 2005 was 3382, and the number of children with CADR was 35. The incidence of CADR among children was 10.34 per thousand patients.

There were 35 children (15.9 %) belonging to the age group 0 – 18 yrs. and 185 adults (84.1 %) > 18 yrs. in age, among the CADR patients. The male to female ratio was 0.95:1 in this study, with 108 males and 112 females. The difference, however, was not statistically significant.

The most common cutaneous adverse drug reaction seen in our patients were maculopapular rash in 22 % (47 / 222), a similar pattern was seen in the adult age group.

Among the paediatric cases, the most common drug eruptions seen were maculopapular rash and toxic epidermal necrolysis (7 cases each). There were 6 cases each of fixed drug eruptions and urticaria, and 3 cases of Stevens Johnson syndrome.

Among the various CADR in adults and children the frequencies were similar in cases of maculopapular reactions, fixed drug eruptions, and Stevens Johnson syndrome.

As compared to adults, the frequency of TEN cases was found to be significantly higher in paediatric age group. Urticaria and erythema multiforme were also seen more in children than in adults.

Rash Type	Child N = 35 (%)	Adults N = 187 (%)	Total N = 222 (%)
Maculopapular	07 (20)	41 (22)	48 (22)
Fixed Drug Eruption	06 (17)	33 (18)	39 (18)
Urticaria	06 (17)	19 (10)	25 (11)
Stevens Johnson Syndrome	03 (09)	19 (10)	22 (10)
Drug Hypersensitivity Syndrome	01 (03)	17 (09)	18 (08)
Toxic Epidermal Necrolysis	07 (20)	10 (05)	17 (08)
Acne Form	00 (0)	15 (08)	15 (07)
Erythema Multiforme	02 (05)	06 (3.5)	8 (04)
Angioedema	01 (03)	05 (03)	6 (03)
Pruritus	00 (00)	03 (02)	3 (02)
Photosensitivity	00 (00)	05 (03)	5 (03)
Hyperpigmentation	01 (03)	02 (01)	3 (02)
Vasculitis	00 (0)	02 (01)	2 (01)
Exfoliative	01 (03)	02 (01)	3 (02)
Lichenoid	00 (00)	02 (01)	2 (01)
Papular	00 (00)	02 (01)	2 (01)
Ecematous	00 (00)	01 (0.5)	1 (01)
Hair Loss	00 (00)	01 (0.5)	1 (01)
Psoriasis Form	00 (00)	01 (0.5)	1 (01)
Ulcers	00 (00)	01 (0.5)	1 (01)
<b>Total</b>	<b>35</b>	<b>187</b>	<b>222</b>

**Table 1. Cutaneous Adverse Drug Reactions**

Rash	Age Group		Total	Chi-Square	Significance (P Value)
	Child N = 35 n (%)	Adult N = 187 n (%)			
Maculopapular	7 (20)	41 (22)	48	0.081	0.487
Ten	7 (20)	10 (05)	17	8.792	0.008
FDE	6 (17)	33 (18)	39	0.01	0.921
Urticaria	6 (17)	19 (10)	25	1.380	0.376
SJS	3 (09)	19 (10)	22	0.094	1.000
EMF	2 (05)	06 (3.5)	08	0.513	0.823
DHS	1 (03)	17 (09)	18	1.571	0.319
Others	3 (09)	40 (22)	43	3.188	0.074

**Table 2. Comparison of Common CADR between Adult and Paediatric Age Groups**

Rash Type	Sex		Total	Chi Square	Significance (p value)
	Male	Female			
Fixed Drug Eruption	27	12	39	7.694	0.006
Maculopapular	21	27	48	0.701	0.403
Stevens Johnson syndrome	14	8	22	2.069	0.15
Urticaria	10	15	25	0.933	0.334
Acneform	9	6	15	0.767	0.381
Drug Hypersensitivity Syndrome	6	12	18	1.948	0.163
Toxic epidermal necrolysis	6	11	17	1.403	0.236
Angioedema	4	2	6	0.762	0.379
Photosensitivity	3	2	5	0.245	0.679
Papular	1	1	2	0.001	0.979
Erythema Multiforme	1	7	8	4.448	0.025
Exfoliative	1	2	3	0.309	0.583
Pruritus	1	2	3	0.302	0.579
Hyperpigmentation	1	2	3	0.302	0.579
Lichenoid	1	1	2	0.001	0.979
Vasculitis	1	1	2	0.001	0.979
Ecematous	1	0	1	1.042	0.232
<b>Total</b>	<b>108</b>	<b>112</b>	<b>220</b>		

**Table 3. CADR among Males and Females**

Among the various rashes seen in males and females, the incidence of fixed drug eruptions was found to be significantly higher in males as compared to females. In case of erythema multiforme, however a trend towards significance was seen in females.

	Maculopapular		DHS		SJS		TEN		Urticaria		FDE		Others		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
DPH	9	39.1	8	34.8	5	21.7	1	4.3	0	0.0	0	0.0	0	0.0	23
CBZ	3	13.0	3	13.0	5	21.7	6	26.1	0	0.0	1	4.3	5	21.7	23
B-lactams	5	38.5	0	0.	3	23.1	1	7.7	3	23.1	1	7.7	0	0.0	13
Cephalosporin	1	10.0	0	0.0	1	10.0	4	40.0	3	30.0	0	0.0	1	10.0	10
Quinolones	4	18.2	0	0.0	3	13.6	1	4.5	2	9.1	8	36.4	4	18.2	22
PCM	3	25.0	0	0.0	2	16.7	0	0.0	2	16.7	4	33.3	1	8.3	12
Tetracyclines	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	5	100	0	0.0	5
NSAIDs	8	25.8	0	0.0	2	6.5	0	0.0	9	29.0	10	32.3	2	6.5	31

Table 4. Common Drugs Implicated and Associated CADR

Among the various drugs implicated, phenytoin was found to be a causative agent in mainly maculopapular reactions (9 / 23). Similarly carbamazepine was found to cause a significantly higher number of toxic epidermal necrosis (6 / 23) and Stevens Johnson syndrome (5 / 23). Tetracyclines were found to cause only fixed drug eruptions. NSAIDs caused mainly fixed drug eruptions, urticaria and maculopapular reactions. A high number of fixed drug reactions were seen in case of paracetamol and quinolones.

Drugs Implicated	Numbers
<b>Drugs Causing Urticaria</b>	
Antimicrobials	16
NSAIDs / Analgesics / Antipyretics	12
Others	8
<b>Total</b>	<b>36</b>
<b>Drugs Causing Urticaria in Children</b>	
Antimicrobials	
Ampicillin	2
Cephalosporins	2
Gentamicin	1
Tinidazole	1
Norfloracin	1
NSAIDs / Antipyretics	
Nimesulide	1
Diclofenac	1
Paracetamol	1
<b>Total</b>	<b>10</b>
<b>Drugs Causing Stevens Johnson Syndrome</b>	
Drugs acting on CNS	
DPH	5
Others	11
Antimicrobials	13
others	9
<b>Total</b>	<b>38</b>
<b>Drugs Causing Stevens Johnson Syndrome in Children</b>	
Antimicrobials	
Penicillins	2
Sulfa	1
drugs acting on CNS	
Phenobarbitone	1
Carbamazepine	1
Paracetamol	1
<b>Total</b>	<b>6</b>
<b>Drugs Causing Toxic Epidermal Necrolysis.</b>	
Antimicrobials	15
Drugs acting on CNS	
Carbamazepine	6
Phenytoin	1
Others	3
<b>Total</b>	<b>25</b>
<b>Drugs Causing Toxic Epidermal Necrolysis in Children</b>	
Antimicrobials	
Cephalosporins	2
Amoxicillin	1
Sulfa	1
Pyrimethamine	1
Carbamazepine	3
Chlorpheniramine maleate	1
Phenylpropanolamine	1
<b>Total</b>	<b>10</b>
<b>Drugs Causing Drug Hypersensitivity Syndrome</b>	
Drugs acting on CNS	
DPH	8
CBZ	4
Phenobarb	1
Dapsone	2
Others	11
<b>Total</b>	<b>26</b>

Table 5. Drugs Causing Urticaria

With regards to site of involvement in cases of FDE, no particular pattern was noted. Most of the common drugs causing FDE involved trunk and limbs. 3 cases of lip involvement were noticed in cases of nimesulide induced FDE. Involvement of genitalia was seen in nimesulide, quinolones, nitroimidazole and cotrimoxazole induced FDE.

Around 25 cases of urticaria (11 %) due to drugs have been noted in this study. The common causative drugs in urticaria were antimicrobial drugs (44 %), followed by analgesics and antipyretics (33 %). Antimicrobials were the most common cause of urticaria in children especially beta lactams and cephalosporins while analgesics and antipyretics constituted the next most common cause.

Malignancies of central nervous system and haematogenous origin were most frequently associated with CADR. Drug hypersensitivity was the most common CADR seen in relation to malignancies.

Infections were found to be commonly associated with maculopapular drug reactions especially upper respiratory tract infections. Also found to be significantly associated were CNS (Central Nervous System) disorders.

Fixed drug eruptions were also found to be commonly associated with infections.

Underlying HIV infection was found in 15 patients of drug rashes. 42 were found to be negative for among HIV positive patients the most common rash seen was maculopapular. Only 4 patients with severe reaction [SJS (Stevens Johnson Syndrome), TEN (Toxic Epidermal Necrolysis), DHS (Drug Hypersensitivity Syndrome)] were seen, all of whom recovered fully.

## DISCUSSION

Adverse drug reactions are an important and common problem in both inpatient and outpatient setting. It is important to keep oneself updated with the knowledge on latest trends in drug reaction with regards to the newer drugs, newer manifestations of older drugs, diagnosis, and management of these drug reactions.

The incidence CADR in this study was found to be 10.18 per thousand outpatients. This is in conformity with most of the reported studies on CADR from India. Mehta et al reported an incidence of 10 per thousand, and Mani et al reported an incidence of 12 per thousand.<sup>3</sup> All the above studies were done in a population that included both inpatients and outpatients. Studies done on hospitalized patients have generally shown a higher incidence 20 - 22 per thousand. The reason for this is perhaps due to the fact that inpatients in general more often tend to have associated

underlying co-morbid conditions such as infections, autoimmune disorders and malignancies which are known to predispose to drug reactions.<sup>2</sup> The hospitalized patients in these studies were also on multiple drugs averaging 6 - 7 per patient, which in itself is a risk factor for CADR.

In this study the incidence of CADR in children, 10.34 per thousand, was similar to that in adults, 10.15 per thousand. In the meta-analysis by Impicciatore,<sup>6</sup> the reported incidence of total ADRs (Adverse Drug Reaction) in paediatric outpatients were 14.6 per thousand, with majority having CADR. The lower incidence of CADR in our study as compared to above may be because of minor CADR being dealt by paediatricians themselves.

The male: female ratio of patients with CADR in this study was 0.95:1. Though the frequency of CADR was higher in the females the difference was not significant. Most of the studies reported in literature show a higher number of females as seen in our study. Although not entirely clear, these differences have been attributed to gender-related differences in pharmacokinetic, immunological and hormonal factors as well as differences in the use of medications by women compared with men.

Among the paediatric patients eighteen were females and 17 were males; however a higher number of males (10) were seen as compared to females (9) in the age group of 0 - 10 years, while the numbers of females were more in the age group of 11 - 18 yrs. with 7 males and nine females. This was similar when compared to the study by Sonntag et al,<sup>7</sup> who reported a male preponderance in CADR in the age group below ten years and a female preponderance in children above ten years. No clear explanation was however given for the above findings.

In this study 35 cases were in the paediatric age group (0 - 18 yrs.) and constituted 15.9 % of all the cases. Of the various types of cutaneous adverse drug reactions in all age groups, maculopapular rashes were found to be the commonest with 47 patients (comprising 21 % of the total). The commonest types of CADR in children reported in literature are also similar to that seen in our study.<sup>8</sup>

In this study the various types of CADR were similar in adult and paediatric age groups. Maculopapular drug rash was the commonest (22 % and 20 % in adult and paediatric age groups respectively). However, the incidence of TEN was found to be significantly higher in paediatric age group (20 %) as compared to adult patients (5 %). Fixed drug eruptions were also common in both adult and paediatric age groups. However, the commonest cause of FDE was antimicrobials in adults but paracetamol in children.

A retrospective study by Khoo et al in Singapore comprising 111 cases of CADR in children (age below 12 years), reported urticarial / angioedema to be the most common reaction (45 %), followed by maculopapular rash (in 32 %), and fixed drug eruptions in 12 % of patients.<sup>9</sup>

The high incidence of TEN in children in this study may be attributed to the fact that, being a tertiary care institute, severe cases of drug reactions were referred here from other hospitals. Also due to the proximity to a major neuropsychiatry centre, mainly antiepileptic induced TEN and SJS were seen.

The most common cause of maculopapular rash in this study were drugs acting on CNS (28 %), (mainly phenytoin), followed by antimicrobial drugs (19 %) and NSAIDs (19 %). This was similar to various other studies.<sup>7,9</sup> Antimicrobials were most common cause in both children and adults. This was in concordance with the studies of CADR in children done by Sharma et al in India<sup>10</sup> and Khoo et al in Singapore,<sup>9</sup> wherein the most common cause of maculopapular rash were antimicrobial drugs, followed closely by drugs acting on the CNS.

The high number of drugs acting on CNS as a cause of maculopapular rashes could partially be explained by the fact that a major neuropsychiatry centre is situated close to our hospital.

Fixed drug eruptions were encountered in 39 patients (17 %) in this study (Photo 12). Among them 33 were adults (85 %) and 6 were children (15 %) In concordance with other studies<sup>6</sup> antimicrobials constituted the major causative drugs (53 %), followed by NSAIDs / analgesics / antipyretics (33 %), in adults. However in children the most common cause was paracetamol with 3 cases attributed to it.

In the studies by Sharma et al<sup>10</sup> and Joseph G Morelli et al<sup>11</sup> (involving children and adolescents), antimicrobials were the most common cause of FDE especially sulfonamides followed by the non-narcotic analgesic and antipyretic drugs. Apart from drugs, food additive like gelatine was also found to cause fixed drug eruption in a case which was confirmed with oral provocation.

Around 25 cases of urticarial (11 %) and 6 cases of angioedema to drugs have been noted in this study, which comprise a total of 13 % of cases, similar to that noted in study done by Sharma et al<sup>10</sup> 19 were adults and 6 were children. The most common cause of urticaria was antimicrobial drugs, followed by analgesics and antipyretics in both adults and children. This was similar to other studies. 6 cases (17 %) of urticaria were seen in the paediatric age group. Antibiotics (ampicillin and cephalosporins) were the most common cause, followed by NSAIDs / antipyretics. This was similar to a study by Sharma et al.<sup>10</sup>

A total of 12 cases (34 %) of toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme were seen in the paediatric age group. This was less as compared to the study by Sharma et al,<sup>12</sup> who reported these reactions comprising 42 % of the total cases. The causes of these reactions in this study were mainly antimicrobials (cephalosporins and penicillin's) (50 %) and antiepileptics (25 %), which was in concordance with other studies.<sup>9</sup>

Drug hypersensitivity was seen in 8 % of cases (18 patients), which comprised of 17 adults and 1 child (Photo 15). As has been described earlier, anticonvulsants were the most common cause, among both the groups in this study also.<sup>13</sup>

A total of 265 drugs were implicated in 185 adults and 50 drugs were implicated in the 35 cases of CADR in children. As seen in other studies,<sup>29,133,140</sup> antimicrobials were the commonest implicated drugs followed by drugs acting on CNS and NSAIDs / analgesics and antipyretics. Of the various drugs implicated in children, 48 % (24 out of 50) were antimicrobials, while in adults it accounted for only 24 % of the drugs. "CNS drugs" accounted for 24 % of all drugs

in children and 22 % in adults. Non-narcotic analgesics, antipyretics and narcotic analgesics formed the third commonest group with 18 % and 15 % of drugs in children and adults respectively. Antitubercular drugs constituted 13 % of drugs in adults while it formed only 2 % of all the drugs in children.

The high incidence of CADR to antimicrobials in children is a common finding in many other reported studies.<sup>14</sup> This could be explained by the fact that the most common indication for drug therapy in children is infections (such as upper respiratory tract infections, fever, or gastroenteritis). Therefore, antimicrobials would, in all likelihood, be the most common group of drugs prescribed in this age group and thus contribute to the maximum number of CADR.

In this study, de-challenge was found to be positive in 194 patients, unknown in 8 patients who were lost for follow-up, negative in 2 patients as they died of complications and not done in 16 patients (all of minor acneiform eruptions, where continuing the drug was indispensable).

Re-challenge in the form of provocation was attempted in 25 patients, 21 of whom were positive (84 %) and 4 negative. Patch test was attempted in 5 cases of fixed drug eruption, out of which 3 were positive (60 %) and 2 were negative. According to studies, patch test has been found to be safe, but reliable only in some types of drug eruptions, mainly fixed drug eruptions, with positive results as high as 75 %, <sup>15</sup> 72.7 %<sup>16</sup> and as low as 10.8 %.<sup>17</sup>

Thus a definite diagnosis of drug eruption due to a particular drug was reliably made in 24 patients (11 %), 129 cases were probable (59 %) where re-challenge could not be attempted and 67 cases were possible (30 %), where more than one drug was implicated.

As compared to above, in the study by Puavilai and Choonhakarn involving 132 patients, a definite diagnosis of drug eruption was found in 19.6 % patients, probable in 43.9 % and possible in 34.8 % patients.

## CONCLUSIONS

Antimicrobials are the most common cause of CADR, in both adults and children, while drugs acting on the central nervous system are a close second. Antimicrobials are the most common cause of maculopapular reactions, urticaria and toxic epidermal necrolysis in both children and adults.

Antiepileptics especially phenytoin is the most common cause of drug hypersensitivity syndrome. Systemic steroids are the most common cause of acneiform eruptions. Though antimicrobials are the most common cause of FDE, NSAIDs particularly nimesulide are also a very common cause of FDE. Paracetamol is the most common cause of FDE in children. Maculopapular rash and drug hypersensitivity reaction are the most common type of CADR caused by phenytoin. Fixed drug eruption is the most common type of CADR caused by tetracycline. The most common type of CADR to NSAIDs is urticaria and fixed drug eruptions. Upper respiratory and urinary tract infections are significantly associated with the occurrence of maculopapular type of

CADR. Maculopapular reactions are the most common type of CADR in patients with HIV disease.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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