

Cutaneous Adverse Drug Reactions: Analysis of Reports at the Drugs, Poison Information, and Pharmacovigilance Center (2002 To 2022) at the University of Benin Teaching Hospital

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ABSTRACT

Background: Cutaneous adverse drug reactions are undesirable changes to the skin and subcutaneous tissue. The reporting pattern of these reactions in Nigeria, had hitherto focused on serious reactions, despite the varied presentation. This preliminary report is intended to describe the profile of cutaneous adverse reactions in an established local pharmacovigilance centre.

Methods: The study reviewed all the individual case safety reports of cutaneous adverse drug reactions submitted to the University of Benin Teaching Hospital's Drugs, Poison Information, and Pharmacovigilance Centre from 2002 to 2022. All reports were analyzed for age, sex, suspected medications, and details of the reaction and dates of the event and medication use. Causality assessment was conducted using the WHO assessment scale. Culprit medicines were classified using the WHO/ATC classification Level II and V.

Results: There were 408(39.1%) cutaneous adverse drug reactions reports found in the database with a mean age of 34.0(21.9%), a female preponderance 260(63.7%). Majority of the reporters were doctors 215(52.7%). These reactions comprised urticaria 68(16.7%), Steven Johnson Syndrome 62(15.2%), rashes 46(11.3%), angioedema 37(9.1%). Serious cutaneous adverse reactions, were reported more 196(48.0%) with 13 fatalities. Culprit medicines classes identified in the study were antimicrobials 222(54.4%), antineoplastics 27(6.6%). The main culprit medicinal products were Nevirapine 46(11.3%), sulphadoxine-pyrimethamine 41(10.0%), sulphamethoxazole-trimethoprim 20(4.9%), Lisinopril 17(4.2%) and artemether-lumenfatrine 16(3.9%).

Conclusion: Cutaneous adverse drug reactions are prevalent and constitute a notable health burden. Prominent drugs causing CADR were antimicrobials, antineoplastic and drugs acting on the renin-angiotensin system. Serious cutaneous ADR, such as SJS, erythema multiforme, and angioedema were significantly reported.

Keywords: Cutaneous adverse drug reactions, Pharmacovigilance, Skin and Subcutaneous tissue

INTRODUCTION

The skin is an easily recognizable organ in the body that has a myriad of protective and other functions (Del Pozzo-Magaña & Liy-Wong, 2022). It can also express unwanted and noxious effects of a drug; this is usually referred to as cutaneous adverse drug reaction. Adverse drug reactions has been defined by the WHO as a physiological response to a drug that is noxious, unintended and occurs at doses used in man for the prophylaxis, diagnosis or therapy of a disease or for the modification of physiological function (World Health Organization, 1972).

Cutaneous adverse drug reactions have also been described as undesirable changes in the skin and subcutaneous tissue structure, and function after drug exposure. Cutaneous adverse drug reactions ranges from mild sometimes self-limiting reactions to serious life threatening reactions such as the toxic epidermal necrolysis (TENS) (Marzano et al., 2016).

The incidence of cutaneous adverse drug reactions in inpatients had ranged from 0.4%-2.2% (Tian et al., 2015; Selvarajah & Choon, 2017). A cohort study of drug-induced hospitalized Nigerians revealed that cutaneous ADRs accounted for the highest number of deaths (28.6%). Skin and subcutaneous tissue system organ classifications (SOCs) were the most frequently reported SOC in a review of individual case safety reports (ICSRs) from Africa compared to the rest of the world (31.4%) (Ampadu et al., 2016). A review of all serious adverse drug reactions in the Nigerian National Pharmacovigilance database showed that the skin and subcutaneous tissue were the most affected organ (25%) (Ogar et al., 2019). Furthermore, an earlier study in the south-south zone of Nigeria had shown that skin and subcutaneous tissue had the highest reported ADRs during the period of the study accounting for 53.7% of all reports received during the period (Opadeyi et al., 2021).

The pathophysiological mechanisms of cutaneous adverse reactions have been described as mainly immune-mediated allergic reactions and non-immune mediated reactions and this can present as mild irritating skin lesions or severe and serious life threatening reactions such as the toxic epidermal necrolysis (TENS) which are frequently fatal (Marzano et al., 2016). Maculopapular rashes, pruritus and Steven Johnson syndrome have been described as frequent presentations as reported to a local pharmacovigilance database in India (Modi et al., 2019) and these were mainly to antibiotics and antiretroviral medications as seen in similar studies from Nigeria (Ogar et al., 2019). Adverse cutaneous drug reactions are also frequently seen

in dermatologic practice (2.9%) of common dermatoses seen in Nigeria at a scoping review (Henshaw et al., 2018).

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serious adverse drug reactions with limited data on the seemingly mild, but nevertheless uncomfortable mild reactions.

Information on the profile of cutaneous adverse drug reactions seen in a homogenous black population like Nigeria is sparse and local pharmacovigilance databases offer a veritable source of presenting such data. This study is intended to describe the cutaneous adverse drug reactions and the culprit medicines. In effect, this preliminary report will aid early identification and management of peculiar drug reactions in this environment.

MATERIALS AND METHODS

This was a retrospective analysis of all submitted individual case safety reports (ICSR) at the University of Benin Teaching Hospitals' Drugs, Poison Information and Pharmacovigilance Centre (DPIPC) which was established in 1989 (Isah & Olowofela, 2014). The UBTH is a tertiary health facility in Southern Nigeria.

Data source: The copies of ICSRs which had been reported to the DPIPC were evaluated. These reports are usually forwarded to the National Pharmacovigilance Centre and the local copies retained and processed in the center. Reports available for this study covered the period from January 2002 to November 2022.

Data analysis: All cutaneous adverse drug reactions in the local database were included. Information sought included, the age, (age group where age was not available), sex, the adverse reactions as stated, the dates of the event started and ended, seriousness of the reaction if stated, the details of the suspected drug- including the generic or trade name, dose, frequency route and the indication for treatment, dates of commencement and end of treatment. The reporter details and year of report noted.

The reactions as reported were subsequently coded as skin and subcutaneous tissues system organ class and described using the Medical dictionary for Drug Regulatory Activities (MedDRA) Preferred Term (Version 25) (Brown et al., 1999).

Serious adverse reactions were noted as reactions that resulted in hospitalization, prolonged hospitalization, life threatening, congenital anomalies or medical conditions requiring interventions, or death of the patient.

The data was reviewed by the authors and duplicates removed from the dataset, the implicated medicines were classified according to the WHO Anatomic Therapeutic Chemical classification level II and IV. Herbal medicines were not classified.

Causality assessment was done using the WHO-UMC scale for causality assessment (Naranjo et al., 1981; WHO-UMC, 2012). ADR were also categorized as serious and non-serious (Council for International Organizations of Medical Sciences, 1999). Data was analyzed using the IBM SPSS software version 21.0 and results are presented descriptively

Ethical approval (ADM/E 22/A/VOL. VII/148311668) was obtained from the hospital ethics and research committee.

RESULTS

A total of 1043 adverse drug reaction reports were obtained over the period, of which 408 (39.1%) were cutaneous adverse reactions. The mean age (SD) of the patients was 34.0(21.9) years and the age group of the reports had adults aged 18-44 years having the largest proportion 171 (41.9%), while children aged 2-11 years had 34(8.3%) reports. There were no reports of neonates (age 0-27 days) with cutaneous ADR. The reports had more females 260(63.7%) and most of the reports were from medical doctors 215(52.7%) Table 1.

Table 1: Characteristics of cutaneous adverse drug reactions reports at the Drugs Poison Information and Pharmacovigilance Center –UBTH from 2002 to 2022.

Characteristics	Frequency (%)
	n=408
Age group(years)	
0-27 days	0(0)
1-23 months	15 (3.7)
2-11years	34 (8.3)
12-17years	18 (4.4)
18-44 years	171(41.9)
45-64 years	96 (23.5)
65-74 years	23 (5.6)
≥75 years	12 (2.9)
Adults (age not stated)	36 (8.8)
Not stated	3 (0.7)
Sex	
Female	260 (63.7)
Male	140 (34.3)
Not Stated	8 (2.0)
Reporter category	
Medical Doctors	215 (52.7)
Pharmacist	185 (45.3)
Not stated	4 (1.0)
Nursing	1 (0.2)
Laboratory scientist	1 (0.2)
Pharmacologist	1 (0.2)
Drug Representative	1 (0.2)
Seriousness	
Yes	196 (48.0)
No	162 (39.7)
Not stated	50 (12.3)

The commonest cutaneous presentations were urticaria 68(16.7%) and Steven Johnson Syndrome (SJS) 62 (15.2%), Rash (unspecified) 46(11.3%), Angioedema 37(9.1%), Pruritus 20(4.9%) while Palmar-plantar erythrodysesthesia syndrome

was observed in 19(4.7%) of the cutaneous ADRs. (Table 2)

Regarding the outcome of the reactions, majority of the patients recovered fully, 159(39.0%), while there were 13 (3.2%) fatalities. These were Steven

Johnson's syndrome 3, Erythema Multiforme 2, Dermatitis Bullous -2, Angioedema-2, Generalized maculopapular rashes-2, Pruritis-1, and Urticaria-1. Serious ADRs occurred in 196(48%).

The implicated medicine classes and specific medications in this study were mainly antibacterials for systemic use 88(21.6%), antiprotozoals 77(18.9%) and antivirals agents for systemic use 57(14.0%), antineoplastics 27(6.6%) (Table 3).

Of the 196 serious adverse drug reactions observed in the study, the diagnoses with the highest proportions were Steven Johnson's syndrome 58(29.6%), angioedema 25(12.8%), urticaria 22(11.2%), Toxic Epidermal Necrolysis 14(7.1%) and rash 12(6.1%) and these reactions were mainly due to antibacterials for systemic use 49(25.0%),

antiprotozoals 39(20%), antiepileptics 15(7.7%), antivirals for systemic use 11 (5.6%) and drugs acting on the renin-angiotensin system 10(5.1%). Main suspected drugs include sulphadoxine-pyrimethamine 28(14.3%), sulphamethoxazole-trimethoprim 14(7.1%), carbamazepine 12(6.1%), ampicillin/cloxacillin 10(5.1%), lisinopril 9 (4.6%), Nevirapine 8(4.1%) among others. (Table 4)

Causality assessment was performed on the reports using the WHO causality assessment scales and it revealed that majority of the reactions were deemed possible 276(67.6%), others were probable 82(20.2%), certain 9(2.2%), while 36(8.8%) were unassessable, and 5(1.2%) were conditional.

Table 2: Clinical Presentation of the cutaneous adverse reactions at the Drugs, Poison Information, and Pharmacovigilance Center –UBTH from 2002 to 2022

Clinical presentation	Non-serious	Not stated	Serious	Frequency n=408(%)
Urticaria	41(25.3)	5(10)	22(11.2)	68(16.7)
Stevens-Johnson syndrome	4(2.5)	0(0)	58(29.6)	62(15.2)
Rash	16(9.9)	18(36.0)	12(6.1)	46(11.3)
Angioedema	11(6.8)	1(2.0)	25(12.8)	37(9.1)
Pruritus	13(8.0)	3(6.0)	4(2.0)	20(4.9)
Rash maculo-papular	11(6.8)	4(8.0)	5(2.6)	20(4.9)
Palmar-plantar erythrodysesthesia syndrome	14(8.6)	3(6.0)	2(1.0)	19(4.7)
Dermatitis bullous	6(3.7)	1(2.0)	10(5.1)	17(4.2)
Toxic epidermal necrolysis	1(0.6)	0(0)	14(7.1)	15(3.7)
Skin exfoliation	7(4.3)	1(2.0)	3(1.5)	11(2.7)
Rash erythematous	2(1.2)	1(2.0)	6(3.1)	9(2.2)
Rash vesicular	5(3.1)	1(2.0)	3(1.5)	9(2.2)
Lip swelling	3(1.9)	1(2.0)	3(1.5)	7(1.7)
Ecchymosis	2(1.2)	0(0)	4(2.0)	6(1.5)
Erythema multiforme	0(0)	0(0)	5(2.6)	5(1.2)
Rash pustular	3(1.9)	2(4.0)	0(0)	5(1.2)
Skin ulcer	2(1.2)	1(2.0)	2(1.0)	5(1.2)
Lichenoid keratosis	2(1.2)	0(0)	2(1.0)	4(1.0)
Dermatitis exfoliative	1(0.6)	0(0)	2(1.0)	3(0.7)
Dermatitis exfoliative generalised	2(1.2)	0(0)	1(0.5)	3(0.7)
Face oedema	1(0.6)	0(0)	2(1.0)	3(0.7)
Rash pruritic	3(1.9)	0(0)	0(0)	3(0.7)
Urticaria popular	2(1.2)	0(0)	1(0.5)	3(0.7)
Alopecia	0(0)	2(4.0)	0(0)	2(0.5)
Cheilitis	1(0.6)	0(0)	1(0.5)	2(0.5)
Exfoliative rash	0(0)	1(2.0)	1(0.5)	2(0.5)
Fixed eruption	0(0)	2(4.0)	0(0)	2(0.5)
Generalised bullous fixed drug eruption	0(0)	0(0)	2(1.0)	2(0.5)
Penile ulceration	0(0)	1(2.0)	1(0.5)	2(0.5)
Rash popular	1(0.6)	0(0)	1(0.5)	2(0.5)
Vaccination site urticaria	1(0.6)	0(0)	1(0.5)	2(0.5)
Others	7(4.3)	2(4.0)	3(1.5)	12(2.9)

Others include; Application site vesicles, hand dermatitis, lip blister, perioral dermatitis, purpura, Rash- morbiliform, papulosquamous, skin burning sensation, hyperpigmentation. Skin necrosis, SLE rash, Eyelid swelling.

Table 3: Medicines causing cutaneous adverse drug reactions reported to the UBTH's Drugs, Poison Information, and Pharmacovigilance Center from 2002 to 2022.

ATC Level II Drug class	Proportion n=408(%)	Most implicated drug per class
Jo1-Antibacterials for systemic use	88(21.6)	Sulphamethoxazole/Trimethoprim 20(22.7),
Po1- Antiprotozoals	77(18.9)	Sulphadoxine/Pyrimethamine 41(53.2)
Jo5-Antivirals for systemic use	57(14.0)	Nevirapine 46(80.7)
Lo1- Antineoplastic agents	27(6.6)	Capecitabine(48.1), docetaxel
Co9-Agents acting on the Renin-Angiotensin System	20(4.9)	Lisinopril 17
No3- Antiepileptics	16(3.9)	Carbamazepine 13
Mo1-Antinflammatory and antirheumatic products	15(3.7)	Diclofenac -9
Jo4- Antimycobacterials	12 (2.9)	Antituberculous combinations
No2-Analgesic	11(2.7)	Metamizole 2
Herbal medicines	9(2.2)	Herbal supplements
Bo1- Antithrombotic agents	6 (1.5)	Warfarin 3
Multiple drugs	5(1.2)	Multiple drugs
Ao2-Drugs for acid related disorders	5(1.2)	Omeprazole 4
Jo7-Vaccines	5(1.2)	Measles live attenuated 2
Co8- Calcium channel blockers	5(1.2)	Amlodipine 4
A10- Drugs used in diabetes	4 (1.0)	Glibenclamide 3
Bo3- Antianaemic preparations	4(1.0)	Ferrous sulphate 3
Mo3- Muscle Relaxants	4(1.0)	Baclofen 2
No5- Pscyholeptics	4(1.0)	Risperidone 2
A11-Vitamins	3(0.7)	Multivitamins -3
Jo2-Antimycotics for systemic use	3(0.7)	Fluconazole-3
Co4-Diuretics	2(0.5)	Amiloride/Hydrochlorothiazide/ Indapamide
Go3- Sex hormone	2(0.5)	Norethisterone
Ho2- Corticosteroids for systemic use	2(0.5)	Dexamethasone
Mo4-Antigoout	2(0.5)	Allopurinol-2
No6- Psychoanaleptics	2(0.5)	Amitriptyline
Po2- Anthelminthics	2(0.5)	Albendazole /Mebendazole
Topical products,	6(1.3)	Antifungal, antiseptic, latex gloves, topical NSAIDs, Ectoparasiticides
Others	10(2.5)	

Others- Opthamologicals, contrast media, drugs for functional gastrointestinal disorders, diagnostic agents, general nutrients, obstructive airway disease drug. UBTH- University of Benin Teaching Hospital.

DISCUSSION

In this study of cutaneous adverse drug reactions, using the ICSRs submitted to a local pharmacovigilance database over a 20-year period, those aged 18-44 years were mostly affected and more in females. The profile of the reactions was wide and varied ranging from different morphology of rashes; maculopapular, erythematous, vesicular and pustular among others. The study also revealed a high proportion of serious cutaneous adverse reactions mainly Steven Johnson's Syndrome, angioedema, urticaria, toxic epidermal necrolysis, and these were mainly due to antibacterials for systemic use such as sulphamethoxazole/trimethoprim, ampicillin/cloxacillin. There were 13 fatalities in this study, comprising mainly of blistering diseases

such as SJS, dermatitis bullous disorders, and erythema multiforme. Angioedema also resulted in 2 fatalities. Other discomforting cutaneous adverse reactions observed in this study were pruritus, palmar-plantar erythrodysesthesia syndrome, alopecia and exfoliative dermatitis. Doctors and pharmacists were the major reporters of these reactions and with the WHO causality assessment, most of the reactions were deemed plausible.

This study, conducted using a local Pharmacovigilance database shows that the prevalence of cutaneous adverse drug reactions was considerable and required evaluation. Other studies have equally shown that CADR's are common (Sushma et al., 2005; Salami et al., 2010; Tian et al., 2015; Modi et al., 2019). In Nigeria, a

review of dermatoses in outpatient clinic also implicated drug-induced aetiology (2.9%) as a common presentation (Henshaw et al., 2018). Dermatological reactions are easily recognized by

patients and physicians alike, thereby making reporting easier. Also, the uncomfortable and unaesthetic nature of the adverse reactions make patients present early.

Table 4: Medicines causing major Serious cutaneous adverse drug reactions in the University of Benin Teaching Hospital's Drugs Poison Information and Pharmacovigilance Center from 2002 to 2022

Reaction	Drugs implicated	Proportion
Steven Johnson Syndrome (58)	Sulfadoxine/Pyrimethamine	18(31.0)
	Sulfamethoxazole/trimethoprim	7(12.1)
	Ampicillin/Cloxacillin	5(8.6)
	Nevirapine	2(1.0)
	Carbamazepine	4(6.9)
	Amoxicillin	3(5.2)
	Allopurinol	2(1.0)
	Diclofenac	3(5.2)
	Zidovudine/Lamivudine/Nevirapine	2(3.4)
	Baclofen	2(3.4)
	Rifampicin	2(3.4)
	Antituberculous agent/Metamizole	2(3.4)
	Artemether-lumenfatrene	1(1.7)
	Dactinomycin/Piroxicam/doxorubicin	3(5.2)
	Herbal supplement/ Thioacetazone/	2(1.7)
Toxic Epidermal Necrolysis	Sufadoxine/pyrimethamine	3(21.4)
	Herbal Supplement	3(21.4)
	Sulfamethoxazole/trimethoprim	2(14.3)
	Amoxicillin	1(7.1)
	Antimalarial/ Chloroquine	2(14.3)
	Multiple drugs	1(7.1)
	Olanzapine	1(7.1)
	Nevirapine	1(7.1)
	Paracetamol combinations/psycholeptics	1(7.1)
	Angioedema	Lisinopril
Ramipril		2
Methocarbamol		1
Pregabalin		1
Herbal medicine		1
Multiple drugs		1
Sodium amidotrizoate		
Others: Paracetamol/Rifampicin/Terbinafine		14(3,4)
Albendazole/amoxicillin-clavulanate/ Ceftriazone/ciprofloxacin/ampicillin- cloxacillin/artemether-lumenfatrene/Artesunate- amodiaquine, Fluconazole, Iron sucrose, Tramadol. Valproic acid		

Common presentations observed in this study were mainly urticaria, SJS, rashes, angioedema, TENS. These were also the most commonly reported reactions in an Indian systematic review (Patel et al., 2014). Other reactions noted in this study were angioedema, and various forms of rashes. It is important to elucidate the types of rashes that are associated with drugs, so this may aid the early identification of ADRs in general practice, and even for trainee physicians. Some

non-serious adverse reactions may be severe and often cause emotional distress to the patients, these can include pruritus, alopecia, penile ulceration, facial oedema as seen in the study. (Sushma et al., 2005; Marzano et al., 2016) There was significant reporting of serious cutaneous adverse reactions (SCARs), which may be due to the reporting bias arising from the perception of the reporters (clinicians and pharmacists). SCAR would be an important

contributor to the global burden of adverse drug reactions. (Adedapo et al., 2021; Pirmohamed, 2004) Previous studies and bulletins from the National Pharmacovigilance Centers also show that SCARs are quite common and can be fatal (National Pharmacovigilance Centre (NPC) National Agency for Food and Drug Administration and Control (NAFDAC), 2018; Oshikoya et al., 2020). Identified serious adverse reactions such as SJS, TENS, angioedema, have been shown to have genetic influences. Furthermore, available reviews have identified genetic polymorphisms associated with various SCARs in other populations, such as carbamazepine-induced SJS/TEN in Caucasians expressing the *HLA-A*31:01* gene and the Chinese expressing *HLA-A*33:03*, and Nevirapine induced SJS/TEN in blacks have a *HLA-C*04:01* (Chan et al., 2015; Tempark et al., 2022). There are very few studies that have evaluated the genetic influences of commonly utilized medications in Africans, and more importantly in Nigerians despite the findings of genetic diversity in black Africans (Rajman et al., 2017). There will be a need to further identify at-risk alleles in Nigerians to avert the development of these reactions to commonly used medicines. It is also interesting to note that majority of the drugs causing Steven Johnson syndrome are the commonly known culprits (Del Pozzo-Magaña & Liy-Wong, 2022).

Non-genetic factors have also been implicated in the development of SCARs, such as the female sex, explained by the augmentation of the immunological processes for the reactions by female sex hormones. The medications implicated in the development of SCAR in this study were commonly prescribed drugs such as sulphamethoxazole-trimethoprim, sulphadoxine-pyrimethamine, carbamazepine and nevirapine, this may be due to the fact that communicable diseases had a high disease burden previously, however, with the changing pattern of morbidities in the country (Oni & Unwin, 2015), the development of angioedema from Lisinopril is noted. A firm approach to understanding the association between the homogeneously black African and the development of SCAR to drugs that have sulphonamides in their structure is required. Of note in this study is the low reporting of cutaneous adverse drug reactions in the paediatric age group, this may be due to non-recognition and attribution of observed skin reactions or dermal reactions to medicines administered to this age group. In clinical parlance, dermal reactions are attributed to some ongoing systemic illness or environmental factors. Another study also showed

few reports of the paediatric age group in patients with SCAR (Oshikoya et al., 2020).

In this study, antimicrobials were the most implicated in the development of cutaneous adverse drug reactions as stated above. Also noted were antivirals, specifically Nevirapine which is used in combination with other highly active antiretroviral therapy (HAART) drugs, Nevirapine has been shown to be a common cause of adverse effects (Pawar et al., 2015), the proportion noted in this study is equally significant. In the previous years, antivirals were the commonest causes of cutaneous ADR (National Pharmacovigilance Centre (NPC), 2012). Another notable finding in this study was the development of angioedema with lisinopril, an angiotensin converting enzyme inhibitor (ACEi), used in the management of hypertension and heart failure. The ACEi have been shown to cause angioedema which is worse in blacks. (Ajayi & Adigun, 2000; Mahmoudpour et al., 2013)

Capecitabine and docetaxel are antineoplastics that were associated with palmar-plantar erythrodysaesthesia syndrome- otherwise known as hand-foot syndrome, this is a condition that affects the quality of life of the affected clients. A cohort study in Brazil found an incidence of 34% of patients on capecitabine developing the syndrome, although the association with dose could not be established but there is a likelihood that genetic factors play a significant role in the development of this syndrome. (Rodrigues de Queiroz et al., 2022)

Herbal medicines also caused cutaneous ADR as well as SCAR in this study, the constituents of these medicines are unknown, therefore it was difficult to perform causality assessment in this instance. Other studies have shown that traditional medicines do cause cutaneous ADR (Barvaliya et al., 2023).

Limitation: this study assessed a wide and varied presentation of cutaneous ADR with some emphasis on the suspected medication and pattern of skin manifestation. It is not exempt from the challenges associated with the spontaneous adverse reaction reporting system where data may be incomplete and other factors which impact on the development of the ADR are not available due to logistic reasons.

CONCLUSION

The study reveal that cutaneous adverse drug reactions are prevalent and constitute a notable health burden. Drugs that were prominent in the causation of CADR were antimicrobials, antineoplastic and drugs acting on the renin-

angiotensin system. There is significant reporting of serious cutaneous ADR drug-induced blistering diseases such as SJS, TENS, erythema multiforme, and angioedema were the prevailing conditions.

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Conflicts of interest

None declared

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