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Patterns of cutaneous adverse drug reactions and most common incriminated drugs at ALERT Hospital, Addis Ababa, Ethiopia: A five year retrospective study

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Abbreviations/ Acronyms

AAU - Addis Ababa University

ADRs - Adverse drug reactions

ADE – Adverse drug event

AED – Anti epileptic drug

AGEP - Acute generalized exanthematous pustulosis

ALERT - All African Leprosy Rehabilitation Training Center

CADRs- Cutaneous adverse drug reactions

DRESS - Drug reaction with eosinophilia and systemic symptoms

ETB – Ethiopian Birr

FDE - Fixed drug eruptions

FMoH - Federal Ministry of Health

G.C. – Gregorian calendar

HMIS – Health Management Information System

IRB- Institutional Review Board

OPD- Out Patient Department

SPSS - Statistical Package for Social Science

MPE - Maculopapular exanthema

NSAIDs - Nonsteroidal anti-inflammatory drugs

SCAR - Severe cutaneous adverse reactions

SJS - Stevens–Johnson syndrome

TEN - Toxic epidermal necrolysis

WHO - World Health Organization

Abstract

Background:

Adverse drug reactions (ADR) is "any unpleasant and unanticipated reaction to a drug that could occur at levels utilized for prevention, diagnosis, or therapy. Cutaneous adverse drug reactions (CADRs) form an important clinical entity in dermatology practice and the severity of such reactions vary from mild to fatal ones. The common culprit drug class to CADRs includes anti-infection drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, and iodinated contrast media.

Objectives:

The objective of this study is to determine the pattern of cutaneous drug reaction and most incriminated drugs in patients who visited ALERT dermatology clinic, Addis Ababa, Ethiopia, from January 2017 to December 2022 GC.

Methods:

A hospital based retrospective crossectional study was conducted at ALERT center on patients who visited the dermatovenerology clinic from January 2017 to December 2022 and were diagnosed with cutaneous drug reaction. A structured data collection checklist was used to assess medical charts. Data was analyzed by using SPSS version 27. Frequency distributions, percentages, tables and charts were used to show descriptive results. Associations were computed using chi square test.

Result:

A total of 67 patients (58.21% females and 41.79% males) were included in the study. Mean age was 27.63 years. The most common CADRs observed in the study were FDE comprising 64.2% of patients followed by MPE accounting for 16.4% and lichenoid drug eruption making up 7.5% of the cases. The most common incriminated drugs noted in the study were cotrimoxazole (11.9%) followed by NSAIDs and others (7.5% each) and fluoroquinolones (6%). CADRs to unspecified drugs were found in 53.7% of the cases.

Conclusion:

The CADRs patterns seen in our study are fairly different from others. Our study has provided baseline information about the proportion of CADRs in our practice and their morphological distribution among different age group, genders, and causative drugs.

Key words : adverse drug reactions, cutaneous adverse drug reactions

1. Introduction

1.1. Background

Adverse drug reactions (ADRs), which are among the important causes of morbidity and mortality globally, will continue to be a public health issue if medicines are used to treat a variety of conditions. According to the World Health Organization(WHO), ADR is "any unpleasant and unanticipated reaction to a drug that could occur at levels utilized for prevention, diagnosis, or therapy". Cutaneous Adverse Drug Reaction (CADR) is any undesirable change in the structure or function of the skin, its appendages or mucous membrane & includes all adverse events related to drug eruption, regardless of the aetiology. Patterns of CADRs and their causative drugs vary among the different populations previously studied(1).

Drug reactions can be grouped into immunologic and nonimmunologic etiologies. The majority (75 to 80%) of ADRs are caused by predictable, nonimmunologic effects. The remaining 20 to 25% of adverse drug events are caused by unpredictable effects that may or may not be immune mediated. Immune-mediated reactions account for 5 to 10% of all drug reactions and comprise true drug hypersensitivity, with IgE-mediated drug allergies falling into this category(2).

The Gell and Coombs classification system states the prominent immune mechanisms that lead to clinical symptoms of drug hypersensitivity. This classification system includes: Type I reactions (IgE-mediated); Type II reactions (cytotoxic); Type III reactions (immune complex); and Type IV reactions (delayed, cell-mediated). However, some drug hypersensitivity reactions pose a difficulty for a distinct classification because of a lack of evidence supporting a predominant immunologic mechanism. These include certain cutaneous drug reactions (i.e., maculopapular rashes, erythroderma, exfoliative dermatitis, and fixed drug reactions and specific drug hypersensitivity syndromes(2).

CADRs form an important clinical subject in dermatology practice and the severity of such reactions range from mild to fatal ones. Although such cutaneous reactions are fairly common, comprehensive information about their incidence, severity and ultimate health effects are often not accessible. Data regarding the safety profile of a drug prior to marketing is primarily based on preclinical and clinical studies and the later involve only a limited number of subjects. However, when drugs are marketed and utilised extensively, new adverse events are unearthed. This in fact re-emphasizes the implementation of an efficient pharmacovigilance system that could generate valuable data for health care providers and their beneficiaries(3).

CADRs are common, make up about 10-30% of all the ADRs(4). At present, there are between 29-35 different cutaneous drug-reaction patterns reported varying from the mostly common, mild dermatitis to an extensively burnt patient(5). These different clinical presentations of CADRs, range from self-limiting skin rash, maculopapular exanthema (MPE), angioedema, urticaria, fixed drug eruptions(FDE) to the life-threatening severe cutaneous adverse reactions (SCARs), including acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens– Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)(6).

The common culprit drug class to CADRs includes anti-infection drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, and iodinated contrast media(6).

Severe and potentially life-threatening eruptions occur in approximately 1 in 1000 hospitalised patients and bears a high risk of morbidity & mortality. Hence, early recognition, evaluation and monitoring of ADRs in particular CADRs are pivotal. It is also important to keep a keen awareness as the pattern of CADRs is changing every year with the introduction of new medications & evolving prescription practices(7).

1.2. Statement of the problem

ADRs are among the top causes of morbidity, hospital admissions, increased health care expense, and even mortality. CADRs account for majority of ADRs in hospitalized patients, which can be caused by a variety of drugs. They have relatively low morbidity but gain significance as they occur very often and require withdrawal of medications. Certain severe CADRs to drugs may result in serious morbidity and even death. Thus, familiarizing one self with the patterns of CADRs and their respective culprit drugs is of an utmost importance in the management(8).

A wide range of commonly prescribed drugs have been incriminated in CADRs, which have resulted in disabling infirmities during hospitalisation and complications following out - door drug therapy. CADRs can present across a broad spectrum, varying from a mild MPE to TEN and life - threatening SJS etc(9).

Diagnosis of CADRs is one of the most challenging clinical problems for the physician. Under-diagnosis and wrong prescription may lead to serious and life-threatening iatrogenic

ADRs(9,10). It is also not uncommon to mislabel a dermatosis as an ADR. This misdiagnosis may unnecessarily preclude from the future use of a certain medication or any related compounds(11).

It is imperative that primary care physicians are able to recognize the common patterns of drug reactions. The prevalence of such reactions will likely rise in the future, and newer, unidentified patterns will probably crop up because of the steady increment of the availability of drugs(11,12). Therefore, a sound knowledge of the patterns of adverse CADRs, a careful history taking and a meticulous approach during the prescription of new drugs can prevent most of the ADRs(13). A study like this will likely fill the gap and add on to our clinical judgement and be a good cornerstone.

1.3. Significance of the study

The present study helps to assess the patterns of CADRs in our hospital by also assessing the associated demographic characteristics such as: age, sex, comorbidity and admission. It also helps to evaluate the most incriminated drugs for CADRs in our hospital. It compares the patterns seen in Ethiopia with that of other African literatures and the patterns seen in other parts of the world looking for similarities and differences.

As there has been no study done in Ethiopia so far on this exact topic, this study will give an insight on the patterns of CADRs and the commonly implicated drugs. This will be helpful for clinicians to be informed about the burden of the commonest patterns of CADRs and SCARs and their subsequent active management.

This study will also help in emphasizing the utility of an efficient pharmacovigilance system that could provide valuable data for policy makers, health care deliverers and their beneficiaries.

The present study can also encourage other researchers to carry out further studies in the field utilizing it as a base**.**

2. Objective of the study

2.1. General objective

- To assess the patterns of various types of CADRs and to evaluate the causative drugs involved at All African Leprosy Rehabilitation Training Center(ALERT), Addis Ababa, Ethiopia, among all patients diagnosed to have CADR, between January 2017 and December 2022 G.C.

3. Methods and Materials

3.1. Study area

The study was conducted at ALERT. It is located in an area locally called Zenebework, Kolfe Keraniyo sub city of Addis Ababa. It was initially established as a treatment center for Hansen's disease (leprosy) and it focuses on rehabilitation of leprosy patients, training programs for leprosy personnel from around the world and leprosy control. The hospital is the main dermatologic center in the country that functions as the referral dermatology institute in and around Addis Ababa, but also gives specialized services in the field of internal medicine, orthopedics, physiotherapy, reconstructive and plastic surgery and ophthalmology.

3.2. Study period

The study was conducted from May 2023 – August 2023 GC.

3.3. Source population

All patients who had visited ALERT center, dermatology clinic from January 2017 to December 2022 GC.

3.4. Study population

All CADR diagnosed patients visiting ALERT center, dermatology clinic in the given time.

3.5. Study design

A five year hospital based retrospective cross-sectional study was conducted to assess the pattern of CADRs and most incriminated drugs during the period of January 2017 to December 2022 in ALERT.

3.6. Eligibility criteria

3.6.1. Inclusion criteria

All CADRs diagnosed patients visiting ALERT dermatology OPD in the mentioned time period.

3.6.2. Exclusion criteria

All incompletely filled medical records.

3.7. Sample size determination and sampling technique

Non probability sampling technique was used. All medical records with a diagnosis of CADRs from Health Management Information System (HMIS) of ALERT dermatology OPD in the given time period were included in the study.

3.8. Study variables

3.8.1. Variables of interest

- Patterns of CADRs
- Age
- Sex
- Causative drugs
- Comorbidity
- Vital signs and general appearance
- Prior similar history

3.9. Operational definitions

CADRs- ADRs that affect the skin.

Incriminated drug - a specific drug that is cited as a possible cause of an ADR after administration.

SCAR - life-threatening CADRs including SJS, TEN, AGEP and DRESS.

Polypharmacy - routine use of 3 or more medications.

Incomplete filling of charts- charts with no clear documentation of the pattern of CADRs.

3.10. Data collection tools and procedures

After obtaining ethical clearance, data was collected from HMIS records of patients visiting ALERT center by using a structured data extraction sheet. The medical records of patients diagnosed with CADRs during the study period were retrieved and evaluated from their medical charts. The CADRs were classified according to predominant pattern of presentation and the possible incriminated drugs recorded in the charts. Out of a total of 79 medical charts with a CADR diagnosis, there were 7 lost cards while 5 charts were misreported on the HMIS. There was not any conflict of interest to declare.

3.11. Data processing and analysis

Data entering, coding and clearing was performed using Epi-info version 7.0 and statistical analysis was done using SPSS (Statistical Package for Social science) version 27. Frequency distributions, percentages, tables and charts were used to show descriptive results. Associations were computed using chi square test. Finally, the study finding was presented using diagrams, tables and figures. A p value < 0.05 was considered as significant.

3.12. Data quality management

A data collection checklist was used. The principal investigator was involved in the data collection with other data collectors who were briefly trained before starting the data collection. The data collection process was closely supervised by the same investigator. Data was checked for completeness, clarity and consistency after being filled each day.

3.13. Ethical considerations

Ethical Clearance was obtained from Institutional Review Board (IRB) of Addis Ababa University (AAU) prior to starting the research. A support letter from the Ethical Committee of Dermatovenereology Department was submitted to ALERT center to retrieve and review patient charts**.** Any identifying information of the patients was not taken. The data collected was not disclosed and remained confidential as it was only passed between the investigators listed on this protocol.

3.14. Data dissemination and utilization

The findings of the study will be submitted to AAU, Department of Dermatovenereology and FMoH. It will also be submitted to scientific journals for possible publication.

4. Result

4.1. Socio-demographic data

Out of a total of 67 patients that were included in the study with a diagnosis of CADRs, majority were found to be in the age group 21 to 40 accounting for 37.3%. Patients aged below 10 years follow making up 22.4%. The ages of the patients ranged from 10 months to 75 years whereas the mean age was 27.63 years.

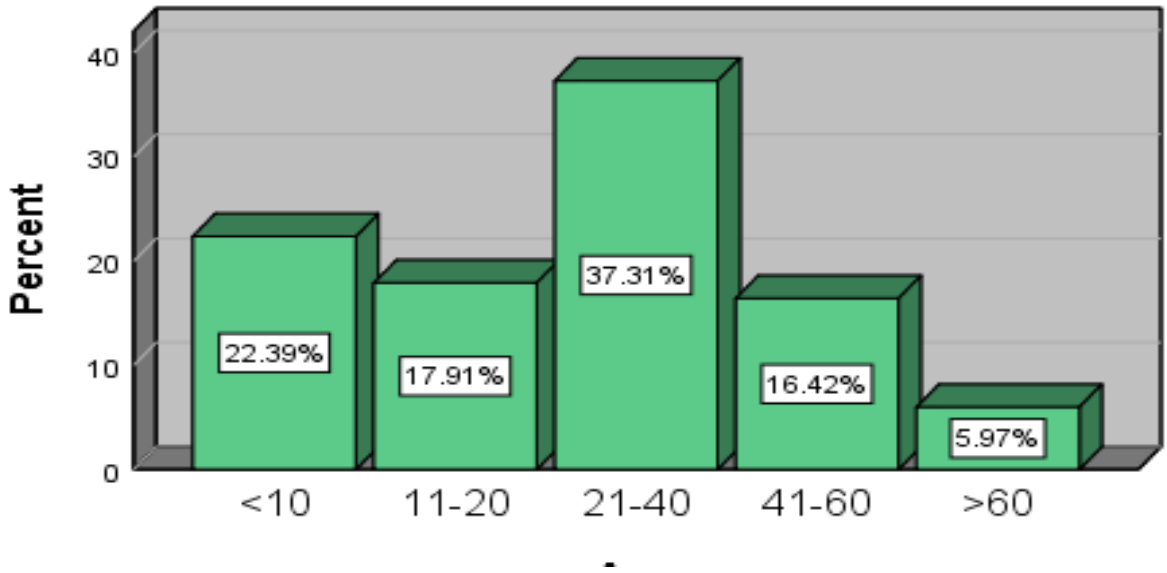

Figure 1 - Age distribution of patients diagnosed with CADRs at ALERT OPD from January 2017 to December 2022.

Out of the 67 patients diagnosed to have CADRs in this five year period, 39 (58.2%) were females and 28 (41.8%) were males; giving male: female of 1.4:1.

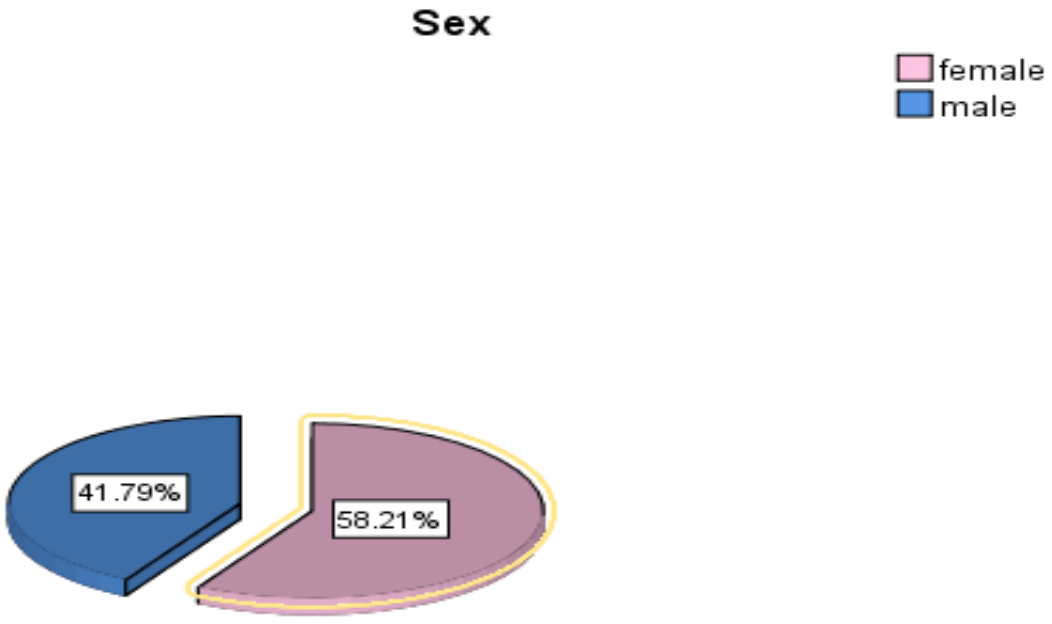

Figure 2 - Sex distributions of CADR diagnosed patients at ALERT OPD from January 2017 to December 2022.

4.2. Clinical Data

The most common pattern of CADR observed in the study was FDE comprising 64.2% of patients followed by MPE accounting for 16.4% and lichenoid drug eruption making up 7.5% of the cases.

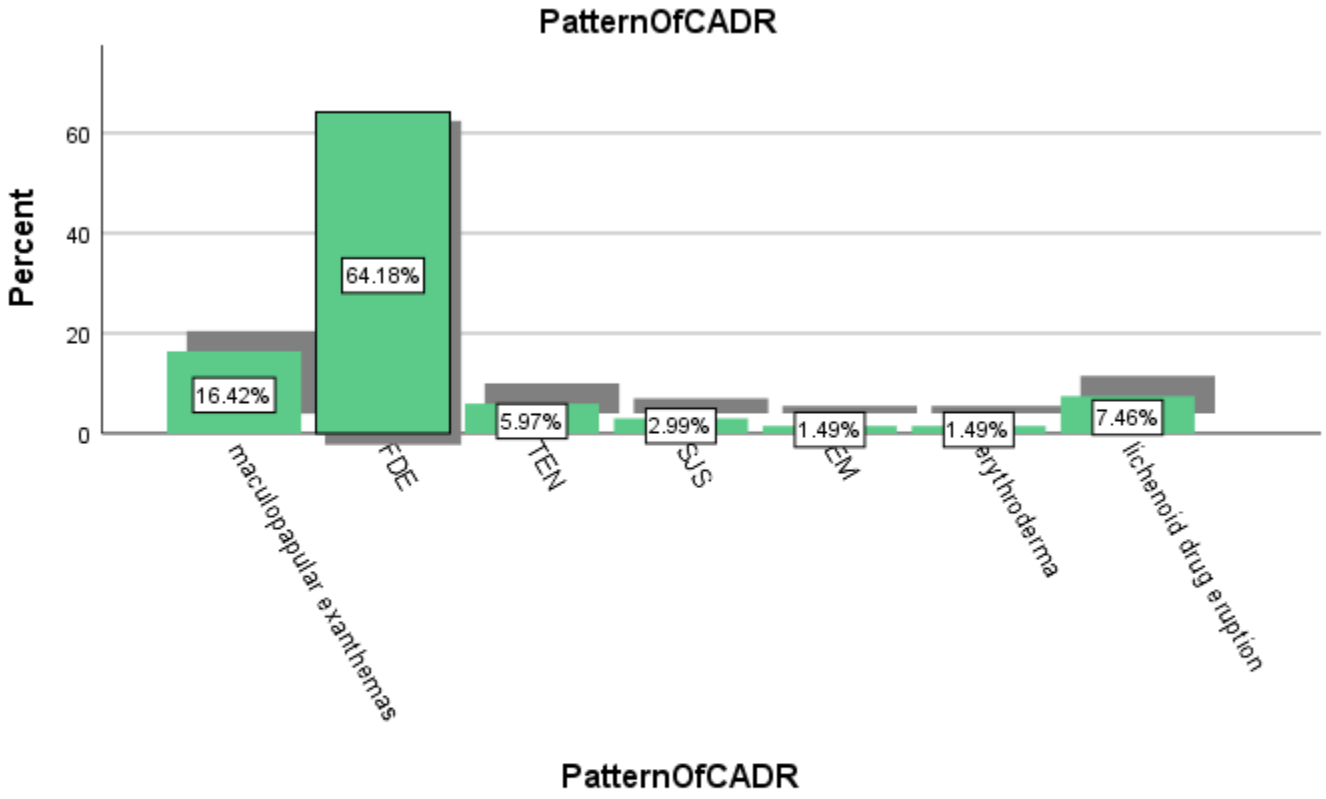

Figure 3 - Patterns of CADRs at ALERT OPD from January 2017 to December 2022.

The most common incriminated drugs noted in the study were cotrimoxazole (11.9%) followed by NSAIDs and others (7.5% each) and fluoroquinolones (6%). CADRs to unspecified drugs were found in 53.7% of the cases.

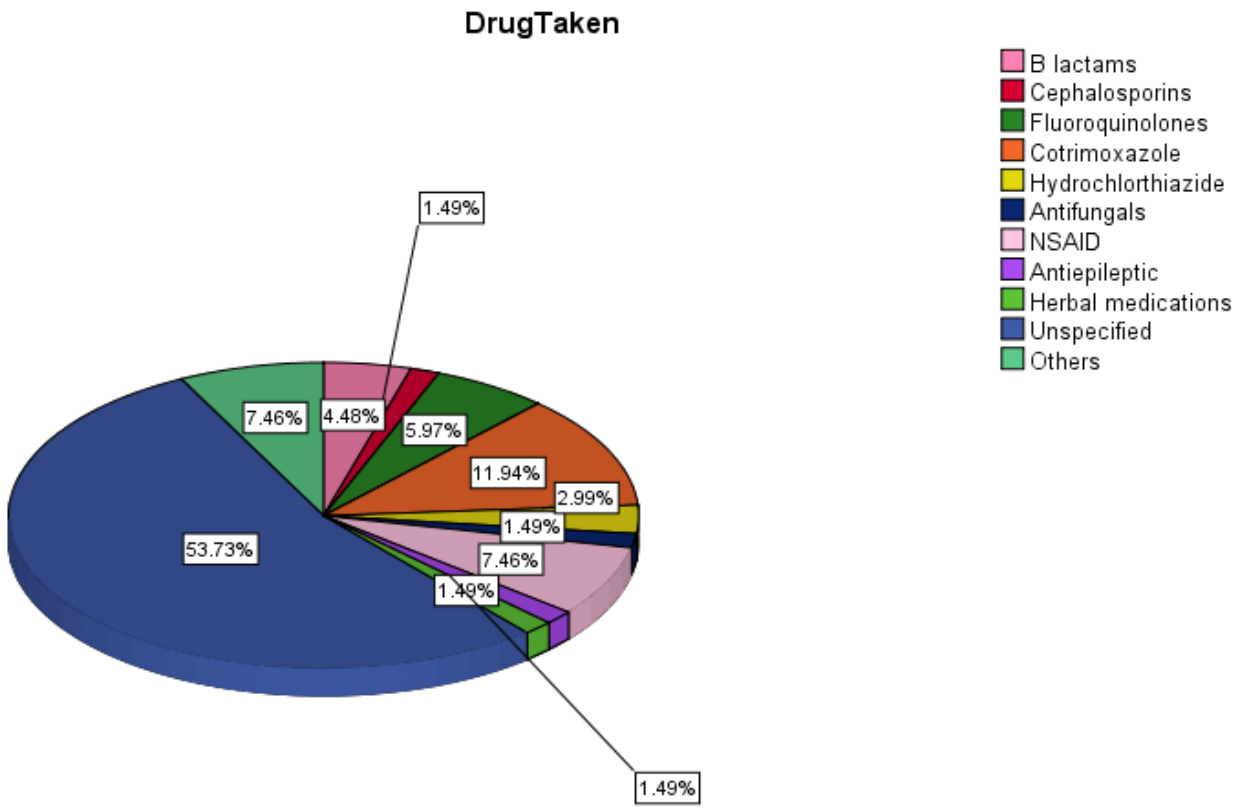

Figure 4 - Incriminated drugs for CADR diagnosed patients at ALERT OPD from January 2017 to December 2022.

The minimum duration of symptoms noted in the study was 3 days whereas the maximum symptom duration was found to be 6 years. Majority of patients (34.3%) had less than 1 week of duration of symptoms followed by those patients who had their symptoms for more than 8 weeks (26.9%).

Table 1 - Duration of symptoms of patients diagnosed with a CADR at ALERT OPD from January 2017 to December 2022.

Duration	Frequency	Percent
Less than 1 week	23	34.3
1-2 weeks	11	16.4
2-8 weeks	15	22.4
Greater than 8 weeks	18	26.9
Total	67	100.0

Overall, 26.9% (18) of the patients had prior history of CADRs while 73.1% (49) didn't have any past history. 37.2% (16) of the FDE diagnosed patients had prior history. The remaining 2 patients were diagnosed with SJS and MPE.

Of all the patients with the CADRs diagnosis in that five year period, 9 (13.4%) had comorbidity whereas 58(86.6%) of them had none. Hypertension and retroviral infections were each found in 4 patients, one of whom had both comorbidities. Diabetes was noted in 1 patient and schizophrenia was reported in 1 patient.

Admission was needed in only 3 (4.5%) of the patients that were diagnosed with CADRs, all of whom were TEN diagnosed patients. All the admitted patients were discharged up on recovery.

Table 2 – Similar prior history of patients diagnosed with a CADR at ALERT OPD from January 2017 to December 2022.

Prior history	Frequency	Percent
Yes	18	26.9
No	49	73.1
Total	67	100.0

Table 3 – Comorbidity of patients diagnosed with a CADR at ALERT OPD from January 2017 to December 2022.

Comorbidity	Frequency	Percent
Yes	9	13.4
No	58	86.6
Total	67	100.0

Table 4 – Admission of patients diagnosed with a CADR at ALERT OPD from January 2017 to December 2022.

Admission	Frequency	Percent
Yes	3	4.5
No	64	95.5

Total	67	100.0

On applying the chi-squares test, it was found that the patterns of CADRs had significant association with the drugs taken (P=0.00).

Cotrimoxazole was the most implicated drug in FDE cases (18.6%) followed by fluoroquinolones (7%) and others (7%). B lactams and NSAIDs follow with 4.7%. Unspecified drugs were the culprits in 55.8% of the cases.

B lactams and NSAIDs were equally the most incriminated drugs for MPE with 9.1%. The remaining 81.8% were caused by unspecified drugs.

Cephalosporins, NSAIDs, herbal medications and others each were implicated in the 4 TEN cases we had. NSAIDs and unspecified drugs were implicated for our 2 cases of SJS.

Hydrochlorothiazide was reported to cause 40% of lichenoid drug eruptions followed by others (20%). Unspecified drugs were noted in 40%.

Antiepileptic was found to be the causative drug in our sole case of erythroderma whereas fluoroquinolones were implicated in the only case of EM we had.

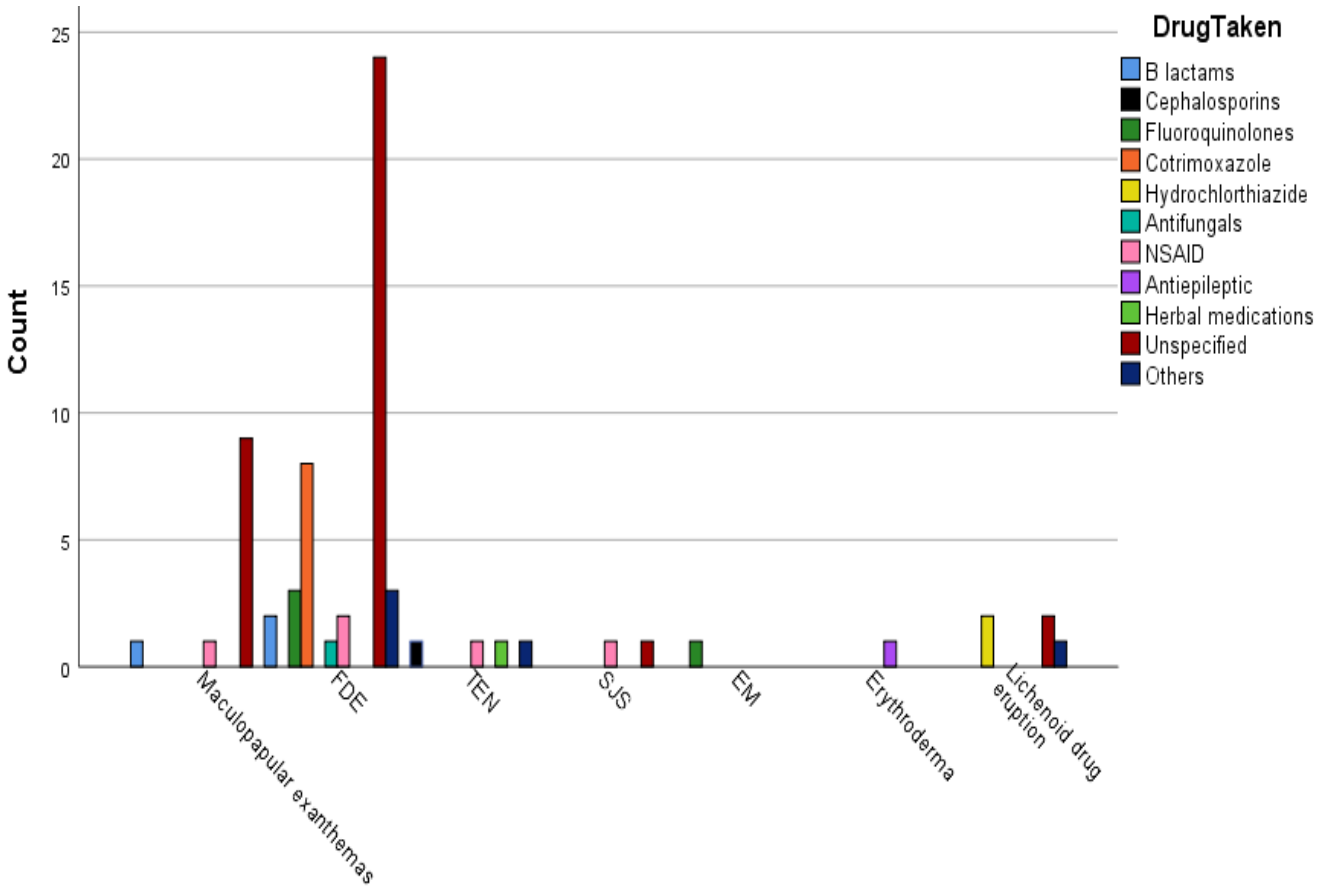

Figure 5 - Cross tabulation of patterns of CADRs and drug taken seen at ALERT OPD from January 2017 to December 2022.

5. Discussion

CADRs are the most common manifestations of ADRs and have various clinical spectra ranging from benign exanthematous eruption to SCADRs. They are an affliction both to the patient and clinician. The present study is a five year retrospective study carried out to determine the patterns of CADRs and the most incriminated drugs.

In this study, the frequency of CADRs was maximum in patients with age group of 21-40 years (37.3%). This is in conformity with studies done by Anant et al, Sushma et al, Jad hav et al and Sharma et al who have noted similar observation(7,8,14,15). A study by Chen et al found 60 -79 years (31.7%) to be the most common age group in contrast to our study which had found only 6%(16).

In our study, females experienced more number of CADRs as compared to males (male: female ratio of 1:1.4). This is true of most studies(7,9,13,14,17–19). Few studies done by Sharma et al, Jha et al, Agrawal et al and Nasrin Nazeer Ahamad et al have reported a male preponderance(15,20–22).

This study has found prior history of CADRs in 26.9% of patients while Das et al and Agrawal et al reported an 18.8%(21,23). A study done by Garg et al noted an 11.6% of prior history of CADRs whiles a study done by Mahatme and Narasimharo saw a 14% of past history(9,24).

The current study found a 13.4% of comorbidity, of which hypertension and retroviral infection comprised 44% each. This is in opposite to the findings by Nasrin Nazeer Ahamad et al who revealed 20% comorbidity among whom; diabetes was the commonest with 50%(22). S D et al also described a 40.5% of comorbidity, among which diabetes comprises 15.3% the cases(13).

Regarding the onset of CADRs, 34.3% of the cases presented in less than a week. This is in consonance with Shalayel et al and Mahatme and Narasimharo who reported 53.7% and 82% of the cases presenting in less than a week respectively(19,24). Similarly, Dimri et al also observed 77.5% of cases presented within 1 week(18).

Most common CADR noted in our study was FDE (64.2%) in accordance with the studies done by Pudukadan and Thappa (31.1%), Patel and Marfatia (30.5%), Nasrin Nazeer Ahamad et al (36%), Jad hav et al (33.8%), Agrawal et al (28.75%)and Sharma et al (33.3%)(14,21,22,25–27). Most other studies conducted on patterns of CADRs have shown MPE to be the commonest. Garg et al (48.8%), Das et al (30.18%), Sharma et al (34.6%), Chen et al (59.5%), Verma et al (29.4%), Dimri et al (33.3%), Khaled et al (57.7%), Sushma et al (42.7%), Ding et al (39.5%), Jha et al (42.64%), Talib et al (22.4%) and shalayel et al (39%) have all observed this well established fact(8,9,15–20,23,28–30).

Anant et al (37.14%), S D et al (32.2%), Chatterjee et al (27.19%) and Mahatme and Narasimharo (30%) found drug induced urticaria as the commonest pattern whereas none was found in our study(7,13,24,31). This variation could be due to the difference in the pattern of drug use, the ill chart keeping and recording as well as the pharmacogenetic traits of the population being studied.

SCARs in total accounted for only 11.94% of our cases. This lower range of occurrence may be explained by the OPD setting of our study. Ding et al, Talib et al, Pudukadan and Thappa, Sushma et al, Das et al, Anant et al, Shalayel et al, Nasrin Nazeer Ahamad et al and Verma et al have all stated a higher percentages of SCARs(7,8,17,19,22,23,26,28,29).

Regarding the most incriminated drugs, our study revealed cotrimoxazole to be the top culprit (11.9%) followed by NSAIDs (7.5%) and others (7.5%). Fluoroquinolones accounted for 6% of CADRs. More than half of the cases were ascribed to be caused by unspecified drugs (53.7%).

Overall picture of our study shows antimicrobials to be the most incriminated drugs (28.35%) followed by NSAIDs (7.5%). This is in concordance with most other studies in these lines. Mahatme and Narasimharo showed antimicrobials to be the most common cause (48%) followed by NSAIDs (24%)(24). Gang et al has reported antimicrobials to have caused 48.8% of CADRs followed by NSAIDs with 32.5%(9). Jad hav et al, Sharma et al, Agrawal et al, Jha et al, Dimri et al, Chen et al and Verma et al have revealed similar observations(14–18,20,21,25).

In agreement with our study, Cotrimoxazole was the top antimicrobial seen in the study done by Mahatme and Narasimharo (20%)(24). Pudukadan and Thappa also noted cotrimoxazole as the most commonly incriminated drug in their study (22.2%)(26). Patel and Marfatia recognized cotrimoxazole as the most implicated drug in their study(27). In the study done by shalayel et al, sulfa groups consisting of cotrimoxazole were the second most common group of antibiotic causing CADRs accounting 25.71%(19). Khaled et al also put cotrimoxazole as the second most common offender following B lactams (14%)(30).

The second most common putative antimicrobial in the current study was fluoroquinolones (6%). In line with this, S D et al revealed fluoroquinolones as the second most common culprit next to NSAIDs (22.1%)(13). Verma et al (20.5%), Chen et al (19.84%) and Shalayel et al (41.5%) have found fluoroquinolones as the most common antimicrobial in their study(16,17,19).

Antiepileptics were seen in only 1.5% of our cases in comparison to Nasrin Nazeer Ahamad et al (20%), Lee et al (11.3%), Agrawal et al (12.5%), Sushma et al (19%), Ding et al (23.8%), Sharma et al (22%), Das et al (11.30%) and Chatterjee et al (32.88%) all of whom have reported higher percentages(8,15,21–23,29,31,32).

Beta lactams and cephalosporins have not taken pride of place in our list of culprit drugs as they did in many other studies done by Khaled et al, Anant et al, Sushma et al, Ding et al, Lee et al,

Jha et al, Agrawal et al, Dimri et al, Nasrin Nazeer Ahamad et al and Mahatme and Narasimharo(7,8,18,20–22,24,29,30,32).

6. Limitations of the study

Retrospective nature of the study has precluded us from doing a standard causality of assessment. The incomplete documentations of history and physical examinations as well as misrecordings in the HMIS and lost cards have an untoward effect on the proceedings and results of this study.

7. Conclusion

The CADRs patterns seen in our study are fairly different from others. FDE was noted as the premier pattern in 64.2% of cases followed by MPE in 16.4% and thirdly lichenoid drug eruptions in 7.5% of patients. The incriminated drugs were more or less similar with other studies except for minor variations. Antimicrobials and NSAIDs were the most common putative drugs. Our study has provided baseline information about the proportion of CADRs in our practice and their morphological distribution among different age group, genders, and causative drugs.

8. Recommendations

Comprehensive knowledge of CADRs and their early recognition with meticulous history taking and cautious approach of management is needed from the clinicians to institute timely measures as novel drugs and newer patterns are emerging. Striving towards patient awareness on keen use of drugs and their interaction shouldn't be taken lightly. We recommend for more extensive ADR monitoring and reporting in the hospital on a regular basis and will be useful in generating more data about ADR. Computerizations of medical records and completeness of relevant informations should be encouraged.

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1 Annexes

1.1 Annex I

Addis Ababa University Department of Dermatovenereology

Data extraction sheet to assess Patterns of cutaneous drug reactions and most incriminated drugs Skin at ALERT from January 2017 to December 2022 G.C.

Medical record number = ____

1) Age (years) = _____
2) Sex
   A. Male
   B. Female
3) Duration of the lesion(s) = _____

4) Similar prior history
   A. Yes
   B. No
5) Comorbidity
   A. No
   B. Yes, Single comorbidity
   C. Two or more comorbidities
6) Polypharmacy
   A. Yes
   B. No
7) Patterns of CADRs
   A. Maculopapular exanthemas
   B. Urticarial eruptions
   C. FDE
   D. DRESS

E. AGEP
F. TEN
G. SJS
H. EM
I. Erythroderma
J. Others

8) Drug history prior to presentation

A. No
B. Yes, a single drug
C. Yes, two and more drug history

9) What drugs were incriminated?

A. B lactams
B. Cephalosporins
C. Fluoroquinolones
D. Cotrimoxazole
E. Sulfa drugs
F. Antifungals
G. NSAIDs
H. Antiepileptics
I. Herbal medications
J. ART drugs
K. Unspecified
L. Others

10) Vital signs

A. Stable
B. Unstable

11) Admission

A. Yes
B. No