

## To Study the Incidence of Cutaneous Adverse Drug Reactions Due To Usage of Anti Microbials In A Tertiary Care Hospital In Kadapa

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### Abstract:

**INTRODUCTION:** Cutaneous adverse drug reactions (CADRS) are undesirable or unintended consequences of drug administration that might cause suffering of the patient, discontinuation of treatment, impaired quality of life and increased economic burden. Knowledge of drugs causing CADRS reduces these consequences and helps in prescribing safer drugs. Nowadays antimicrobials are used irrationally and CADRS are more common with them. **OBJECTIVE:** To study the incidence of CADRS with the usage of antimicrobial, to determine their clinical causality, severity and preventability. **MATERIALS AND METHODS:** An observational study is conducted from 2017 to 2019 to analyse CADRS reported from pharmacovigilance unit, GMC, Kadapa as per CDSCO form. Causality, severity and preventability are assessed using relevant scales. **RESULTS:** Out of 600 ADRS reported during this period 219 are CADRS. Male preponderance (53%) is seen, age group of 18-40 yrs (55%) were most affected. Maximum CADRS are seen with cephalosporins, penicillins, fluoroquinolones followed by antiretroviral, antiviral drugs. Maculopapular rash is the most common followed by fixed dose eruptions, erythematous rash and others. Severe CADRS like stevens-johnson syndrome are also seen. Causative drugs are withdrawn in most of the cases. Causality assessment indicated 83% as probable and 17 % as possible cases. 83% of CADRS are of moderate severity, 13% are less severe and only 4% of severe CADRS are recorded. 84% are definitely preventable, 13% are probably and 3% are not preventable. **CONCLUSION:** CADRS can be prevented by proper recording of their data with the help of pharmacovigilance, avoiding self medication and prescription of other alternative safer drugs with early diagnosis of CADRS.

**Keywords:** CADRS, causality, preventability, severity.

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### I. Introduction

Drugs no matter how safe and efficacious, are always associated with risk of adverse effects<sup>[1]</sup>. Adverse drug reaction is any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug. Cutaneous adverse drug reactions are unpredictable and include various different skin conditions of varying degrees of severity. There is a wide spectrum of CADRS ranging from transient maculopapular rash to fatal Steven Johnson Syndrome<sup>[2]</sup>. They may develop promptly or only after prolonged medication or even stoppage of drug. They are more common with multiple drug therapy and in elderly. An incidence of 10-25% CADRS has been documented in different clinical settings. CADRS may lead to discontinuation of treatment, impairment of quality of life, increased cost of patient care.<sup>[3]</sup>

Now a day's antimicrobials are prescribed irrationally and are used by patients for self medication without the doctor's prescription. Antimicrobials like third generation cephalosporins like ceftriaxone, cefixime, cefuroxime, lactam antibiotics like Amoxicillin, Piperacillin and their combinations with clavulanic acid and Tazobactam, Fluoroquinolones, Sulfonamides, Macrolides, multiple drug therapy with anti tubercular and antileprotic drugs cause different CADRS. Knowledge of these antimicrobials causing CADRS helps in prescribing safer drugs and early recognition and withdrawing of drug CADRS causative drug, avoid patient suffering and also avoid medico legal issues against doctors<sup>[4]</sup>.

Pharmacovigilance has been defined by WHO (2002) as the science and activities relating to the detection assessment, monitoring and prevention of adverse effects or any other drug related problems. It helps in educating doctors about ADRS, reducing the risk of drug related harm to the patient and issue public

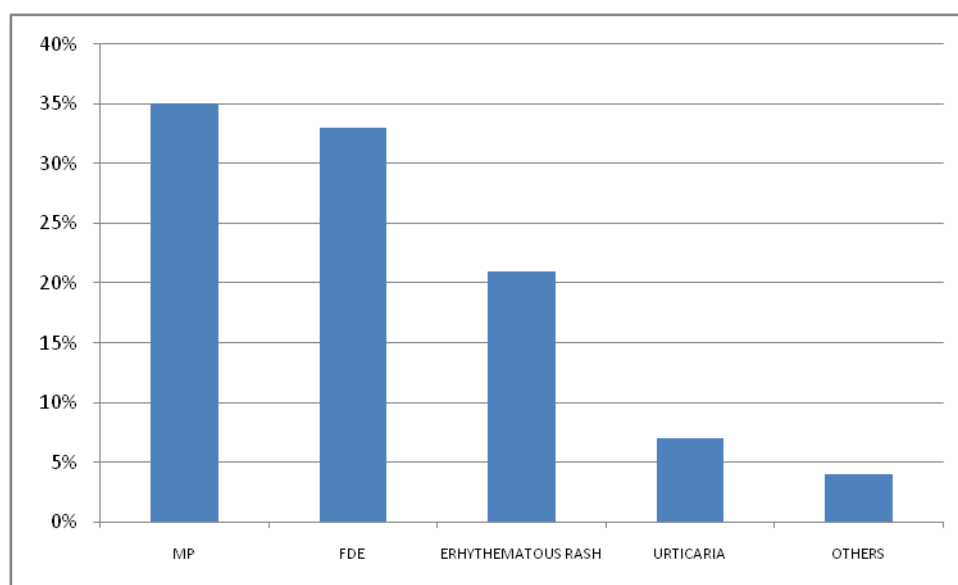
warnings when warranted. Monitoring and reporting of ADRS is an integral part of drug therapy but is still at infant stage in India. As new drugs are being introduced every year, every health care professional must have knowledge about the importance of Pharmacovigilance. Government Medical College, Kadapa is one of the ADR monitoring center under Pharmacovigilance Programme of India<sup>[5]</sup>. This study is undertaken to assess the clinical spectrum, causality, severity and preventability of various CADRS reported from GMC.

## II. Materials And Methods

This is an observational study conducted from June 2016 to June 2019 to determine the incidence of CADRS due to usage of antimicrobials from Pharmacovigilance unit, GMC, Kadapa. Patient's demographics, clinical and drug data, CADRS incidence, time of occurrence, causative drug details, outcome and severity are collected from CDSO forms. Causality is assessed by WHO-ADR probability scale<sup>[6]</sup>, severity by modified Hartwig and Siegel severity scale<sup>[7]</sup> and preventability by Schumock and Thornton scale<sup>[8]</sup>. The characteristics of CADRS are analysed using descriptive statistics. Results are expressed as percentages, odds ratio etc.

## III. Results

A total of 600 ADRS are reported during the study period of which 219 are CADRS. Of the total CADRS cases males constituted 53% and females 47%. The age group of 18-40yrs (55%) are the most affected followed by 41-60 yrs(22%) 0-20 yrs(15%) and above 60 yrs(8%). Of all the antimicrobial agents third generation cephalosporins like ceftriaxone, cefixime, cefotaxime, cefuroxime are the most common causative agents of CADRS followed by penicillins like amoxicillin, piperacillin and their combinations with clavulanic acid and tazobactam, antiretroviral drugs, antitubercular drugs, macrolides, sulphonamides. Among the CADRS the most common is maculopapular rash (35%) followed by fixed dose eruptions (33%), erythematous rash (21%), urticaria (7%) and others (4%) (Fig-1). Maculopapular rash is mostly seen with ceftriaxone, nevirapine. Fixed dose eruptions with fluoroquinolones. Most severe CADRS like Steven Johnson Syndrome are seen with ceftriaxone, cefuroxime, nevirapine. Few cases of dapsone hypersensitivity syndrome are also seen. Angioedema is seen with ceftriaxone, efavirenz. Maximum numbers of cases are seen with oral route of administration (72%) followed by parenteral route (20%) and topical (8%) (Fig-2). The causative drug is withdrawn in 95% of cases with prescription of alternative safer drug. No cases of mortality are recorded. 40% of cases required additional treatment with topical steroids, antihistaminic drugs etc. As per WHO-UMC probability scale 83% had probable causality and 17% had possible (fig-3) Majority of CADRS is of moderate severity (83%), severe (41%), mild (13%) (Fig-4). Preventability scales indicates 84% to be not preventable, 13% probably preventable and 3% definitely preventable (Fig-5).



**Fig1:** Mild to moderate CADRS

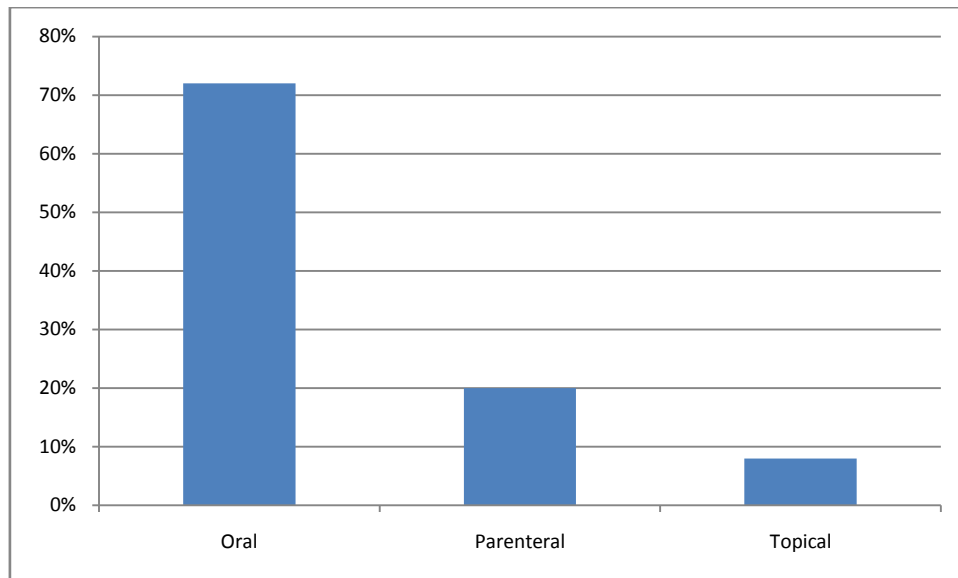


Fig2: Routes of drug administration

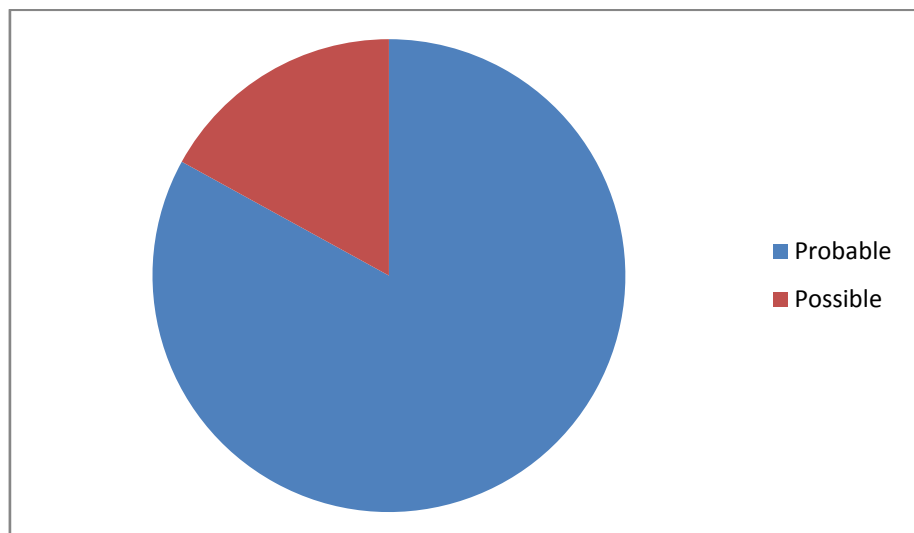


Fig3: Causality assessment of CADRS

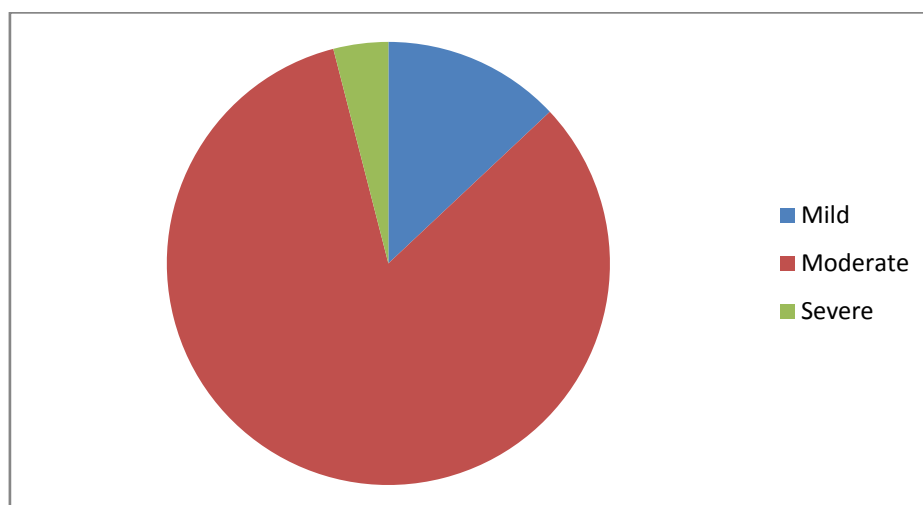


Fig4: Severity Assessment

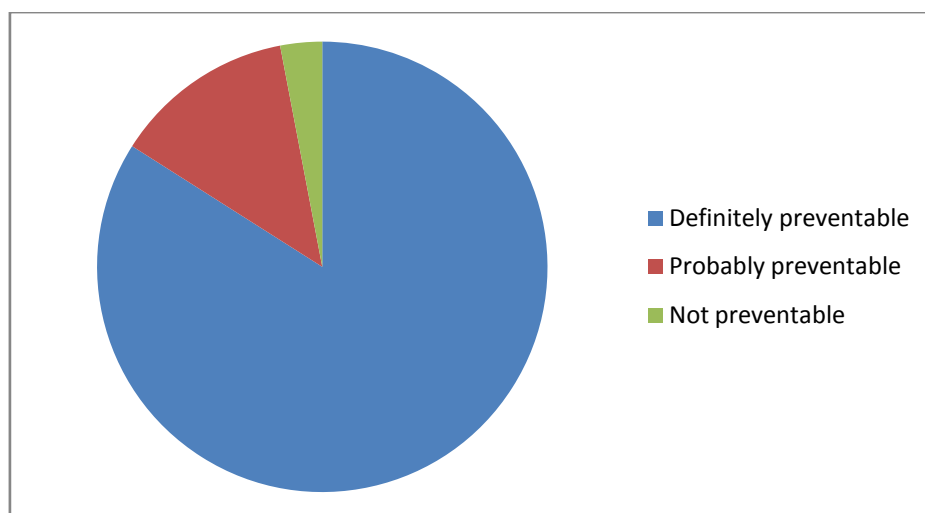


Fig5: Preventability Assessment

#### IV. Discussion

As innovation in medicine occurs and new drugs continue to be developed, there is a potential for increase in the number of CADRS. However true incidence of CADRS is difficult to determine because mild transient reactions are not reported. On the other hand skin changes due to other aetiology like viruses are sometimes incorrectly attributed to drugs. Self medication also a contributory factor for increase in CADRS as they don't have proper knowledge about the drugs. Even though self medication facilitates easy access to medicines and reduce healthcare costs, more studies are required to evaluate its impact and role at various healthcare sectors. Not warning a patient about potential adverse effects, prescribing a related medication with cross-reactivity are common medico legal pitfalls.

CADRS may lead to poor quality of life due to hospitalisation, prolonged hospitality, increased morbidity, and mortality in severe cases as well as economic burden on the patient. Knowledge of drugs related CADRS helps in early diagnosis and thereby reduce hospitality as well as morality which can be done with proper recording of cases with CADRS in pharmacovigilance unit.

In this study a total of CADRS are recorded from June 2016 to June 2019. Majority of cases are recorded in males which is similar to Sharma et al. study in Jammu<sup>[9]</sup>. Age group between 19-40 yrs are affected which is similar to previous studies. Kongkaew et.al reported that higher number of CADRS in elderly is probably due to polypharmacy and altered pharmacokinetics in them. This study showed maculopapular rash as the most common reaction followed by fixed dose eruptions and erythematous rash which are similar to Saha et al report<sup>[10]</sup>. Maculopapular rashes are seen with ceftriaxone, nevirapine which required stoppage of drugs and topical treatment with steroids or oral antihistaminics to relieve itching. Fixed dose eruptions are more common with fluoroquinolones<sup>[11]</sup>. Many cases of fixed dose eruptions due to self medication with fixed dose combination of fluoroquinolones and cross sensitivity between the same group of drugs is seen. They are also treated similarly like maculopapular rash. Steven Johnson Syndrome is an acute life-threatening mucocutaneous reaction characterised by extensive necrosis and detachment of the epidermis from skin. Its incidence is estimated to be 0.4 -1.2/million person years and has a mortality rate of nearly 1-5%<sup>[12]</sup>. They are usually caused by sulphonamides. Identification and withdrawal of causative drug are the important steps in treatment of SJS. They may require additional treatment like management of skin wounds, fluid and nutritional status, electrolyte balance, renal and airway functioning and adequate pain control. A few cases of Dapsone Hypersensitivity syndrome are reported that might result several weeks to months after treatment initiation<sup>[13]</sup>. Identification of genetical polymorphism offers the possibility of avoiding high risk drugs in genetically susceptible individuals<sup>[14]</sup>.

According to WHO-UMC causality assessment majority of CADRS that occurred in our study had a probable causal relationship with drug. Causality could not be established as definite because rechallange was not done due to ethical considerations. Some CADRS has possible causality mostly owing to concurrent use of other medications. 10% are preventable, common reason being self medication by patient without knowledge of drug reaction due to drug, as well as improper recording of previous drug history. Majority CADRS (85%) are not preventable according to Modified Schumock and Thornton scale. Most of CADRS are of moderate severity as per Modified Hartwig and Siegel severity scale. Mild CADRS (10%) are less which might be due to self-limiting and underreporting. Severe CADRS like SJS (5%) are reported but there was no mortality.

## V. Conclusion

The present study demonstrated that CADRS are more common with antimicrobial drugs like third generation cephalosporins, penicillins, fluoroquinolones, antiretroviral drugs, sulphonamides. Maculopapular rash is the most common among CADRS followed by fixed dose eruptions and severe CADRS like SJS.

CADRS are found due to self-medication and improper recording of previous history of drug allergy. A few cases of Dapsone hypersensitivity syndrome are also recorded. Early diagnosis of CADRS reduces the patient hospitality and mortality and economic burden. Knowledge of these CADRS helps physicians in prescribing alternative drugs which are safe as well as avoid medico legal cases against physicians. Pharmacovigilance helps in monitoring CADRS and prevent them as well as improve public awareness regarding safety of drugs and avoid CADRS due to self medication. Self-medication should be discouraged<sup>[15]</sup>.

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