

Adverse Cutaneous Drug Reactions in Paediatric patients in a Tertiary Care Hospital-Study of causality, preventability and severity

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Abstract:

Objective: To study the dermatological adverse drug reactions (CADRs) in paediatric patients in a tertiary care teaching hospital.

Methods: A retrospective study was undertaken to analyse adverse drug events in paediatric department of a tertiary care teaching hospital. Case sheets were studied and analysed for data of CADRs and dermatological adverse event marked as ADR by the consultant dermatologist and paediatrician was included in the study. Causality, preventability and severity were analysed by Pharmacologist using standard scales. Gender inclination, most common class of drug causing dermatological ADRs, types of dermatological ADRs including most common ADR, associated risk factors, mono pharmacy or polypharmacy were included in the study.

Results: 2015 medical record sheets were analysed in a period of one year (january2016-december2016).104 patients were identified with dermatological ADRs. Overall incidence was 5.15% of which 58% were females. Antimicrobials were the commonest drug class(71.15%) causing dermatological ADRs followed by NSAIDs(11.53%),antiepileptics(10.57%) and others(2.88%).76 % of ADRs were of moderate degree (assessed by Modified Hartwig and Siegel Scale) .79% cases fell in probable category of preventability assessed by Modified Schumock and Thornton Scale. According to Naranjo's scale of causality assessment, 71.15 % cases scored into probable, 21.15 % definitive and 7.69% were of possible category. Maculopapular rash (64.42%) followed by FDE (18.26%), urticaria (15.38%) were the CADRs that occurred in most patients .74% cases were prescribed polypharmacy.

Conclusion: Dermatological adverse affects though just a part of the whole spectrum of ADR is a matter of concern because it causes apprehension in parents along with associated morbidity and mortality in patients. More effective ADR reporting, early intervention and more studies especially in paediatric age group covering various aspects of ADRs are required.

Keywords: Adverse drug reactions, Causality, Naranjo's scale, CADRs (cutaneous adverse drug reactions), polypharmacy.

I. Introduction

New drugs are launched and will be coming in market always. Vivekanandan Kalaiselvan *et al* mentioned in an article that India, with a current population of 1.27 billion, is the fourth largest producers of pharmaceuticals in the world with more than 6000 licensed manufacturers and over 60,000 branded formulations in the market^[1]. The drug usage is ever increasing and so are the ADRs along with a change in the clinical spectrum and appearance of new ADRs. Paediatric age group is either left out or ignored due to ethical, moral and practical issues regarding clinical trials and so suffer even more. Vigilance and awareness along with more studies in children are required to keep them safe or reduce the harm. With the improvement in ADR reporting because of availability of various helpline facilities, android application, PSURs and reporting forms in various languages, data input of ADR has improved. Various studies have been conducted around Pharmacovigilance and have revealed that ADRs are increasingly leading to hospitalization and constitute a significant economic burden on patients in India.^{[2]. [3]. [4]} ADRs are underreported though the culture of reporting under Pharmacovigilance programme is improving, there is a long way to go and ADRs are definitely proving to be expensive. As far as paediatric population is concerned, situation is even worse as drug testing and clinical trials in this population are very limited. A review states that incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children (pooled estimate of 2.9% (2.6%, 3.1%)) and from 0.6% to 16.8% of all children exposed to a drug during hospital stay^[5].

The physiological differences in children and adults affect the treatment of drug in the body. Pharmacokinetics and pharmacodynamics of many commonly used drugs vary significantly between these two age groups of patients^[6]. Drug metabolism differs in young children and information on efficacy and toxic

effects of drugs is rarely available^[7]. Dreifuss et al stated that ADR data in adults cannot be relied upon to predict ADRs in children^[11]. Children are not young adults so the data derived for adults cannot be calculated down to children resulting in ADRs occurring often in them. Worldwide there is deficiency of sufficient data about the safety profile of drugs in paediatric population and India is no exception. Moreover, incidence may be on increase because of lack of this data, increased drug resistance, polypharmacy & indiscriminate use of drugs.

Cutaneous adverse drug reactions (CADRs) are most commonly reported type of ADRs and are responsible for the majority of ADRs in hospitalized children. It is estimated that 2.5% of children who are treated with a drug, and up to 12% of children treated with an antibiotic, will experience a CADR. It has been found that 80% of drug allergies attributed to beta-lactam and sulfa antibiotics and only 30% of the cases were related to opioid analgesics^[8]. Another important issue with ADRs is that drug eruptions, which are a frequent diagnostic problem for the clinician in an outpatient clinic, commonly have to be differentiated from a viral exanthema^[10]. The skin is the organ most frequently and prominently affected by drug-induced allergic reactions and various genetic and environmental factors may predispose to these allergic reactions and at least 29 drug-related cutaneous reaction patterns have been reported^[14,15,16]. The correlation between drug use in children and incidence of ADRs has been a matter of growing awareness in several recent studies^[9]. Such issues are not commonly reported though very often seen. So more studies, infact detailed studies in paediatric group is required.

A meta-analysis of 17 prospective studies has shown that ADRs in children are a significant public health issue all over the world & methodologically sound drug surveillance studies are necessary for an effective promotion of a safer use of drugs in children^[12]. Safety data of drugs can thus not be applied to children and therefore more studies are required. ADR reporting is one way to get information regarding adverse drug reactions occurring in children based on which changes in package inserts, dose adjustments, withdrawal of drug usage in children or other such measures may be undertaken to ensure safety. An active drug surveillance system is needed to capture risk information in children^[13]. So the Present study has been undertaken in a tertiary care hospital to assess the various parameters regarding CADRs to generate data about the status of problem, reporting culture and treatment options. Results will generate awareness and will influence the diagnosis, intervention and treatment practices. More and more studies are required to ensure safe use of drugs in children. Hence, this study will help in adding information to the present scenario.

II. Objectives

To study and analyse medical record case sheets of paediatric patients to assess CADRs, common drug classes responsible, causality, severity and preventability.

III. Material & Methods

A retrospective study was undertaken in the department of Pharmacology, Dermatology & Paediatrics of Modern institute of medical sciences, Indore, a tertiary care teaching hospital. Medical record sheets were analysed for the CADRs in the study duration (january2016-december2016). Study protocol was approved by institutional ethics committee. Discretion of information acquired was secured & all the measures to maintain confidentiality were undertaken. Inclusion criteria consisted of all in patients of either gender between the age's 0–16years. Any undesirable and unintended event marked as CADR was included in data.

Analysis

- a) All the results were calculated in percentages and proportions.
- b) CADRs- types
- c) Class of drug prescribed and the particular drug
- d) Causality (assessed by Naranjo's algorithmic scale). This is the most common assessment tool of ADR, and

Verifies the chances of whether an ADR is essentially due to the drug or it is the result of other causes, the likelihood is consigned by the score, termed as definite, probable or possible^[17]. (e) Severity of ADR (assessed by Modified Hartwig and Siegel Scale). Examples of ADRs assessed as severe are those that caused death, directly life-threatening, lengthened hospitalization or shift to a higher level of clinical care

- f) Preventability was assessed by Modified Schumock and Thornton Scale

IV. Results

1)104 cases of ADRs were reported in the study duration of one year with overall incidence of **5.15%**, of which **58.65%** occurred in females (Fig.1). 2) Anti microbial agents was the class of drugs (**71.15%**) most commonly responsible for causing CADRs. NSAIDs were responsible for causing CADRs in 11.53% of

patients. Antiepileptics were close by, responsible in about 10.57% of cases while other drug classes were involved in 2.88% of cases. (Fig.2).

- 3) Polypharmacy was prescribed in about 74% cases (Fig.3).
- 4) The most common ADR that occurred was **maculopapular rashes** presenting in 64.42% of patients, followed by FDE occurring in 18.26% of patients & 15.38% suffered urticaria. Photosensitization was reported in 0.96% patients and STS in 0.96% of patients (Fig.4).
- 5) Hartwig and Siegel scale for assessing severity was used. Most of the ADRs were of **moderate degree (76%)**, while only 1% of cases were reported of severe degree although no deaths were reported (Fig.5).
- 6) Preventability of suspected ADRs was assessed by using Modified Schumock and Thornton scale and the results revealed that **50.96% of ADRs were probably preventable**, 37.5% ADRs were definitely preventable and 11.5% were under the category not preventable (Fig.6)
- 7) According to Naranjo's scale of causality assessment 71.15% cases were of **probable causality score**, 21.15% cases had definite score & possible score was for 7.69% cases, (Fig.7).

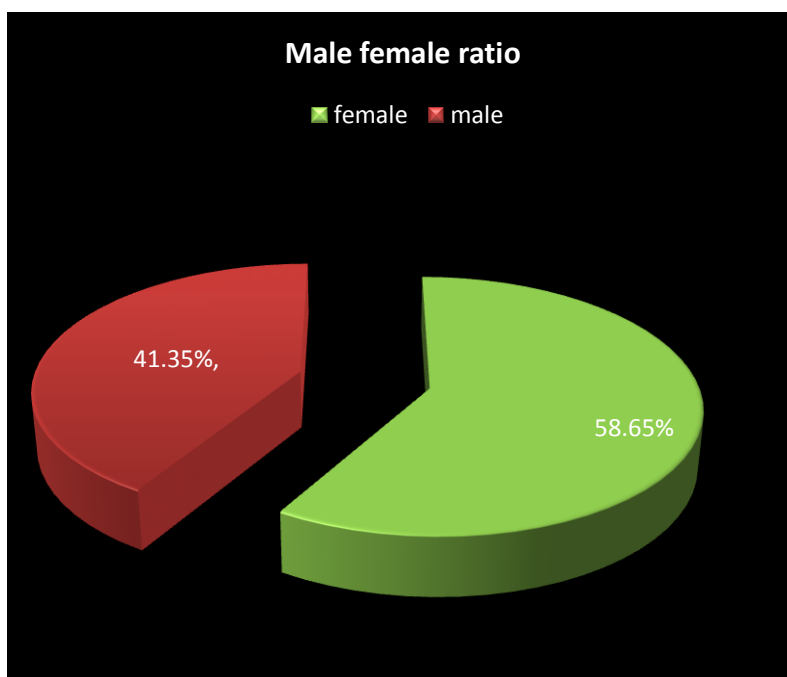


Fig.1

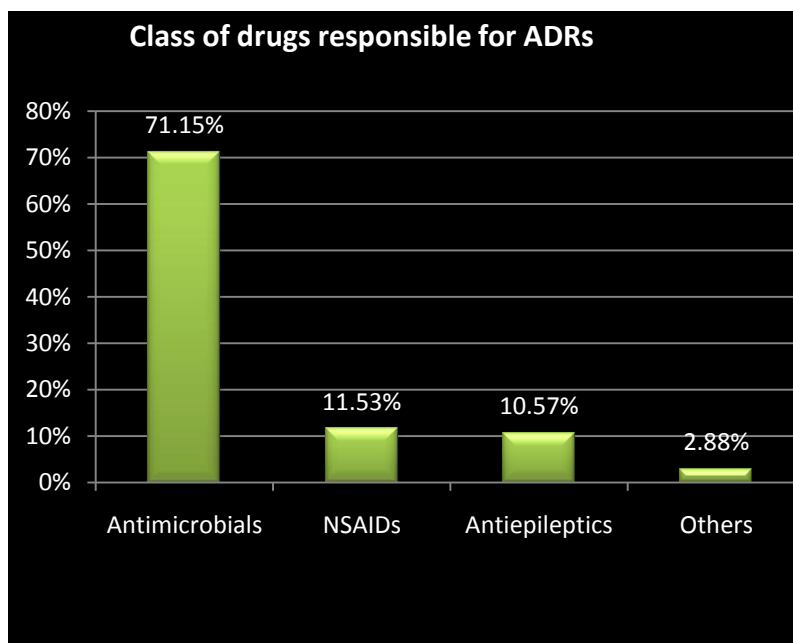


Fig.2

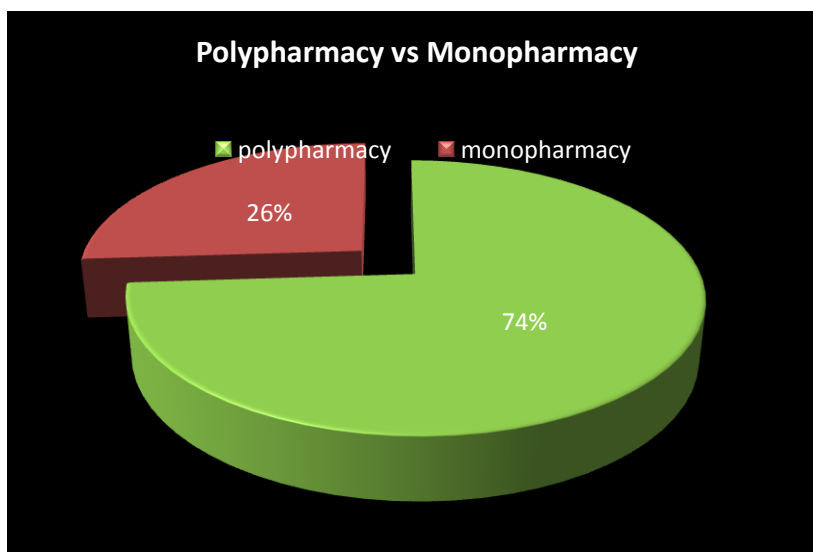


Fig.3

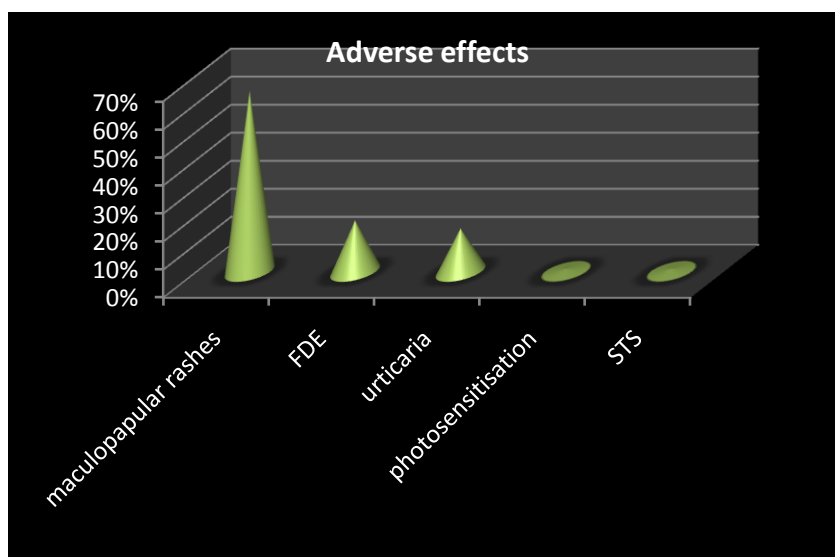


Fig.4

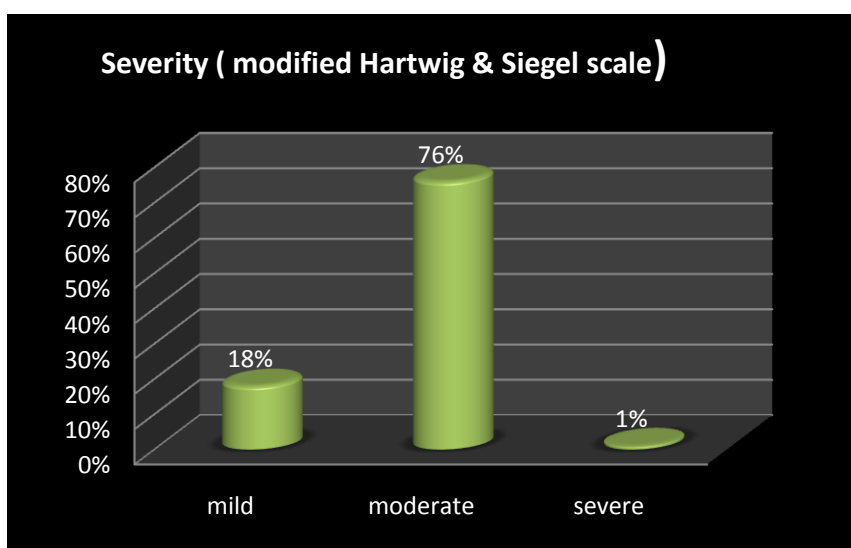


Fig.5

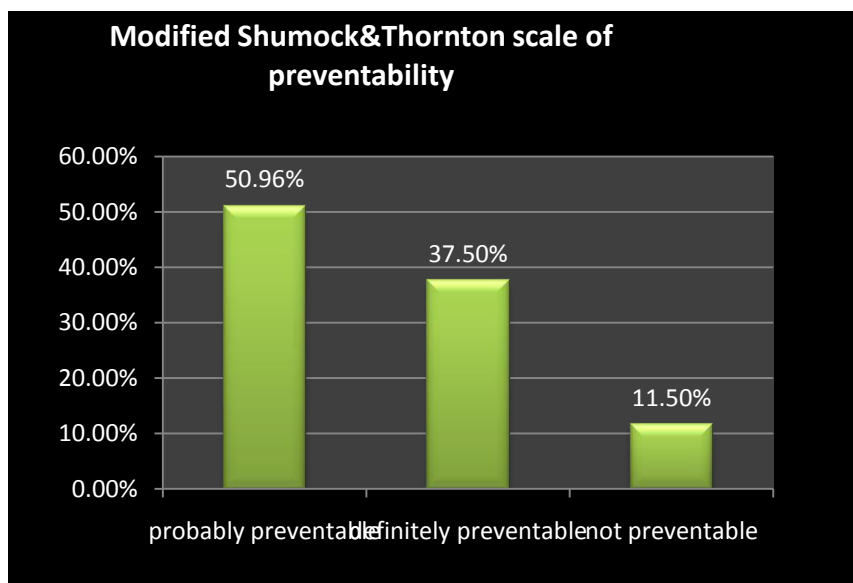


Fig.6

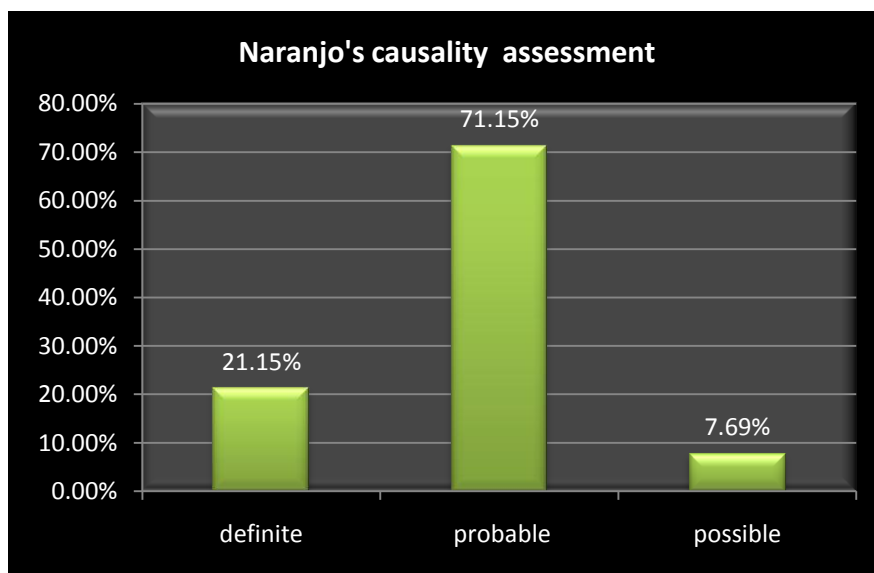


Fig.7

V. Discussion

A total of 104 cases of CADR were included in the study, in duration of one year. Elderly and paediatric patients are particularly vulnerable to ADRs because drugs are less likely to be studied extensively in these extremes of age, and drug absorption and metabolism are more variable and less predictable in both of these groups. Efforts are needed to predict and prevent the occurrence of ADRs in children^{[28][29]}. A little higher incidence was found in female patients(58.65%). Similar finding in a study where about 63% females were found to be affected was reported by Priyadharsini *et al* 2011^[21]. Though few studies have found higher incidence in males, one of them reporting about 68.52 % of ADRs presenting in male children^[22]. In fact a study comprising of age group 3 months to 98 years reported that the adult group comprised the largest portion of patients (64.0%), followed by the elderly group (32.5%) and children (3.5%). Females comprised 66.9% of all patients, with similar distributions in the adult and elderly subgroups but female children comprised less than half of the paediatric group, which represented a significant difference from the other age groups $p < 0.001$ ^[23]. The difference could be due to difference in demography or composition of population and hence, a larger sample size and longer duration of study in different populations may produce a more reliable outcome.

About 74% patients were prescribed polypharmacy which is an established cause of ADRs. It is an additive risk of drug–drug interaction and important predictor of ADR^{[5][24]}. ADRs may occur due to drug interaction, synergism, duplication, additive effect, discontinuation of therapy, changing the dose to save money,

skipping some medications and physiological antagonism^[28]. It's highly recommended to avoid prescribing multiple drugs and use the drugs rationally. Children are more vulnerable to ADRs owing to their immature physiological functions which affect the pharmacodynamics and pharmacokinetics of drugs differently as that from adults.

Indiscriminate use of anti microbials increases the incidence of ADRs and cutaneous ADRs are the commonest. In our study Antimicrobial drugs were responsible for about 71.15% cases of CADRs. It's consistent with the findings in reported literature. Systematic review by Tejas et al states major suspect groups as antimicrobials (45.46%), NSAIDs (20.87%), antiepileptics (14.57%) and corticosteroids (3.87%). They reported commonly implicated drugs were sulfa (13.32%), β -lactams (8.96%), carbamazepine (6.65%), phenytoin (6.46%), fluoroquinolones (5.12%), ibuprofen (4.71%), nitroimidazole (4.17%), antituberculars (2.81%), topical betamethasone (2.34%), diclofenac (2.32%) and aspirin (2.26%)^[27]. Antibiotics were responsible in causing 67% of ADRs in a similar study which found rashes and urticaria comprising 37% of data^[21]. A recent study found among anti-infectives, drugs most commonly implicated in ADRs were amoxicillin + clavulanate (21.87 %) followed by ceftriaxone (20.31 %) ^[22]. Similar findings were reported in a study which found antibiotics as major class of drugs associated with the ADRs (67%) and cutaneous ADRs as the most common manifestations of such reactions (37%). The drugs were vancomycin, cloxacillin, amoxicillin, ampicillin, meropenem, ciprofloxacin, and cefixime^[21]

Maculopapular rashes were the commonest in 64.42% of patients, followed by FDE occurring in 18.26% of patients & 15.38% suffered urticaria. In a systematic review of CADRs in Indian population, 38 different types of CADRs were observed. Maculopapular rash (32.39%), FDEs (20.13%) and urticaria (17.49%) were commonly reported^[27]. So our findings are consistent though this review includes adult population too. Rashes and urticaria were the most common type of ADR (37%) reported by another study conducted on paediatric age group^[21]. Another retrospective study on 90 children reported maculopapular eruption (MPE) (57.7%), acute urticaria (16.6%) and fixed drug eruption (14.4%)^[30]

Naranjo's algorithm for causality assessment of ADRs is a widely used scale^[17] and was used in our study. 71.15% cases were of probable causality score, 21.15% cases had definite score & possible score was for 7.69% cases, (Fig.7). Priyadharsini and et al reported about 80% of the ADRs of probable causality and 87% were of probable preventability. The median preventability of ADRs in hospitals has been reported as 35.2 % (18.7%-73.2%)^[25]. Preventability assessed by modified Shumock & Thornton scale in our study revealed that 50.96% ADRs were probably preventable, 37.5% ADRs were definitely preventable and 11.5% were under the category not preventable. Another study reported Majority (87.5 %) of the ADRs were of 'probable' causality category and 96.9 % were not preventable.^[23]. A systematic review and meta analysis reported that implementing CPOE (computerized provider order entry) is associated with greater than 50% decline in pADE (Preventable adverse drug events) rates in hospital-related settings, medication errors decline to a similar degree^[31]. Classification and evaluation of ADRs in terms of severity can recognize the root cause of ADRs and appropriate steps by healthcare providers can improve paediatric Pharmacovigilance^[5]. In our study, one case was recognized as severe type and that there was no mortality due to ADR. Most of the preventable adverse drug events take place in prescribing stage of medication, improper prescribing judgment and inadequate patient monitoring are the most frequent causes identified for preventability of adverse drug events. Severity assessment by Hartwig and Siegel scale could identify about 76% cases fall into moderate category and only one fell into severe class whereas, no death was reported because of ADRs.

VI. Conclusion

Children are more vulnerable and prone to ADRs but not many studies have been undertaken in paediatrics age group. The effects last longer and sometimes for lifelong in this age group. Cutaneous ADRs are the commonest and create panic in patients and parents. Early diagnosis, treatment, awareness about the same, monitoring and reporting needs to be done along with more and more studies to generate data which will ensure safety indices to improve and avoid undesirable consequences. It will generate awareness in medical personnel to address the issue as early as possible in case of unavoidable consequences. Most of the ADRs are still in the category which could be prevented and the figure if managed well would reduce the incidence to very low index. Causality assessment shows that if awareness about the same is there along with more study data available, the ADRs can be predicted and avoided or at least early management be ensued. The drugs which are responsible in most cases for causing CADRs for example anti microbial agents, their indiscriminate use can be avoided. All the hospitals should have ADR reporting culture and should generate their own data to understand their status and develop strategies to curb the same. Children are our future; giving them a beautiful and healthy life is securing our tomorrow.

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