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Original Research Article

# Pattern of adverse drug reactions due to antibiotics in a tertiary care hospital

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## ABSTRACT

**Background:** Adverse reactions are known to occur with all classes of drugs and the incidence of adverse drug reactions (ADRs) due to antibiotics has increased with rise in infectious diseases contributing significantly to the increased health care costs.

**Methods:** This retrospective observational study analysed the ADRs due to antibiotics that were reported by spontaneous reporting to ADR monitoring centre (AMC), functioning from Department of Pharmacology, ESIC-MC and PGIMSR. The total study period was 48 months from January 2013 to December 2016. During this period, all the ADRs due to antibiotics reported to the AMC were included in the study. This study analysed the retrospective data to find out the pattern of adverse drug reactions due to antibiotic drug class. Causality, severity and preventability were assessed using standard scales.

**Results:** During the study period, a total of 228 ADRs due to antibiotic use were reported among 179 patients. Gender-wise distribution showed that males were slightly more affected than females by the ADRs due to antibiotics [93(52%) Vs. 86 (48%)]. Out of the total 179 antibiotics administered to the patients, beta-lactam antibiotics dominated followed by nitroimidazoles, quinolones and glycopeptide antibiotics in causing ADRs. Rashes and itching were most common ADRs followed by breathlessness and hypotensive episodes. Causality was assessed by Naranjo algorithm scale and causality was definite in 16 (7%), probable in 87 (38%) and possible in 125 (55%). Severity of the ADRs was assessed by Hartwig and Siegel scale and it was found that most of the ADRs 198 (87%) were of mild severity and 30 (13%) were of moderate severity and none of them were severe or lethal. Preventability was assessed by Schumock and Thornton scale and it was found that only 24 (11%) were preventable, 74 (32%) were probably preventable and 130 (57%) were not preventable.

**Conclusions:** The study concluded that ADRs due to antibiotics are common and few of them resulted in increased healthcare cost due to the need for some interventions and increased length of hospital stay. The health system should promote the spontaneous reporting of ADRs due to antibiotics, proper documentation and periodic reporting to regional pharmacovigilance centers to ensure drug safety.

**Keywords:** Adverse drug reaction, Antibiotics, Beta-lactam antibiotics

## INTRODUCTION

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is a noxious, unintended, and often unavoidable response to normal therapeutic doses of a medicine.[1] ADRs are associated with marked socioeconomic loss to lengthy hospitalization stays and associated morbidity and the hospital admission rate due to ADRs is over 10% in some countries.[2,3] Detecting ADRs and establishing preventive measures is essential for patient safety. Therefore, the importance of pharmacovigilance (PV) must be emphasized. Furthermore efficient spontaneous reporting system is necessary to uncover ADRs.[1] Several ADR reporting and monitoring systems, including computerized surveillance systems, have encouraged the monitoring of ADRs at in-hospital regional PV centers, and could promote the early identification or prevention of ADRs with properly

designed ADR detection methods.[4,5] Periodical evaluation and analysis of reported ADRs filed during PV enhances the understanding of the ADR magnitude and patterns.

Antibiotics are used commonly in routine practice for treatment and prophylaxis of various disease conditions. But, like all other drugs, they also show some ADRs in various patient conditions.

According to a study conducted by Novotny et al, the most troublesome classes of drugs contributing to ADRs were antibiotics followed by antitumor agents, they are responsible for the recorded adverse effects in approximately 16% and 15% of cases, respectively.[6] Antibiotics belong to different classes such as penicillins, cephalosporins, sulfonamides, quinolones and aminoglycosides, and they vary in their mechanism of action and adverse effects.

More than 70% of ICU patients receive antibiotics for therapy or prophylaxis, with much of this use being empiric and over half of the recipients receiving multiple agents. The total costs associated with antibiotics are not only related to antibiotic use itself, but also to co-medication, drug interactions and adverse drug events.[7] This study was done to find out the pattern of ADRs due to antibiotic class of drugs in patients of a tertiary care hospital.

## METHODS

This retrospective observational study analysed the ADRs due to antibiotics that were reported by spontaneous reporting to ADR monitoring centre (AMC), functioning from Department of Pharmacology, ESIC-MC and PGIMSR. The total study period was 48 months from January 2013 to December 2016. During this period, all the ADRs due to antibiotics reported to the AMC were included in the study. Patients of all age groups who developed ADRs due to antibiotics were included for the study. This study analysed the retrospective data to find out the pattern of ADRs due to antibiotic drug class. Data was expressed as numbers and percentages. The causality assessment of the reported ADRs was carried out using the ‘‘Naranjo causality assessment scale”. In the Naranjo Algorithm, the drug reaction can be classified as definite, probable, or possible.[8] The modified Hartwig and Siegel scale classifies severity of ADR as mild, moderate or severe with various levels according to factors like requirements for preventable change in treatment, duration of hospital stay, and the disability produced by the ADR.[9] The modified Schumock and Thornton scale classifies ADRs as definitely preventable, probably and not preventable based on a set of questions for each level.[10]

## RESULTS

During the study period, a total of 228 ADRs due to antibiotic use were reported among 179 patients. Gender-wise distribution showed that males were slightly more affected than females by the ADRs due to antibiotics [93(52%) Vs. 86 (48%)] (Figure 1).

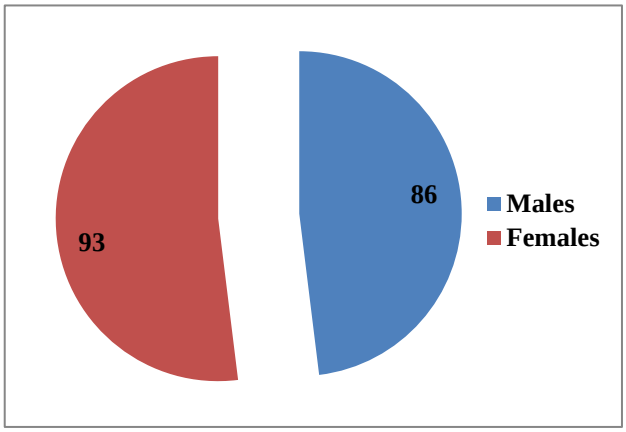


**Figure 1: Number of males and females who had ADRs due to antibiotics.**

Adult patients (149) were more affected by ADRs than geriatric patients (17) and children (13). Out of the total 179 antibiotics administered to the patients, beta-lactam antibiotics dominated followed by nitroimidazoles, quinolones and glycopeptide antibiotics (Figure 2).

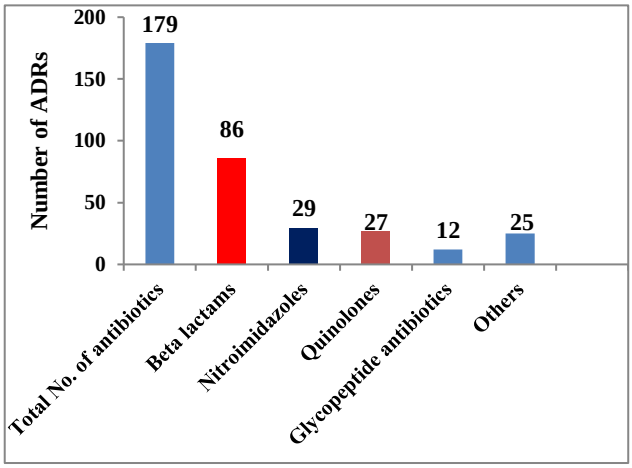


**Figure 2: ADRs due to various therapeutic classes of antibiotics.**

Among the beta-lactam antibiotics, ceftriaxone (58), cefixime (4), cefoperazone+sulbactam (1), ertapenem (3), piperacillin+tazobactam (10), meropenem (1), amoxicillin (4), amoxicillin+clavulanic acid (5) caused the ADRs. Metronidazole (29) was the nitroimidazole causing ADRs. Among the quinolones, ciprofloxacin (21) followed by levofloxacin (4) and moxifloxacin (2) caused the ADRs. Fifteen ADRs were due to Vancomycin (12) and co-trimoxazole (1) and doxycycline (2) antibiotics. Antitubercular (ATT) drugs (17) and antifungal (5) caused the ADRs in 22 patients.

Rashes and itching were most common ADRs reported followed by hypotensive episodes and breathlessness (Figure 3).

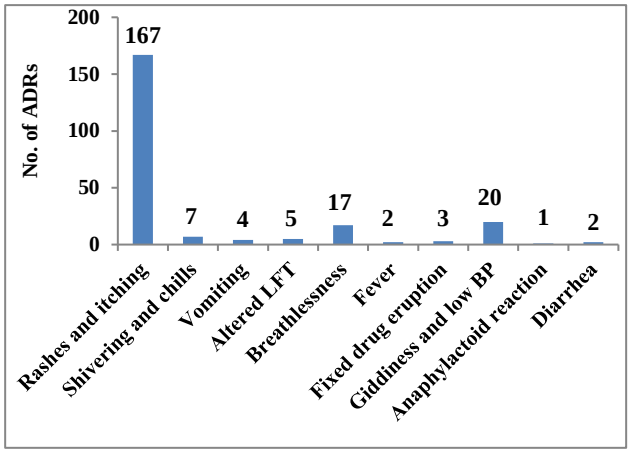


**Figure 3: Pattern of adverse drug reactions to various antibiotics.**

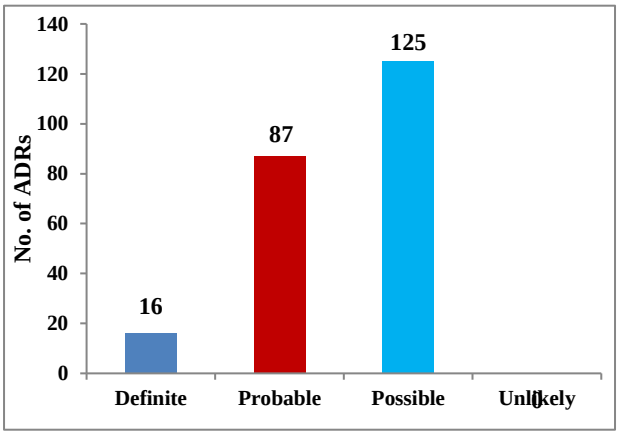


**Figure 4: Causality assessment of ADRs using the Naranjo scale.**

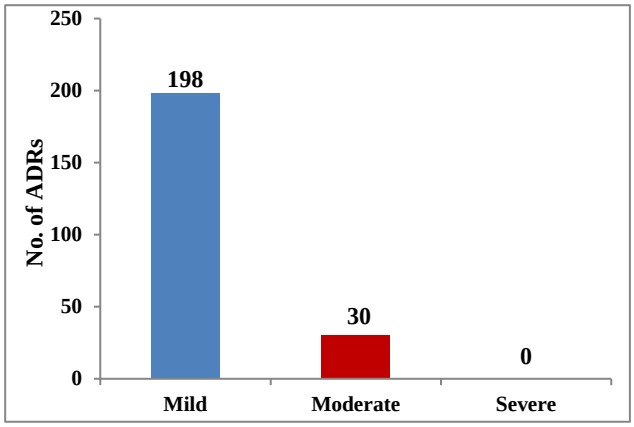


**Figure 5: Level of severity of reported ADRs Using the modified Hartwig and Siegel scale.**

Other ADRs included shivering, chills, vomiting, altered liver function tests (LFT), fever, fixed drug eruption, anaphylactoid reaction and diarrhea. Causality was assessed by Naranjo algorithm scale and causality was definite in 16 (7 %), probable in 87 (38%) and possible in 125 (55%) (Figure 4).

Severity of the ADRs was assessed by Hartwig and siegel scale and it was found that most of the ADRs were of mild severity 198 (87%) and 30 (13%) were of moderate severity (Figure 5) and none of them were severe or lethal. Preventability was assessed by Schumock and Thornton scale and it was found that only 24 (11%) were preventable, 74 (32%) were probably preventable and 130 (57%) were not preventable (Figure 6).

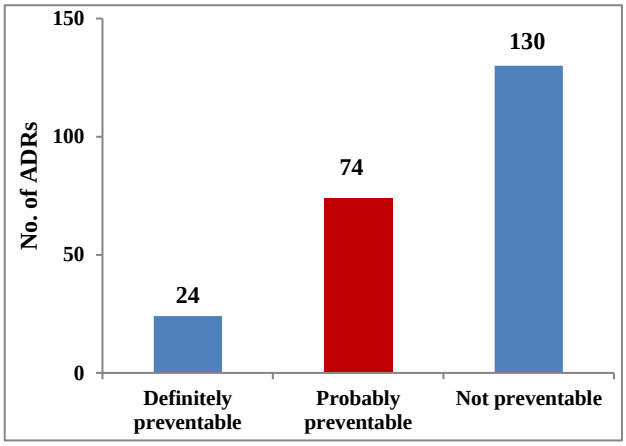


**Figure 6: Preventability of reported ADRs using the modified Shumock and Thornton method.**

## DISCUSSION

ADRs are important cause of mortality and morbidity in both hospitalized and ambulatory patients. So there is a need to study ADRs seriously to create awareness about ADRs among patients to motivate health care professionals in the hospital to report ADRs and to minimize the risk. Early detection, evaluation and monitoring of ADR are essential to reduce harm to patients and thus improve public health.[8,11] In Darchy's report, antibiotics accounted for 11% of iatrogenic disease. Classen states that, although adverse reactions seem to occur in a small proportion of antibiotic courses, the frequency of antibiotic use makes them account for 23% of all adverse events recorded.[8,12,13]

Males were slightly more affected than females by the ADRs due to antibiotics in our study. Predominance of any gender being affected by ADR may also be due to the number of males or females admitted to the hospital during that period as seen in the study conducted by Shamna et al.[7] Geriatric patients were more prone to antibiotic ADRs due to age related pharmacokinetic and pharmacodynamic changes and the presence of co-morbid illnesses and polypharmacy along with infectious diseases. In our study, age-wise distribution showed the predominance of adult patients followed by geriatric and pediatric patients. This may be because of more adults being admitted to the

hospital during this period and patients with less than 60 years were considered in the adult group. This finding is in contrast to a study conducted by Shamna et al, where ADRs due to antibiotics were observed more in geriatric age group.[7] Third generation cephalosporins accounted for the majority of the ADRs. The cephalosporins and fluoroquinolones were the most used antibiotic class in the inpatient settings, so that the reported ADRs were also more in these drug classes. A study conducted by Stavreva et al, also revealed the predominance of cephalosporins as the main cause for ADRs.[9,12] Dermatological system was most commonly affected manifesting as rashes and itching in majority of the cases. This was followed by cardiovascular system presenting as hypotensive episodes and respiratory manifestations including breathlessness. Four other studies also showed the predominance of cutaneous manifestations.[7,13-15]

The causality assessment of ADRs was done using the Naranjo scale in which no reactions were found to be unlikely and majority were possible with a less number of probable and definite reactions. These data correlate with the study of Starveva et al, Jimmy Jose et al, Priyadharshini et al, where the causality was possible in most of the ADRs.[7,12,16,17] Preventability was assessed by Shumock and Thornton method which showed that majority of the reactions were not preventable 130 (57%) and only 24 (11%) were preventable which also shows that rational antibiotic policy plays an important role in selection of the antibiotics which exists in our hospital. According to a study conducted by Bates, antibiotics were responsible for 9% of preventable and 30% of non-preventable ADRs.[18]

Suspected ADRs were analysed for the outcome which showed that the offending drug was withdrawn in many of the cases. The dose had to be altered in some patients while no change was made with the suspected drug in others considering the risk benefit ratio in specific patients and in some cases, the use of antibiotic was according to the culture and sensitivity reports. Drug rechallenge was not attempted in any of the cases. In our study most of the reactions were mild followed by moderate severity. Majority of the patients recovered from the ADR and none of the reactions were severe or lethal. Jimmy Jose et al, also found that moderate and mild reactions were more in their study. There were some severe reactions reported while majority of the suspected drugs was withdrawn and 70% of the patients recovered.[16] All the cases needed treatment for recovery from the reactions in which many of them were treated symptomatically. The study carried out by Stavreva et al, and Priyadharsini et al, also showed that the severity was moderate for the reported ADRs.[12,17]

## CONCLUSION

Adverse Drug Reactions are one of the important drug related issue in the hospital setting and is a challenge for ensuring drug safety. Antibiotics are used for treatment and prophylaxis of various infectious conditions and are considered as safer drugs when used rationally. Antibiotics also cause ADRs in various clinical situations as seen with other classes of drugs. Spontaneous reporting of ADRs to antibiotics is fairly good in our hospital setting as shown in the number of ADRs to antibiotics. Our study revealed the occurrence of mild to moderate ADRs and none of them were serious or lethal. Few of them resulted in increased healthcare cost due to the need for some interventions and increased length of hospital stay. More awareness is required among the health fraternity to recognize and report ADRs due to antibiotics.

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