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### RESEARCH ARTICLE

#### A STUDY ON ADVERSE DRUG REACTION PATTERNS OF INJECTABLE ANTIBIOTICS REPORTED IN THE PHARMACOVIGILANCE CENTRE OF A TERTIARY CARE TEACHING INSTITUTE, MANIPUR

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#### Abstract

**Background:** Antibiotics are one of the most commonly used drugs in hospitalised patients and are sometimes associated with significant safety concerns. However, there is still insufficient data about the incidence of adverse drug reactions (ADR) especially in case of injectable antibiotics. This study was done to assess the severity and pattern of different types of adverse drug reaction that occurs with commonly used injectable antibiotics.

**Method:** A retrospective cross-sectional study was done at Pharmacovigilance centre RIMS utilizing data from January 2018 till December 2019.

**Result:** A total of 146 patients who presented with antibiotic associated ADR reported during the study period were included in this study. Incidence was higher in males (90) as compared to females (56). The most common injectable antibiotic responsible for ADR was found to be the cephalosporin group (42.6%). A total of 178 different ADRs were observed among 146 patients, out of which the dermatological system (27.4%) was the most commonly affected system. On evaluation of WHO-UMC causality assessment of ADRs, majority were found to be possible (64.4%).

**Conclusion:** Injectable antibiotics are one of the most important drugs used for treatment of various clinical conditions and the sheer magnitude of their usage among hospitalised patients requires special monitoring especially with respect to the adverse reactions they can cause. A more active pharmacovigilance is needed for better understanding of the types of injectable antibiotics associated ADRs. Active monitoring can also help promote rational use of these important life saving drugs.

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**Introduction:-**

Antibiotics are substances that are produced by microorganisms but they can selectively suppress the growth of other microorganisms at very low concentrations. In some clinical conditions they can even kill the invading microorganisms. They are one of the most frequently used drugs but are also commonly misused as well. Their importance in medical practice is apparent especially in a developing country like India where the burden of infectious diseases is still very predominant.<sup>1</sup> It has been reported that developing countries contribute to approximately 76% of the global antibiotic use and the various types of antibiotics themselves rank as the most commonly prescribed medications globally. This widespread use of antibiotics makes patients more susceptible to antibiotic related adverse drug reactions (ADR).<sup>2</sup> In fact, some studies conducted in tertiary level hospitals have even reported that antibiotics contributed to 40% of the total ADRs.<sup>3</sup> The reason for this high incidence of antibiotic related ADRs could be because, roughly 50% of all hospitalised patients are observed to receive at least one antibiotic, either oral or injectable during their hospital admission.<sup>4</sup>

Adverse drug reaction, according to World Health Organisation (WHO) is defined as “any response to a drug which is noxious and unintended, and which occurs in doses normally used in man for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological function”.<sup>5</sup> When hospitalised patients develop ADR, it can result in increased morbidity, prolongation of hospital stay, increased medical expenses or even death in some unfortunate cases, due to which ADRs have been considered as one of the major public health problems.<sup>3</sup> ADRs have been identified to be the 4<sup>th</sup>/6<sup>th</sup> cause of death among hospitalised patients and it is estimated that approximately 5% of all hospitalised patients eventually develop ADR during the course of their hospital stay. Several factors which can lead to ADR have been identified. The commonly identified ones are patient related factors like age, gender, body mass index, immune status of the patients, presence of chronic illness like kidney disease, and drug related factors like polypharmacy, dose, route and frequency of drug administration.<sup>6</sup>

Adverse reaction due to antibiotics can be mild where the patient may experience mild itching with rash, but sometimes it can lead to more serious effects like end organ toxic effects, and subsequent infection with antibiotic resistant microorganisms.<sup>4</sup> In some unfortunate cases antibiotic associated ADRs may also lead to *Clostridium difficile* infection (CDI), methicillin resistant *staphylococcus aureus* infection and vancomycin resistant Enterococcus infection.<sup>7</sup>

It is estimated that approximately 50% of ADRs that occur are preventable.<sup>8</sup> Moreover some studies have reported that the durations of antibiotic therapy are needlessly prolonged in many cases and that approximately 20 – 30% of inpatient days of antibiotic therapy are unnecessary.<sup>4</sup> A study conducted in India had reported that, antibiotics were responsible for 35 – 40% of the total ADRs that occurred during their study period. Due to less sample size during pre-marketing clinical trials, antibiotic related ADRs are also often undetected.<sup>9</sup> Hence, active ADR monitoring with the help of a robust Pharmacovigilance system, seems to be one of the measures to decrease the incidence of antibiotic associated adverse reactions.<sup>8</sup>

**Aims and Objectives:-**

The main aims and objectives of this study are:

1. To assess the severity and pattern of the various types of adverse drug reaction that occurs with the use of injectable antibiotics
2. To assess the prevalence of antibiotic associated ADRs with respect to age and gender.

**Materials and Methods:-**

A retrospective cross-sectional study was conducted at department of Pharmacology, Regional Institute of Medical Sciences (RIMS) Imphal. Data for the study were obtained from the Pharmacovigilance centre of RIMS after obtaining permission from the Pharmacovigilance co-ordinator of the centre. ADRs are reported to the centre from various clinical departments of RIMS by using suspected adverse drug reactions reporting forms prescribed by National Coordination Centre (NCC), Pharmacovigilance Programme of India (PvPI). The Pharmacovigilance associate of the centre then enters the details of the ADRs in ‘Vigiflow’ software provided by Uppsala Monitoring Centre (UMC) for reporting to the NCC. The standard operating procedure of IPCSOP no. IPC/PvPI/QA/013 is followed by the Pharmacovigilance centre for reporting of ADRs to NCC.<sup>10</sup>

**Inclusion criteria:**

ADRs associated with injectable antibiotics which were reported during January 2018 upto December 2019.

**Exclusion criteria:**

Patients on treatment with oral antibiotics.

**Evaluation of data:**

World health organization (WHO) Uppsala monitoring centre (UMC) causality assessment scale was used where the ADRs were classified into certain, probable, possible, unlikely, conditional and un-assessable.<sup>11</sup>The prevalence of ADR with respect to age, gender and the type of antibiotics used and systems affected were also evaluated.

**Data analysis:**

The data collected were computed using Microsoft (MS) Excel and expressed as numbers and percentages.

**Results:-**

A total of 146 patients who presented with a total of 176 ADRs were selected for this study. The patients were classified according to age, sex and the type of antibiotic associated ADR, the systems affected and causality assessment of the ADR.

**Gender distribution:**

Out of the 146 patients included in the study, 90 (61.6%) were males and 56 (38.4%) were females.

**Table I:-** Gender distribution.

Gender	Total number	Percentage
Male	90	61.6%
Female	56	38.4%

**Age distribution:**

The age groups were categorized under four groups at 20 years gap interval. Majority (37%) of the cases were observed in the 40 – 59 years age group.

**Table II:-** Age wise distribution.

Sl no	Age group distribution	Number of Patients	Percentage
1.	0 – 19 years	19	13%
2.	20 – 39 years	44	30.1%
3.	40 – 59 years	54	37%
4.	≥60 years	29	19.9%

**Frequency of ADR caused by different classes of injectable antibiotics:**

A total of fourteen different antibiotics were found to cause ADRs in 146 patients, and in 2 patients, the ADR was caused by more than one antibiotic. The most common antibiotic contributing to ADR was found to be the cephalosporin group of antibiotics, where a total of 63 patients (42.6%) were reported to develop adverse reactions.

**Table III:-** Antibiotic class wise distribution.

Causative drug class	Causative drug	No. of Patients	Frequency (%)
Cephalosporins Total = 63 (42.6 %)	Ceftriaxone	26	17.6 %
	Ceftriaxone + Sulbactam	35	23.6 %
	Cefotaxime	2	1.4 %
Penicillins Total 40 (27 %)	Piperacillin + Tazobactam	33	22.3 %
	Amoxicillin + Clavulanic acid	7	4.7 %
Fluroquinolones Total 20 (13.5 %)	Levofloxacin	13	8.8 %
	Ofloxacin + Ornidazole	7	4.7 %
Aminoglycosides Total 4 (2.7 %)	Amikacin	3	2 %
	Streptomycin	1	0.7 %
Others	Vancomycin	6	4 %

Total = 21 (14.2%)	Meropenem	5	3.4 %
	Azithromycin	4	2.7 %
	Metronidazole	4	2.7 %
	Linezolid	2	1.4 %

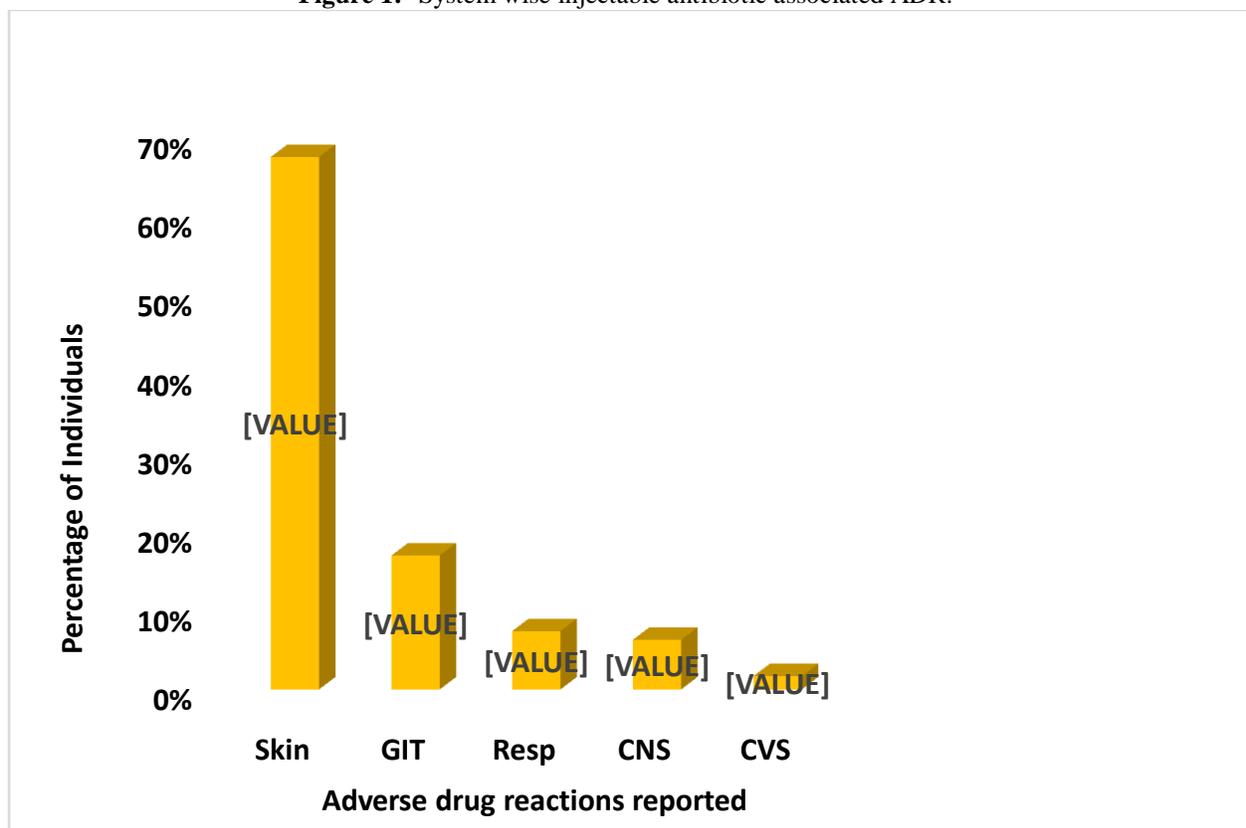
Organ – system wise distribution of injectable antibiotic associated ADRs:

The most common system involved is the dermatological system, where a total of 119 ADRs were recorded (67.6%)

**Table IV:-** System wise distribution of ADR.

System	ADRs	No. of patients	Frequency
Dermatological system Total 119 (67.6%)	Maculopapular rash	68	38.6%
	Injection site reaction	34	19.3%
	Vesiculobullous rash	10	5.7%
	Toxic epidermal necrolysis	2	1.1%
	Generalised itching	5	2.8%
G.I.T. Total 30 (17%)	Diarrhoea	2	1.1%
	Abdominal pain	10	5.7%
	Nausea & Vomiting	18	10.2%
Respiratory System Total 13 (7.4%)	Shortness of breath, cough	13	7.4%
C.N.S. Total 11 (6.3%)	Headache & dizziness	5	2.8%
	Tingling & numbness	3	1.7%
	Restlessness & anxiety	3	1.7%
C.V.S. Total 3 (1.7%)	Fall in B.P.	2	1.1%
	Anaphylactic shock	1	0.6%
	Total	176 ADRs	

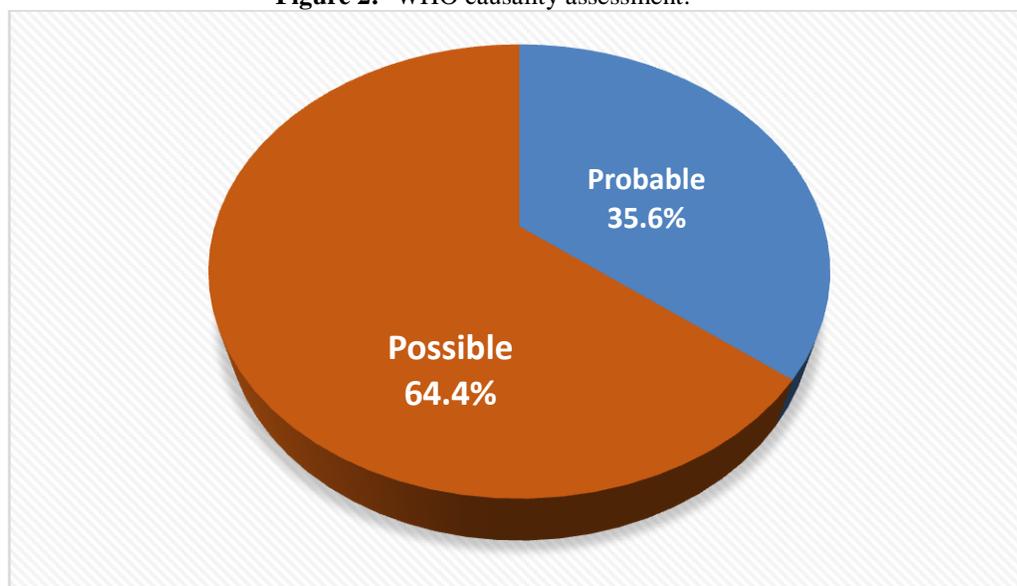
**Figure 1:-** System wise injectable antibiotic associated ADR.



Causality assessment based on WHO-UMC causality assessment scale:

A total 146 individual case sheet reports (ICSR) were analysed for this study, out of which 94 were found to be probable and 52 were found to be possible.

**Figure 2:-** WHO causality assessment.



### Discussion:-

Antibiotics remain one of the most important drugs available in allopathic medicine because they are among the few drugs which can lead to complete cure of a disease. When used rationally, they are quite safe, but due to misuse and other factors, many adverse effects have also been associated with its use.<sup>9</sup>In this present study, a total of 698 patients with ADRs were reported to the Pharmacovigilance centre during the period from January 2018 up to December 2019, out of which 146 ADR's (20.9%) were found to be due to injectable antibiotics alone. This finding is quite similar to the study done by Hagiya et al<sup>12</sup> which showed that 17.1% of ADRs were related to antibiotics. However, in a study done by Priyadharsini R et al<sup>13</sup> antibiotic associated ADRs contributed to 67% of all ADRs reported.

In this study, ADRs were observed to be more in males (61.6%) as compared to females (38.4%). Male predominance (58%) was also noted by Bhattacharjee P et al<sup>14</sup> and Shamna M et al<sup>15</sup> but Shehab N et al<sup>16</sup> have observed significant female predominance (67%) while Saha A et al<sup>17</sup> observed the prevalence of ADR in male and female to be more or less similar. The reason for gender specific difference has not been proven but the possible reasons could be the difference in body mass index, fat composition, drug susceptibility, hormonal effects or due to genetic variability.<sup>18</sup> Other studies also claim that male predominance could simply be due to higher hospital admission rate of male patients.<sup>14</sup>

The age group most commonly affected was found to be between 40 – 59 years (37%) followed by the age group between 20 – 29 years (30%). Similar finding was observed by Vijaishri R & Andhuvan G<sup>19</sup> where the most common incidence of ADR was found to be in the age group of 45 – 65 years (41.96%). This is in contrast to Jayanthi CR et al<sup>9</sup> where majority of ADRs were observed in the younger age group of 21 – 40 years (55%). Like gender, the significance of age with respect to the development of ADR is also not fully understood at the moment, but some studies have concluded that ADR may be more in adult age group due to their increased frequency of hospital visit and subsequent admission.<sup>6</sup> Contrary to all these facts, the study done by Eluwa et al<sup>20</sup> have argued that age and gender may not be an important factor in determining the incidence of ADRs.

The cephalosporin group of injectable antibiotics were responsible for majority of the ADRs contributing to 42.6%, among which the combination of ceftriaxone & sulbactam was the most common (23.6%). Penicillin group of antibiotics came in second and were found to be responsible for 27% of the ADRs reported. This is similar to the

studies done by Richa et al<sup>21</sup> and Dhar K et al<sup>22</sup> where cephalosporins contributed to 37.7% and 28.5% of all cases. However, in both studies, injection ceftriaxone alone and not combination was found to be the most common. Cephalosporins are undoubtedly the most commonly used antibiotics since they are effective against both gram-negative and gram-positive microorganisms. Hence, this wide usage of the drug could be one of the reasons for high incidence of ADR. Most ADRs associated with cephalosporins are found to be mild. Potentially life-threatening reactions due to cephalosporins are rare and the most commonly encountered severe adverse effect is found to be the development of *Clostridium difficile* infection within 90 days from exposure to the drug, which is also quite rare.<sup>23</sup> Contrary to this, studies like Behera SK et al<sup>6</sup> and Arulappen AL et al<sup>24</sup> have observed penicillin group to be the most common cause of antibiotic associated adverse reactions.

The dermatological system (67.6%) was found to be the system most affected in relation to antibiotic associated ADRs followed by the gastro-intestinal system (17%). Similar findings were observed by Jayanthi CR et al<sup>9</sup> where dermatological system was the most common system involved (58%) followed by the GIT (36%). However, Vijaishri R & Andhuvan G<sup>19</sup> have reported GIT to be the most commonly affected system (46%) followed by the dermatological system (10%). In this study, 2 cases of toxic epidermal necrolysis (T.E.N) were observed, one due to ceftriaxone and the other due to levofloxacin. One case of anaphylactic shock was also observed which was due to Piperacillin + Tazobactam combination.

Causality assessment was done using WHO-UMC causality assessment scale where 64.4% of cases were found to be possible and 35.6% of cases were found to be probable. Dhar K et al<sup>22</sup> also observed similar findings where 61.9% of cases were found to be possible and 25.3% were found to be probable. However, opposite findings were observed by Jayanthi CR et al<sup>9</sup> where 78% cases were found to be probable and 22% cases were found to be possible.

### **Conclusion:-**

Monitoring of antibiotic associated ADRs is important since they are one of the most commonly used drugs, especially in hospitalised patients. Antibiotics are generally safe drugs but can also cause devastating reactions in some unfortunate cases. This study has focused on the adverse reactions due to injectable antibiotics, where it was observed that cephalosporins contributed to majority of the ADRs but they were found to be mostly mild in nature. Penicillins and fluoroquinolones though contributing to a lesser percentage of the total ADRs were found to be associated with more severe ADRs. Active Pharmacovigilance remains one of the key factors for easy monitoring of adverse reactions due to antibiotics and for better understanding of the toxicities related to antibiotic use. Active pharmacovigilance will also help in early detection and management of ADRs which will in turn help in decreasing the burden of ADRs and also hopefully promote rational use of these important life-saving drugs. The Pharmacovigilance programme of India (PvPI) is still in the initial stage of development and hence more studies are needed to help strengthen and promote PvPI especially in the north east region of India.

### **Limitations**

1. This study was retrospective in nature and data was analysed using only the suspected adverse drug reaction reporting form which had been submitted to the Pharmacovigilance centre, hence a more in-depth analysis of the ADRs which could have been done by interaction with patients was not possible.
2. Since the study relied solely on the spontaneous ADR reporting system, many ADRs that were not reported could have been missed out.

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### **Conflict of interest**

The authors declare that there are no conflicts of interest.

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