

## A study on the usage of antimicrobial agents and adverse drug reaction of antimicrobial used in a tertiary care hospital in North East India

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### ABSTRACT

**Background:** Irrational use of antimicrobial agents (AMAs) has led to large scale development of drug resistance and adverse drug reactions (ADRs) which has become a growing world-wide concern. The study was conducted to analyze the prescribing pattern of AMAs and to evaluate the reported ADR of the AMAs prescribed.

**Methods:** A prospective study was conducted by analyzing 900 case sheets receiving AMAs in a tertiary care hospital. The study plan included analysis of average number of AMA prescribed, morbidity profile of patients, types of AMAs used, drug prescribed by generic/brand name, injectable AMA preparations and appropriateness of indication of AMA used. Thirty reported cases of ADR were evaluated for their casualty by Narnajo's scale and severity by Hartwigs scale.

**Results:** Average number of drugs per prescription was 1.54. Most common morbidity was fever due to various causes. 86.2% of AMA used was antibiotics. About 72.0% of AMAs were prescribed by generic name. Percentage of injectable preparation was 85.0%. 65.0% of drugs were prescribed from Essential drug list (EDL). Most offending drug for ADR was fixed drug combination (FDC) 30.0%. Common organ system involved was skin (63.3%). Most of the ADR were possible (80.0%) and mild (76.6%) in nature.

**Conclusions:** Average number of AMAs per prescription was 1.54. Percentage of drug prescribed by generic name is encouraging. However use of injectable preparation was very high. Majority of AMAs prescribed were antibiotics which is also very high. Periodic prescription audit will provide feedback to the prescribers and help in reducing the prescribing error and ADR cases.

**Keywords:** Antimicrobial agents, Adverse drug reactions, Generic name, Prescription audit

### INTRODUCTION

Antimicrobial agents are the most commonly prescribed group of drugs but they are one of the most abused drugs as well. It is estimated that 20-50% of antibiotic used are inappropriate resulting in increased risk of side effects, increase morbidity and mortality, higher cost and

increased rate of antimicrobial resistance (AMR) in community pathogens.<sup>1</sup> Antibiotic resistance has posed a threat to global health especially in developing countries like India where maximum burden of infectious disease prevail. The main contributing factor of these problems are irrational prescription, self medication and over the counter availability of AMAs.<sup>2</sup> More than 50% of all

medicines worldwide are prescribed, dispensed and sold inappropriately and 50% of patients fail to take them correctly.<sup>3</sup>

Various findings highlighted that there was a high incidence (>30%) of irrational prescribing pattern among the prescribers.<sup>4,5</sup> Non rational prescription usually indicate lack of training on part of prescriber. Training programme of health care professionals as well as periodic audit may improve the rational use of medications and reduce prescribing error. Apart from this drug utilization studies (DUS) can evaluate the rational drug prescribing by evaluating the quality of medical prescription and provide optimum quality of drug therapy.

The empirical use of AMA is the most important factor for increase incidence of ADR and which is very common in clinical practice. ADR reporting is often missed due to lack of awareness and drug safety monitoring. It accounts for 2-6% of all hospital admissions.<sup>6</sup> The incidence of ADR varies as low as 0.15% to as high as 30% and incidence of fatal ADR is 0.23% to 0.4%.<sup>7,8</sup> Drug monitoring is crucial to provide drug safety to the population. It generates valid data on different aspects of ADR and help to evaluate the assessment of causality, severity and preventability. The base of ADR data is spontaneous reporting but awareness about ADR reporting is still very poor amongst the health care professionals hence there is gross under reporting of ADR cases. The present study was under taken to see the usage pattern of AMAs at in patient department (IPD) of Medicine and to evaluate the ADR reported in these cases.

**METHODS**

A prospective study was carried out in IPD of Medicine department of Gauhati Medical College Hospital (GMCH) situated in Kamrup district of Guwahati, Assam which caters both rural and urban population of Assam and as well as other North Eastern States of India.

Nine hundred case sheets of IPD were analyzed over a period of one year from August 2014 to July 2015. The sample size of the study was calculated based on admission on emergency day of the six units of the Medicine department. The patients were selected by systematic random sampling to avoid bias. Hundred fifty case sheets from each of the six units were selected.

**Inclusion criteria**

- All the patients above 12 years admitted in the IPD of medicine on the emergency day.
- Patients of either sex.
- AMAs prescribed to the patients for treatment as well as for prophylaxis.

**Exclusion criteria**

- Incomplete information from the case sheets.
- Cases discharged within 24 hours of admission.

- Patients referred to other departments.
- Patients left against medical advice.

The study based on two types of observations.

- Prescribing pattern of AMAs.
- ADR of AMAs prescribed.

**Statistical assessment**

Data were analyzed descriptively and summarized using tables, bar diagrams and pie charts.

**RESULTS**

The demographic profile of the patient revealed 52.4% (n=472) were male and 47.6% (n = 428) were female. Mean age of the patient was 43.4 years (Table 1).

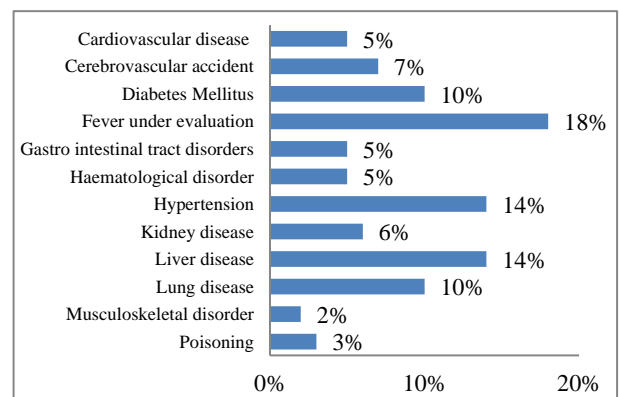
**Table 1: Gender wise distribution of patients.**

Sex	Frequency	Percent
Male	472	52.4
Female	428	47.6
Total	900	100.0

Highest numbers of patients were prescribed one AMA (59.9%) and two AMA in 26.9% and three and more than three in 13.2%. The average number of AMAs per prescription was 1.54 (Table 2).

**Table 2: Average number of AMAs/ prescription.**

No. of AMAs	Frequency	%
1	539	59.9
2	242	26.9
3 and >3	119	13.2
Total	900	100.0
Mean	1.54	
SD	0.81	



**Figure 1: Morbidity profile of patients.**

A wide spectrum of morbidity pattern was observed. Maximum cases were fever under evaluation (18.1%) and

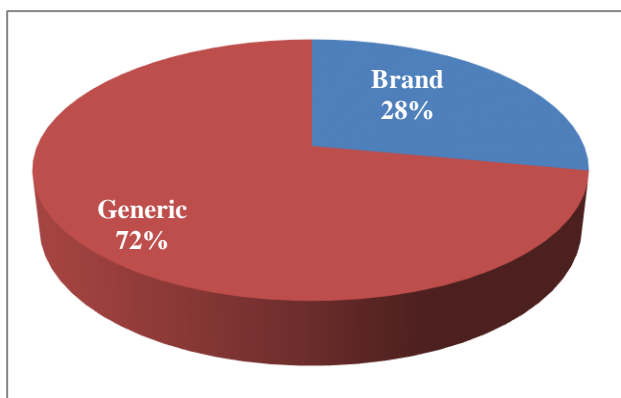
this is followed by liver disease (14.3%), hypertension (14.1%) and lung disease constituted (10.3%) (Figure 1).

Out of total 1389 AMAs prescribed in 900 patients, 1197 (86.2%) were antibiotics and other AMAs comprised of 13.8%. Out of antibiotics cephalosporin topped the list (39.9%) followed by FDC (25.7%). This is followed by quinolones (4.9%) and beta lactum (3.7%). Other AMAs constituted of metrogyl, artesunate, antifungal, anti retroviral therapy, anti tubercular drugs, anti viral and anti helminthic drugs (Table3).

**Table 3: Group of commonly prescribed AMA (Antibiotics and other AMAs).**

Group of drug	Frequency	%
Cephalosporins	555	39.96%
Fixed drug combination (FDC)	357	25.70%
Quinolones	69	4.97%
Beta lactams (carbapenems and monobactams)	52	3.74%
Macrolide	46	3.31%
Aminoglycoside	30	2.16%
Oxazolidinone	27	1.94%
Glycopeptides	20	1.44%
Gut antibiotic	15	1.08%
Tetracycline	9	0.65%
Lincosamide	9	0.65%
Sulfonamide	8	0.58%
Other AMAs	192	13.82%
Total	1389	

Most of the drugs (72.0%) were prescribed by generic name and 28.0% of drugs were prescribed by brand name (Figure 2).



**Figure 2: Distribution of group of drugs prescribed by brand/generic name.**

Maximum number of patients received AMA by injectable route (85.0%) and 15.0% by oral route (Figure 3).

The appropriateness of prescription in regards to indication of AMA use was 74.3%. The duration, dose and

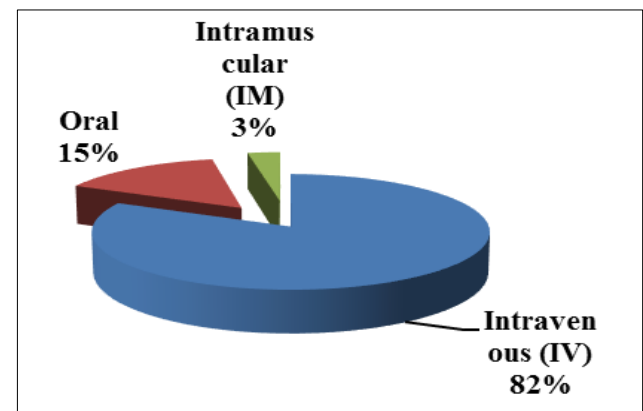
frequency were 75.5%, 85.2% and 83.2% respectively (Table 4).

**Table 4: Appropriateness of AMA use.**

Appropriateness	Frequency	%
Indication	668	74.3%
Duration	679	75.5%
Dose	766	85.2%
Frequency	748	83.2%

In this study the values of prescribing indicators are:

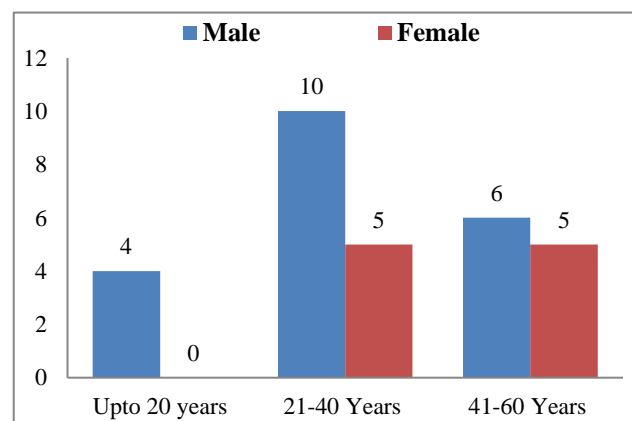
1. Average number of AMAs per prescription - 1.54.
2. Percentage of AMAs prescribed in generic name >72.0%.
3. Percentage of AMAs prescribed in injectable form 85.0%.
4. Percentage of drug prescribed from EDL (WHO norm) 65.0%



**Figure 3: Route of administration.**

**ADR cases**

The demographic pattern of ADR cases showed that 50.0% of males and females were in age group of 21-40 years. Sex distribution revealed 66.7% (n = 20) were males and 33.3% (n=10) were females (Figure 4).



**Figure 4: Age and sex distribution of ADR cases.**

The most common therapeutic class of drug causing ADR was FDC (30.0%) followed by anti retroviral therapy (ART) (26.7%) and cephalosporin (16.7%) (Table 5).

**Table 5: Antimicrobial Agents (AMAs) responsible for ADR.**

Groups of drugs	Frequency	%
Cephalosporin	5	16.7
Quinolones	3	10.0
Fixed drug combinations	9	30.0
Anti retroviral therapy	8	26.7
Anti tubercular therapy	3	10.0
Anti fungals	1	3.3
Tetracyclines	1	3.3

**Table 6: Organ system involved in ADR cases.**

Reaction	Frequency	%
Skin	19	63.3
Gastro intestinal System	4	13.3
Central Nervous System	2	6.7
Genito urinary System	2	6.4
Haematological	1	3.7
Respiratory	2	6.6
Total	30	100.0

**Table 7: Clinical manifestation in different organ system in ADR cases.**

ADRs	Number of ADRs, N = 30
Skin (19)	
Rashes with itching	6
Itching all over the body	4
Maculo papular rash	3
Erythematous itching plaque	3
Painful purpuric lesion	1
Itchy scaly papular lesion	1
Acneform drug eruption	1
Gastro Intestinal tract (4)	
Gastritis and Anorexia	1
Nausea, Vomiting and Abdominal pain	1
Dyspepsia	1
Diarrhoea and anorexia	1
Central Nervous System (2)	
Giddiness and Insomnia	1
Headache and Vertigo	1
Musculo Skeletal System (2)	
Tendinitis	1
Generalised weakness	1
Respiratory System (2)	
Difficulty in breathing	1
Cough and Wheezing	1
Hematological (1)	
Anaemia	1

The most common organ system involved in ADR was skin (63.3%) followed by gastrointestinal system (13.3%) and central nervous system (CNS) (6.7%) (Table 6).

The common clinical manifestation of ADR was rash with itching (n=6) and itching all over the body (n=4) followed by maculopapular rash (n=3) and erythematous itching plaque (n=3) (Table 7).

Causality assessment based on Naranjo's scale revealed majority of the suspected ADR cases were probable 80.0% (n = 24), possible 16.7% (n=5) and only 3.3% (n=1) were definite.

As per Hartwig's severity assessment scale majority of the ADR were mild 76.6% (n = 23), 23.4 % (n =6) were moderate and none of the cases were severe (Table 8).

**Table 8: Distribution of Causality and severity assessment of ADR cases.**

Parameter	Number of ADR (%) N = 30
Causality	
Doubtful; ≤0	0 (0.0)
Possible; 1-4	5 (16.7)
Probable; 5-8	24 (80.0)
Definite; ≥9	1 (3.3)
Severity	
Mild	23 (76.6)
Moderate	7 (23.4)
Severe	0 (0.0)

## DISCUSSION

In this study 50.2% of the patients were in the age group of 41-60 years and higher percentage of females was in the lower age group than males. Sex distribution showed male preponderance which was also observed by many authors.<sup>9-11</sup> The average number of AMA prescribed was low (1.54). Mono therapy of AMA was observed in 59.9% of cases. Increase in number of drugs per prescription increases the risk of drug interaction various side effects, increase cost and increases the prescribing error. This study tallies with the study of Khan et al., and Ahmed et al.<sup>11,12</sup>

The most common diagnosis was febrile illness (18.0%) and they are mostly clinically diagnosed either as typhoid or malaria or dengue and other bacterial and viral infections. For these cases AMAs are rather randomly prescribed without waiting for the time consuming laboratory test so that patients are not deprived of the benefits of early treatment. So, culture and sensitivity test were not done in most of the cases in early stage. Higher percentage of liver disease like hepatitis, cirrhosis was mostly due to alcohol abuse which was found to be very common in North East India.

Amongst the AMA prescribed 86.2% were antibiotics and cephalosporin topped the list (39.9%) followed by FDC (25.7%). Cephalosporin was widely prescribed because of its high potent action, availability in various formulations and its broad spectrum activity. Higher percentage of use of cephalosporin was observed in developing countries like India (82.0%) and Pakistan (65.2%).<sup>13,14</sup>

Indiscriminate use of FDC can lead to various adverse effects, drug interaction. So, it should be avoided as far as possible.

In this study 72.0% of AMAs were prescribed by generic name. As per WHO recommendation it should be 100%. But 72.0% is quite high as compared to other studies. Our study tallies with the findings of Admane et al, but this is in contrast to many studies.<sup>10,11,15,16</sup> This is due to doubt about the efficacy and bioavailability of generic formulations in physicians. Generic drugs are equally effective as brand name drugs and they are less costly.

The reason for higher percentage of patients receiving drugs through IV route is probably due to emergency intervention. When a patient is critically ill, unconscious and diagnosis is not confirmed at the time of admission many drugs are given empirically by IV route. Moreover, most patients received 3<sup>rd</sup> generation cephalosporin (Inj. Ceftriaxone, Inj. Cefotaxim) which is given by IV route. Over use of injection increases economic burden on patients as well as on health exchequer. This study was in concurrence with other authors.<sup>11,17</sup> This is in contrast to the finding of other studies.<sup>5,15</sup>

The prescriptions were mostly appropriate as regards dose, duration, frequency and indication.

It is observed that 50.0% of male and female belonged to the age group of 21-40 years. ADR is reported more in males (66.7%) as compared to females (33.3%). Majority of the ADR were reported in male patients and tallies with the finding of.<sup>18-20</sup> In this study FDC was the most common offending agent causing ADR which is in conformity with other studies.<sup>10,21</sup> FDCs are found to be most indiscriminately prescribed AMAs in variety of infection. Incidence of ADR rises with the rise in drug intake. Many epidemiological studies of ADR have shown that number of concurrently used drugs is the most important predictor of these complications. Result of the study has shown FDCs to be maximally contributing for ADR unlike cephalosporin reported in other study.<sup>22,23</sup> The causality assessment by Naranjo's scale showed that most of the cases categorised as probable (80.0%) and 16.7% were categorised as possible and very small percentage fall in definite category. This is in conformity with similar studies.<sup>24-26</sup>

As per severity assessment scale majority of the cases were mild followed by moderate and none of the reported cases were severe. Jimmy Jose et al found that moderate and mild reactions were more but in contrast to our studies they

also found some severe reactions.<sup>24</sup> The suspected drug was discontinued in 36.7% of the cases and withdrawn in some cases and treated symptomatically. Most of the patients recovered.

## CONCLUSION

This type of study can provide a framework for continuous prescription audit in health care institutions and help in creating a data base for comparisons of future trends in prescribing pattern of AMAs and help in framing policies towards rational use of drugs. Under reporting of ADR can be reduced by improving spontaneous reporting by sensitising the health care professionals.

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