

## Antibiotics-related adverse drug reactions at a tertiary care hospital in North India

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### ABSTRACT

**Background:** Antibiotics are considered to be commonly used drugs in hospital setting due to higher prevalence of infectious diseases especially in India. So, the present study was conducted to assess the incidence of adverse drug reactions (ADRs) due to antibiotics and analyze for causality of adverse drug events reported.

**Methods:** The present retrospective and observational, study was conducted in BPS GMC for women, Khanpur Kalan, Sonapat, Haryana which is a 500 bedded government medical hospital situated in rural area between March 2016 to February 2019 (i.e., 3 years). Patients of either sex or age who developed ADRs by any route were included in the study.

**Results:** 300 (38.65%) cases were reported due to antibiotics out of total 776 ADR cases. 3% cases were serious. Adults (65%) were found to be most commonly affected by ADRs. Among antibiotics, cephalosporins and penicillins (15.98%) were the major culprit to cause adverse events followed by nitroimidazoles (15.2%) and antitubercular drugs and fluoro quinolones (13.16%). The most affected organ system was skin (49.33%) followed by the gastrointestinal system (33%). As per WHO scale of causality assessment, 33.33% and 67.67% reported cases were found to probably and possibly related to adverse events respectively.

**Conclusions:** Antibiotics are most commonly prescribed drugs so its monitoring regarding ADRs may benefit the clinicians in early identification and management of ADRs so that quality of life of patient can be safeguarded at an earliest.

**Keywords:** Pharmacovigilance, ADR, Pharmacovigilance Program of India, Antibiotics

### INTRODUCTION

World Health Organisation (WHO) defines adverse drug reaction (ADR) as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function.” Adverse drug reaction is the 7th most common cause of death with 6.5% of admissions in National Health Service (NHS) hospitals is due to ADRs.<sup>1</sup> Sometimes, ADR-related costs may exceed the cost of the treatment of disease.<sup>2</sup>

Antibiotics are considered to be the commonly used drugs in hospital setting due to higher prevalence of infectious diseases especially in India. These are observed to be the main culprit of ADRs.<sup>3,4</sup> 3.2-40.9% of ADRs are reported due to antibiotics as per various studies conducted in Indian population.<sup>5-8</sup> This may be because of self-medication, over-the-counter use, and irrational prescription. Also excessive and irrational use of antibiotics may cause antibiotic resistance.<sup>9</sup> Thus, the rational use of antibiotics is a major health need.

Phatak et al rightly said that “drugs are double edged weapons”, so ADR monitoring is one of the crucial part during the treatment period of patient.<sup>10</sup>

Uppsala monitoring centre, Sweden in collaboration with WHO was first established in the year 1971 with its important role in maintaining the international database of ADRs.

In order to prevent and monitor ADRs, pharmacovigilance centers are being established in tertiary care centres in India. Establishing an antibiotic policy in every institution and ensuring that the best choice among antibiotics should be prescribed by physicians can also prevent ADRs.

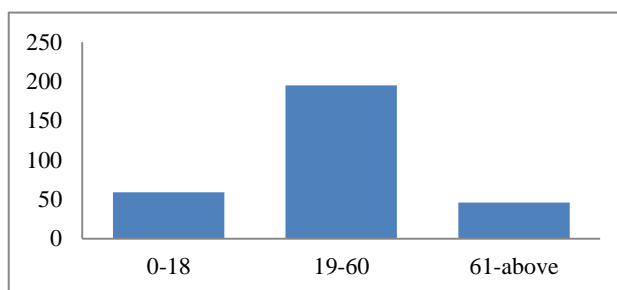
Thus, the present study was conducted to assess the incidence of ADRs due to antibiotics and analyze for causality of adverse drug events reported to ADR Monitoring Centre, Department of Pharmacology, BPS GMC for women, Khanpur Kalan, Sonapat, Haryana, India.

**METHODS**

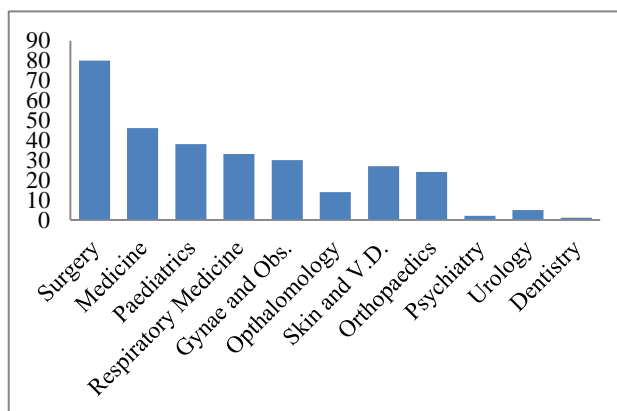
The present retrospective, observational study was conducted in northern tertiary care hospital situated in rural area. The Department of Pharmacology, BPS GMC for women, Khanpur Kalan, Sonapat, Haryana, India which is one of the ADR monitoring centre (AMC) under the Pharmacovigilance Program of India (PvPI) since January 2014. Suspected adverse events due to antibiotics were analyzed from the data collected from OPD and IPD of all clinical departments of hospital on regular basis for a period of 3 years from March 2016 to February 2019. All patients of either sex and of any age who developed ADRs due to antibiotics by any route during the above mentioned time period were included in the study. The causality assessment of the reported ADRs was carried using WHO-UMC scale for causality assessment scale. In the WHO-UMC scale, the causality terms used are certain, probable, possible, unlikely, conditional and unassessable.

**RESULTS**

A total of 776 ADR cases were reported during the study period of 3 years. Out of total 776 cases, 300 (38.65%) cases were reported due to antibiotics. Out of 300 cases reported, 272 (90.66%) cases were reported in IPD and 28 (9.34%) cases were reported in OPD setup. Our study revealed that female patients (52.34%) predominated over male patients (47.66%) in ADR occurrence. Age distribution showed maximum ADR occurrence in adults 195 (65%) followed by children 59 (19.67%) and geriatrics 46 (15.33%) (Figure 1). Maximum number of ADRs were reported from surgery department (80) followed by medicine (46), paediatrics (38) and respiratory medicine (33) (Figure 2).



**Figure 1: Age group distribution of ADRs.**



**Figure 2: Department wise distribution of ADRs.**

**Table 1: Therapeutic class of antibiotics implicated to cause ADR.**

S. no.	Class of drug	No. of cases reported	% of ADR
1	Penicillins (augmentin, amoxicillin, tazobactam, Piptaz	51	17
2	Cephalosporins (ceftriaxone, cephalexin, cefixime, cefotaxime)	51	17
3	Quinolones (ciprofloxacin, levofloxacin, ofloxacin, Moxicip KT	42	14
4	Nitroimidazoles (metronidazole, tinidazole)	39	13
5	Aminoglycosides (amikacin, gentamicin, streptomycin)	17	5.67
6	Macrolides (azithromycin)	2	0.67
7	Glycopeptide (vancomycin)	13	8.33
8	Oxazolidinone (linezolid)	4	1.33
9	Sulfonamides (septra, sulfasalazine)	4	1.33
10	Carbapenems (meropenem)	4	1.33
11	Antitubercular drugs	42	14

Continued.

S. no.	Class of drug	No. of cases reported	% of ADR
12	<b>Combined antibiotics (Ciplox TZ), doxorubicin, nitrofurantoin, norfloxacin/tinidazole, norfloxacin or tinidazole, nefzone</b>	30	10
13	<b>Tetracycline (doxycycline)</b>	1	0.33

Among the antimicrobial agents, cephalosporins (ceftriaxone, cephalexin, cefixime, cefotaxime)- 51 (15.98%) and penicillins (augmentin, amoxicillin, tazobactam, Piptaz)- 51 (15.98%) were found to be the major culprit to cause adverse events. Nitroimidazoles (metronidazole, tinidazole)- 48 (15.12%), antitubercular drugs-42 (13.16%) and quinolones (ciprofloxacin, levofloxacin, ofloxacin, Moxicip KT)- 42 (13.16%) were 2<sup>nd</sup> and 3<sup>rd</sup> the most common culprits. Other antibiotics like aminoglycosides (amikacin, gentamicin, and streptomycin), glycopeptide (vancomycin), sulfonamides (septrax, sulfasalazine), oxazolidinone (linezolid), carbapenems (meropenem), macrolides (azithromycin) and tetracycline (doxycycline), doxorubicin, nitrofurantoin were also reported to cause adverse events (Table 1).

Almost all the ADRs (94%) were observed in patients receiving combination drug therapy (i.e., >2 medicines) when compared to patients receiving single drug therapy. 38 (11.19%) cases were reported due to fixed drug combinations like ciprofloxacin or tinidazole, norfloxacin or tinidazole, norfloxacin or tinidazole, ceftriaxone or sulbactam.

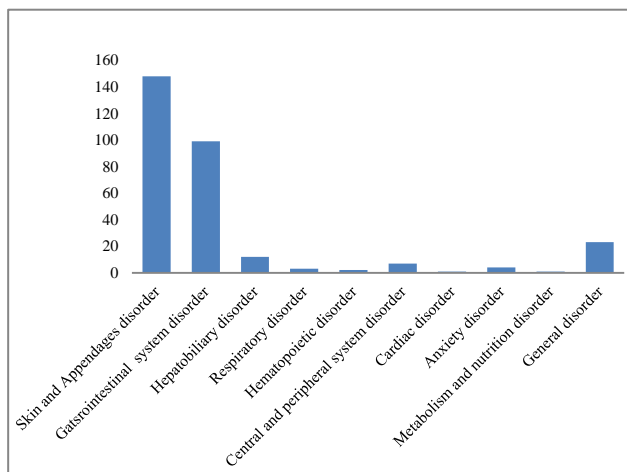


Figure 3: Organ system affected due to ADRs.

Table 2: Serious ADRs and implicated drugs with dose and route of administration.

S. no.	Drug reaction	Drugs implicated with dose and route of administration	Condition indicated for
1.	Steven Johnson Syndrome	Inj. ciprofloxacin Inj. metronidazole	Acute gastroenteritis
2.	Raised serum urea and creatinine levels	Inj. gentamicin	Postoperative antibiotic
3.	Hypokalemia	Inj. Meropenem Inj. hydrocortisone Inj. meropenem	Post-operative antibiotic Swelling in intra-abdominal region

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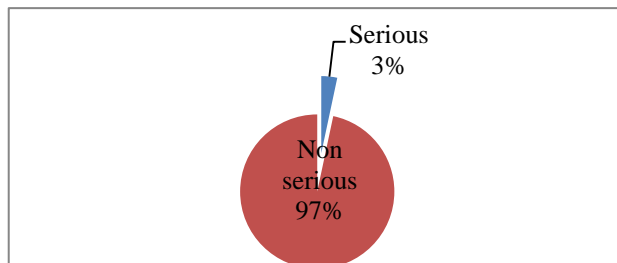


Figure 4: Seriousness of ADRs due to antibiotics.

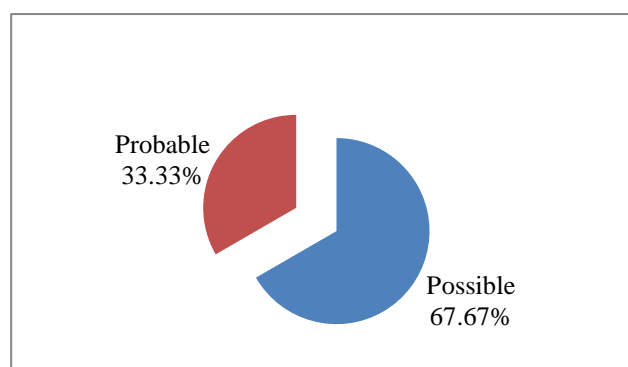
The most affected organ system was skin (49.33%) followed by the gastrointestinal system (33%) (Figure 3). 10 (3.33%) cases were serious and 290 (96.67%) were non-serious (Figure 4).

Most of the ADR were found to be ‘type A’ reaction. Frequently observed types of ADRs were rashes (20.67%), vomiting (14.67%), itching (13.67%), diarrhea (11.00%), fever (4.67%), raised liver enzymes (3.67%), swelling of skin, fixed drug eruption and erythema (2.67%), etc. The other ADRs that were observed included decreased appetite, cough, neutropenia, facial puffiness, headache, shivering, psoriasiform rash, halitosis, alopecia, darkening of nails, dizziness, palpitation, lichenoid drug eruption, urticaria, peeling of skin, metallic taste, excoriated skin lesions, restlessness, etc.

Rare and serious adverse events (SUSAR) reported was vancomycin induced seizure and ceftriaxone and paracetamol induced urticarial vasculitis. The serious ADRs reported were antitubercular drugs induced elevated liver enzymes, hyperbilirubinaemia and excoriated skin lesions, hepatitis, psoriasiform rash; ciprofloxacin and metronidazole induced Stevens Johnson syndrome; ciprofloxacin or tinidazole induced neutropenia and meropenem and hydrocortisone induced hypokalemia, gentamicin induced raised serum urea and creatinine levels, ciprofloxacin induced facial edema, breathlessness and tachycardia (Table 2).

S. no.	Drug reaction	Drugs implicated with dose and route of administration	Condition indicated for
4.	Neutropenia	Tab. ciprofloxacin or tinidazole	Acute gastroenteritis
5.	Facial edema with breathlessness, tachycardia	Inj. ciprofloxacin	Acute gastroenteritis
6.	Elevated liver enzymes, elevated bilirubin levels, excoriated skin lesions, hepatitis, psoriasis form rash	Antitubercular drugs (isoniazid, rifampicin, pyrazinamide and ethambutol tablets)	Respiratory tuberculosis
<b>Unexpected and serious ADR and implicated drugs with dose and route of administration</b>			
1.	Seizure	Inj. vancomycin (200 mg IV)	Pleural fluid effusion
2.	Urticarial vasculitis	Inj. ceftriaxone (1 g IV) Tab. paracetamol (500 mg oral)	Upper respiratory tract infection

Number of cases reported in causality assessment was done as per WHO-UMC scale of causality assessment. 33.33% reported cases were found to probably related to adverse events and 66.67% cases were found to be possibly related to adverse events using WHO-UMC scale (Figure 5).



**Figure 5: Causality assessment using WHO-UMC scale.**

## DISCUSSION

ADRs are considered to be one of the reasons for increase in healthcare cost nowadays. They are even one of the major causes of death among patients. Antibiotics are responsible for 11% of iatrogenic disease as per Darchy's report.<sup>11</sup> So this retrospective study was conducted to highlight the status of adverse drug reactions due to antibiotics in a tertiary care hospital so that healthcare professionals get sensitized about commonly observed ADRs due to antibiotics which will help to minimize risks among patients.

The incidence rate of antibiotic adverse reactions in this study was found to be 38.65%, which is comparable to other study by Geer et al 2016.<sup>8</sup> ADR occurrences due to antibiotics is more in female than in male as per our study. Age analysis showed the predominance of adult patients followed by children and geriatrics that may be due to age related pharmacokinetic and pharmacodynamic changes and the presence of comorbid illnesses and multiple drugs along with infectious diseases. The study conducted by Stavreva et al and Hussain et al also showed adult age group and female

predominance which is in contrast to study conducted by Jose et al that showed male predominance.<sup>12-15</sup>

Maximum number of adverse drug reactions was reported from surgery department which was followed by general medicine and pediatrics departments. The reason for this result can be usage of antibiotics at high frequency for treatment and prophylaxis of various diseases in these departments. Skin and GIT were documented to be the common organ system affected by adverse drug reactions due to antibiotic. This study also revealed the same which is in resemblance to various studies conducted earlier.<sup>13,14,16</sup> Other studies also showed the predominance of cutaneous manifestations to be the main cause for ADRs.<sup>11,16,19</sup> In one study, predominance of the gastrointestinal system followed by the skin in ADR occurrence was also reported.<sup>17,18</sup> Rash and itching were found to be most commonly reported adverse drug reactions affecting dermatological system. Many previous studies showed predominance of such adverse drug reactions.<sup>13,16,19</sup>

The penicillins and cephalosporins were reported to be the major culprits of adverse drug reactions among antibiotic class in inpatient settings, followed by fluoroquinolones and nitroimidazoles. A study conducted by Stavreva et al also revealed the predominance of beta-lactams.<sup>11</sup> Cephalosporins and fluoroquinolones were the major group contributing to adverse drug reactions as per one of the study.<sup>13</sup> Vancomycin and penicillins were most frequent antibiotics causing adverse drug reactions in the study of Priyadharsini et al.<sup>12,13,20</sup>

Type A ADR was found to be predominated in our study according to Rawlin and Thompson classification of ADR which is same as the study conducted by Richa et al.<sup>12,16</sup> While in another study by Suthar and Desai, all the reported reactions were Type B reactions.<sup>21</sup>

The causality assessment of ADRs was done using the WHO UMC causality assessment scale in which no reactions were found to be unlikely and majority were probable with a less number of possible reactions. These data correlate with the study of Richa et al and opposite to the study by Modi et al because they reported more number of possible reactions.<sup>22-25</sup>

## CONCLUSION

Antibiotics are most commonly prescribed drugs so its monitoring regarding adverse drug reactions is an important need. In our study, penicillin and cephalosporins were the most common causes of ADRs among antibiotics. The most frequently experienced clinical feature was cutaneous reactions. This study may benefit the clinicians in early identification and management of adverse drug reactions due to antibiotics so that quality of life of patient can be safeguarded at an earliest.

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