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ANTIMICROBIALS ASSOCIATED ADVERSE DRUG REACTION PROFILING

Pharma

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ABSTRACT

Introduction: The World Health Organization has defined an adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function" ADRs are one of the major causes of iatrogenic disease, which refers to health complications induced inadvertently by medical treatment. These reactions can significantly impact patient health and healthcare systems. **Objective:** To study aimed to assess frequency, class of antibiotics, symptoms, causality, the severity of antimicrobial-associated ADRs, and see the demographic distribution relation to age, sex of the patient. **Material And Methods:** ADRs were collected and filled in suspected ADR reporting forms and sent via vigiflow to the National Coordination Centre-Pharmacovigilance Programme of India (NCC-PvPI). These ADR reports, termed individual case safety reports (ICSRs), were analyzed from November 2022 to October 2023. A study was conducted in Department of Medical Intensive Care Unit (MICU) at JLN Medical College, Ajmer. **Results:** Out of 400 cases, A total no. of 724 AMA prescribed. All patients (both male and female) above 18 years who was admitted to Medical ICU. A total of 232 (58%) were males, and 168 (42%) were females. The adverse drug reactions observed in the study population were studied: out of total 44 ADRs were observed with AMA. Thrombophlebitis was common ADR (8.25%), (1%) had diarrhoea, (1%) experienced nausea, and vomiting. Additionally (0.5%) had hypokalaemia, and (0.25%) had QT prolongation. **Discussion/Conclusions:** Antimicrobials play a crucial role in treating infections, and utmost vigilance during antimicrobials prescription reduces the frequency and severity of the ADRs, thereby reducing the morbidity and mortality and the pharmacoeconomic burden to the health care system. Pharmacovigilance must be boosted to ensure the safe and effective use of antibiotics and reduce the occurrence of ADRs.

KEYWORDS

Antimicrobials agents (AMA) adverse drug reactions (ADRs), Medical intensive care unit (MICU), Individual case safety reports (ICSRs) severity of ADRs causality assessment.

INTRODUCTION

Antimicrobials are the most prescribed medication worldwide and their use is constantly increasing. The World Health Organization (WHO) report on surveillance of antibiotic consumption between 2016 and 2018 shows an overall consumption ranging from 4.4 to 64.4 Defined Daily Doses (DDD) per 1000 inhabitants per day.[1] The World Health Organization has defined an adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function".[2] ADRs are one of the major causes of iatrogenic disease, which refers to health complications induced inadvertently by medical treatment. These reactions can significantly impact patient health and healthcare systems. ADRs may result in hospital admissions or prolonged hospital stays, adding to the burden on healthcare facilities and increasing overall medical costs. In severe cases, ADRs can lead to permanent disability or even death, highlighting the critical need for vigilant drug monitoring and patient safety protocols. India is among the leading consumer of antibiotics, and its consumption increased from 3.2 billion DDDs in the year 2000 to 6.5 billion DDDs in 2015, amounting to a 103% rise.[3] Globally, consumption of antibiotics increased from 8.2 to 13.6 DDD per 1000 inhabitants per day from the year 2000 to 2015, amounting to a 65% rise.[4] This surge in antibiotic usage in India is attributed to increased incidence of infectious diseases, mass manufacturing of generic antibiotics that are cheaper, increased income, and availability of government health insurance schemes. Availability of antibiotics without prescription is another major issue in India; therefore, red strip labelling of packages has been made mandatory to reduce dispensing without prescription. Increased use of antibiotics is associated with an increase in antimicrobial resistance and an increased incidence of adverse drug reactions (ADRs).[5] Adverse drug reaction (ADR), as defined by the World Health Organization (WHO), is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" [6] ADRs can occur with any class of drugs, and over half of the hospitalized patients receive at least one antibiotic during their hospital stay, of which 55.5% ADRs are definitely preventable and accounts for 20–50% of the drug expenditure in thehospitals.[7] Adverse drug reactions (ADRs) are any unwanted/uncomfortable effects from medication resulting in physical, mental, and functional injuries.[8] ADRs experienced by hospitalized patients are associated with increased morbidity and mortality, prolonged hospitalization, and increased medical expense.[9] For this reason, several studies have suggested that ADRs are a major public health concern.[10] Disease prevalence, economic status, culture, and ethnicity all contribute to different ADR patterns.[11, 12] The overall incidence of ADRs varies by study but ranges from 0.15% to 30%. [8,13]

MATERIAL AND METHODS

This cross sectional quantitative observational study (November 2022 to October 2023) conducted in the department of Medical intensive care unit (MICU) at Jawahar Lal Nehru Medical College and associated group of hospitals, Ajmer, Rajasthan, India. Present study was conducted in JLN Medical College and attached Hospitals. The study encompassed all individuals aged 18 and above, regardless of gender, who were admitted to the Medical ICU and willing to provide informed consent, from November 2022 to October 2023.

A standardized data collection form was developed to gather socio-demographic and clinical information on the subjects.

Information on the patient's knowledge regarding drug treatment and the practice of self-medication was obtained. The DDD (Defined Daily Dose) represents the estimated average daily maintenance dose of a drug when used by adults for its primary intended purpose.

DDD/100 bed days= (Total dose in mg in the patients selected × 100) / (DDD of the drug × study duration (days) × bed strength × average bed occupancy rate).

Proper approval was taken from ethical committee after informed consent form patients/guardians.

Study Design: Hospital based prospective study.

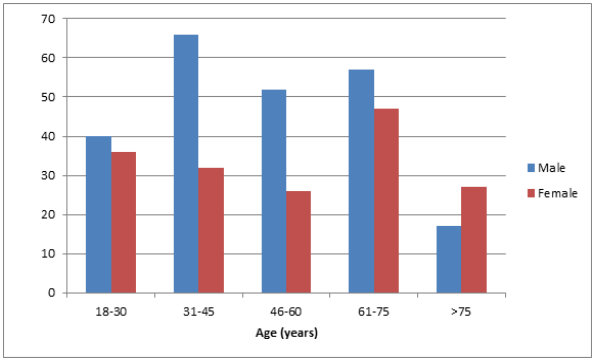
Study Duration: Duration from November 2022 to October 2023. Drug utilization pattern of antimicrobials in Medical Intensive Care Unit.

RESULTS

The age distribution of patients was as follows: For ages 18-30, there were 36 females and 40 males, totalling 76 patients. For ages 31-45, there were 32 females and 66 males, making a total of 98 patients. In the 46-60 age range, there were 26 females and 52 males, with a total of 78 patients. For ages 61-75, there were 47 females and 57 males, total 104 patients. Lastly, for those over 75 years, there were 27 females and 17 males, resulting in a total of 44 patients. **Table (1)**

Table 1: Distribution Of Cases According To Age And Gender.

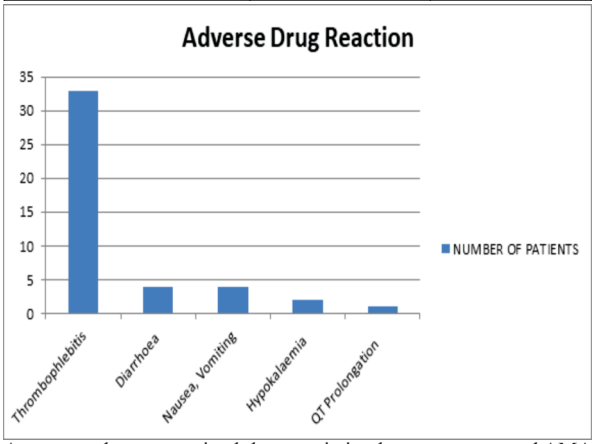
Age Distribution (years)	Male	Female	Total
18-30	40	36	76
31-45	66	32	98
46-60	52	26	78
61-75	57	47	104
>75	17	27	44
Total	**232**	**168**	**400**



The adverse drug reactions observed in the study population were studied: out of total 44 ADRs were observed with AMA. Thrombophlebitis was common ADR (8.25%), 4 patients (1%) had diarrhoea, 4 patients (1%) experienced nausea, and vomiting. Additionally, 2 patients (0.5%) had hypokalaemia, and 1 patient (0.25%) had QT prolongation. **Table (2)**

Table 2: Distribution Of Cases According To ADR

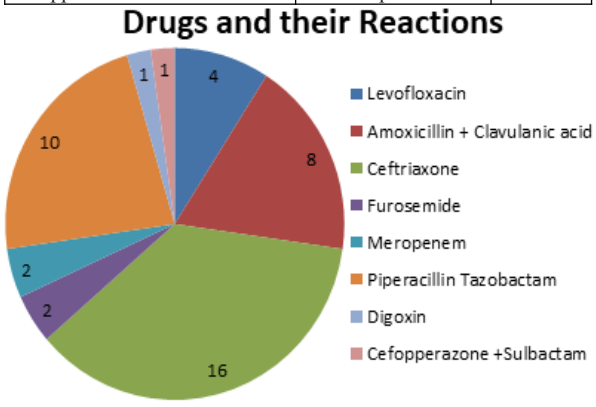
ADVERSE DRUG REACTIONS	NUMBER OF PATIENTS	Percentage (%)
Thrombophlebitis	33	8.25 %
Diarrhoea	04	1 %
Nausea, Vomiting	04	1 %
Hypokalaemia	02	0.5 %
QT Prolongation	01	0.25%



Among study we examined the association between suspected AMA and adverse drug reactions (ADR). Thrombophlebitis was common ADR with Ceftriaxone 14 patients, Amoxicillin Plus Clavulanic acid 8 patients and piperacillin + Tazobactam was associated with thrombophlebitis in 8 patients, meropenem was implicated in thrombophlebitis in 2 patient cefoperazone + Sulbactam was associated with thrombophlebitis in 1 patient. levofloxacin was associated with diarrhoea in 4 patients. Ceftriaxone and Piperacillin + Tazobactam was associated to nausea and vomiting in 2 patients. During the present study ADRs related to other AMA were also observed. Furosemide caused hypokalaemia in 2 patients. Digoxin was associated to QT prolongation in 1 patient. **Table (3)**

Table 3: Distribution Of Cases According To Suspected Cause Of ADR

Suspected Drugs	ADR	No. of patients
Levofloxacin	Diarrhoea	4
Amoxicillin + Clavulanic acid	Thrombophlebitis	8
Ceftriaxone	Thrombophlebitis	14
	Nausea, Vomiting	2
Furosemide	Hypokalaemia	2
Meropenem	Thrombophlebitis	2
Piperacillin Tazobactam	Thrombophlebitis	8
	Nausea, Vomiting	2
Digoxin	QT Prolongation	1
Cefopperazone +Sulbactam	Thrombophlebitis	1



DISCUSSION

The age distribution of patients is as follows: Among the female patients, 36 (21.43%) were aged 18-30 years, 32 (19.05%) were aged 31-45 years, 26 (15.48%) were aged 46-60 years, 47 (27.98%) were aged 61-75 years, and 27 (16.07%) were aged over 75 years. In comparison, the male patients consisted of 40 (17.24%) in the 18-30 age group, 66 (28.45%) in the 31-45 age group, 52 (22.41%) in the 46-60 age group, 57 (24.57%) in the 61-75 age group, and 17 (7.33%) in the over 75 age group. The total number of patients in each age group were 76 for 18-30 years, 98 for 31-45 years, 78 for 46-60 years, 104 for 61-75 years, and 44 for those over 75 years. In our study male common age group was 31-45 year, 66 (28.45%) patients, and female common age group for MICU admission was 61-75 year, 47(27.98%) patients. Men are more likely to develop infectious diseases than women. Myocardial infarction is becoming more common in young adult male, because women have higher levels of estrogen and progesterone which help keep blood vessels healthy and lower the risk of heart disease. Men have less of these hormones.

In the study by ANN S J et al[14] which included 123 ICU patients, 82 were male and 41 were female, reflecting a similar male predominance observed by Gajbhiya VP et al.[17] in their research on antimicrobial agents in an ICU setting. Gawali U P et al[15] found that out of their patients, 87 were male and 63 were female. Conversely, Smythe et al.[18] reported an equal number of male and female ICU patients with an average age of 65 years. Another Iranian study highlighted a higher proportion of male patients at 68% compared to female patients at 32%.[19]

ADVERSE DRUG REACTIONS:

In our study, adverse drug reactions (ADRs) were observed as follows: thrombophlebitis in 8.25% of patients, diarrhea in 1%, nausea and vomiting in 1%, hypokalemia in 0.5%, and QT prolongation in 0.25%. ADRS are undesirable effects of medications used in normal dose. ADRS can occur during treatment in an ICU. Critically ill patients are at especially high risk because of medical complexity numerous high alert medications, complex and often challenging drug dosing, medication regimens, error related to the ICU environment.

Dhar K et al[20] found that in their study on ADRs related to antibiotics, the majority were categorized as possible (78, 61.9%), with fewer classified as probable or definite. In contrast, the study by ANN S J et al.[14] observed a higher incidence of probable ADRs (30.77%). The increased incidence of ADRs in this study could be attributed to polypharmacy, noted in 65.85% of prescriptions. Rational prescribing practices might have reduced the occurrence of ADRs. The adverse

drug reactions (ADRs) reported in the study included nausea in 30.77% of cases, gastritis and hypersensitivity, each accounting for 23.08%. Diarrhea was observed in 15.38% of cases, and urticaria was the least common, occurring in 7.69% of the population.

Badar V A et al[21] identified infection as the primary indication for antibiotic use in 64.9% of cases, followed by symptomatic treatment (24%) and prophylactic use (11%). The percentage of patients treated for infections was 45%, which is lower compared to figures reported in other studies.

Suspected Cause Of ADR:

Our analysis revealed that Ceftriaxone was associated with thrombophlebitis in 14 patients and nausea and vomiting in 2 patients. Amoxicillin + Clavulanic acid and Piperacillin + Tazobactam each caused thrombophlebitis in 8 patients, with Piperacillin + Tazobactam also leading to nausea and vomiting in 2 patients. Levofloxacin was linked to diarrhea in 4 patients. Furosemide and Meropenem each caused adverse effects in 2 patients, with Furosemide leading to hypokalemia and Meropenem to thrombophlebitis. Digoxin was linked to QT prolongation in 1 patient, and Cefoperazone + Sulbactam was associated with thrombophlebitis in 1 patient.

Khirasaria R et al[16] observed similar trends, with Piperacillin + Tazobactam causing thrombophlebitis in 10 patients, and Ceftriaxone leading to both thrombophlebitis and hypersensitivity in 6 patients. Amoxicillin + Clavulanate caused thrombophlebitis in 3 patients, Levofloxacin was linked to diarrhea in 5 patients, and Metronidazole resulted in a severe allergic reaction in 7 patients. Vancomycin was associated with a rash in 2 patients.

CONCLUSION

Antimicrobials play a crucial role in treating infections, and utmost vigilance during antimicrobials prescription reduces the frequency and severity of the ADRs, thereby reducing the morbidity and mortality and the pharmacoeconomic burden to the health care system. Pharmacovigilance must be boosted to ensure the safe and effective use of antibiotics and reduce the occurrence of ADRs. Periodic analysis of antibiotic safety data will help assess the accurate burden of ADRs in terms of patient morbidity and mortality, human resources, and financial resources; and help formulate guidelines and policies to prevent or reduce the frequency and severity of ADRs, and contribute to antibiotic stewardship.

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