Research Article

A Study of Adverse Drug Reaction Patterns Associated with Commonly Used Antibiotics in A Tertiary Care Facility in Northern Rajasthan, India.

Anta Sharma*[1], Akhilesh Sengar[1], Dr. Mahbubur Rahman[2], Rashmi Khanijau[3], Dr. Dharmendra Ahuja[4]
[1]Student, Department of Pharmacology, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India.
[2] Assistant Professor, Department of Pharmacy Practice, JB Institute of Pharmacy, Guwahati, Assam, India.
[3]Associate Professor, Department of Pharmacology, Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur, Rajasthan, India.
[4]Dean and Director, Faculty of Pharmaceutical Sciences, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India.
***Corresponding author's E-mail:** antasharma9@gmail.com

Received: 06-06-2024; **Revised:** 30-08-2024; **Accepted:** 10-09-2024; **Published on:** 15-09-2024.

ABSTRACT

Globally, adverse drug reactions (ADRs) constitute a major cause of illness and mortality in the healthcare industry. To describe the occurrence, trends, and management approaches of antibiotic-related adverse drug reactions (ADRs), this study examines the environment of these events in a tertiary hospital in Rajasthan, India. The study found that 16.42% of the 280 individuals receiving antibiotics experienced adverse drug reactions1. Most instances (52.17%) were male patients, which may indicate gender-specific vulnerabilities in how the body reacts to medicine. Elderly patients showed increased vulnerability; they accounted for 45.62% of ADR cases, highlighting the challenges associated with administering antibiotic therapy to this population. The systemic nature of antibiotic-induced side effects was highlighted by the frequency with which the gastrointestinal tract (39.13%) and skin (32.60%) were impacted. The two most common antibiotic classes linked to ADRs were penicillins (34.78%) and cephalosporins (28.26%), highlighting the importance of prudent prescription practices and close observation. The management techniques that produced the best results, with recovery noted in most cases, involved stopping antibiotics (45.65%) and adjusting dosages (34.78%). 63.04% of ADRs were determined to be preventable by preventability assessments, indicating possible areas for improving medication safety procedures and reducing hazards. In 69.56% of cases, causation assessments revealed likely relationships, which influenced clinical judgment and improved treatment strategies. These results highlight the complex issues surrounding antibiotic administration and support the need for specialized interventions to improve patient safety and maximize healthcare results in tertiary settings. Insights into antibiotic-related adverse drug reactions (ADRs) are provided by this study, which helps shape evidence-based practices and programs targeted at enhancing pharmaceutical safety and patient care tactics in hospital settings.

Keywords: Antibiotics, Adverse Drug Reaction, Pharmacovigilance, Antibiotic Stewardship, Clinical Management.

INTRODUCTION

According to the World Health Organization, an Adverse Drug Reaction (ADR) is defined as any harmful reaction to a medication that occurs during its clinical use, surpassing the drug's intended effects. This encompasses adverse and unintended reactions occurring at standard therapeutic doses used in humans for preventing, diagnosing, treating diseases, or modifying physiological functions[1]. Therefore, overdoses (deliberate or not), drug misuse, unsuccessful treatments, and mistakes made when administering medication are not included in this definition. One known risk of medication therapy is adverse responses. ADRs are significant contributors to morbidity and mortality in both ambulatory and hospitalized patients. ADRs are indeed substantial contributors to mortality worldwide, ranking among the top 10 primary causes of death in numerous nations[2]. Therefore, conducting a thorough analysis of ADRs is imperative to raise patient knowledge of them, encourage hospital staff to report ADRs, and reduce associated risks. Decrease patient harm and enhance public health by implementing early detection, assessment, and monitoring of ADR[3].

Every year, more and more pharmaceutical products are produced, leading to novel medications' introduction. Therefore, the WHO was aware of the necessity of an active surveillance system to get rid of dangerous medications that had made their way onto the market. This served as the foundation for the WHO's international drug monitoring program. FDA started gathering reports of ADRs (ADRs) in 1960 and supported hospital drug monitoring. The United Kingdom launched the Yellow Card Program in 1964 [4,5]. The WHO launched its global drug monitoring program in 1968. a pilot program that began in ten nations with national reporting mechanisms for ADRs that are already in place. Since then, the network has grown dramatically as more nations have established national pharmacy surveillance centres to record ADRs. At the moment, 86 nations are taking part in the initiative, which is run by WHO and its Uppsala, Sweden-based collaborating centre[5].

In India, adverse medication reaction monitoring began almost ten years ago (1982). Five centres were established to initiate a statewide monitoring program. The All-India Institute of Medical Sciences Department of Pharmacology in New Delhi is home to the National Pharmacovigilance Centre, the organization's nodal centre. It is connected to the Uppsala, Sweden-based WHO Collaborating Center for ADR Monitoring. The others can be found at the Seth GS Medical College-special centre in Mumbai, JIPMER in

Pondicherry, KGMC in Lucknow, and PGI in Chandigarh. There are three stages to it: the first involves tracking institutional responses, the second involves governmental organizations like the Central Governmental Health Scheme (CGHS), and the third part is intended to involve general practitioners [6]. The majority of physician-initiated (voluntary) ADR monitoring programs have had some degree of effectiveness.

The largest problem with the voluntary reporting system has been underreporting, which can be attributed to many factors including an increase in workload, the belief that reporting will not improve things, ignorance of unfavourable events, and a fear of facing legal action. Antibiotic-associated ADRs (ADRs) are not well estimated globally, with varying incidences recorded in the USA (20%), South Korea (62.8%), Uganda (19%), and India (40.9%)[7]. Prior research assessing antibiotic-associated ADRs (ADRs) has several limitations. For example, it primarily evaluated ADRs related to a particular class of antibiotics and evaluated ADRs in in-hospital settings or utilizing hospital databases without monitoring after discharge.

The objective of the research was to assess the occurrence of antibiotics, usage patterns, and factors contributing to ADRs among patients undergoing antibiotic treatment at a tertiary care hospital in Rajasthan.

Factors contributing to ADRs

Patient-related factors:

- **Age**: Geriatric patients (aged 60 and above) are more prone to ADRs due to physiological changes, polypharmacy, and altered pharmacokinetics and pharmacodynamics. Paediatrics face risks like kernicterus and hemolytic anaemia from antibiotics and hearing loss from aminoglycosides[8].
- **Gender**: Women tend to experience more ADRs than men, influenced by higher medication usage rates, differing pharmacological responses, and hormonal factors affecting drug metabolism.
- **Pregnancy**: Drug use during pregnancy can lead to teratogenic effects and prolonged pharmacological effects on the fetus, with specific medications like phenytoin and methotrexate known for significant risks[9].
- **Concurrent diseases**: Conditions like hepatic or renal disease alter drug metabolism and elimination, increasing the risk of toxicity from medications like digoxin or aminoglycosides[10].
- **Genetics**: Genetic variations influence susceptibility to ADRs with certain medications, such as G6PD deficiency predisposing individuals to hemolytic anaemia with drugs like nitrofurantoin[11].

Drug-related factors:

- **Dose**: Overdosing increases the likelihood of severe ADRs, impacting drug efficacy and potentially causing resistance, as seen with acyclovir misuse[12].
- **Formulation**: Differences in drug formulations affect absorption rates and side effect profiles, with examples like nitrofurantoin macro crystals causing fewer gastrointestinal side effects compared to microcrystalline formulations[13].
- **Physicochemical characteristics**: Factors such as pH, lipid solubility, and protein binding influence a drug's bioavailability and distribution, affecting its overall efficacy and potential side effects[14].
- **Administration**: Routes of drug administration (e.g., IV, IM, oral) impact bioavailability and onset of action, influencing drug toxicity and efficacy. For example, rapid IV infusions of certain drugs can increase the risk of adverse effects like nephrotoxicity or cardiac complications[15].

External elements:

- **Environmental factors**: Temperature extremes can exacerbate ADRs, particularly with medications like anticholinergics and diuretics, which can lead to heat-related complications such as heat stroke or dehydration[16].

Multiple-drug treatments:

- **Polypharmacy**: Combining multiple medications increases the complexity of managing ADRs due to drug interactions, cumulative effects, and varied pharmacological responses in patients with complex medical conditions[17].

Antibiotics related ADRs

Antibiotics play a crucial role in combating bacterial infections and saving lives. However, their use is accompanied by the risk of adverse drug reactions (ADRs), which range from mild to severe. This comprehensive review explores various aspects of antibiotic-related ADRs, encompassing epidemiology, mechanisms, clinical manifestations, management strategies, and preventive measures. Understanding these complexities is essential for healthcare professionals to optimize patient care and promote safer antibiotic use [18,19]

Mechanisms of Antibiotic-Related ADRs

ADRs associated with antibiotics can arise through pharmacological effects, immunological reactions, and off-target effects. Pharmacological effects include intended actions like gastrointestinal upset and hepatotoxicity. Immunological reactions involve hypersensitivity responses such as rash, urticaria, or anaphylaxis. Off-target effects disrupt normal cellular functions, leading to outcomes like neurotoxicity or nephrotoxicity, necessitating accurate diagnosis and management [20,21].

Clinical Manifestations of Antibiotic-Related ADRs

Antibiotic-related ADRs manifest across various organ systems with diverse clinical presentations. Common symptoms include gastrointestinal disturbances, cutaneous reactions, respiratory issues, and systemic symptoms. Severe reactions like anaphylaxis or drug-induced liver injury require prompt intervention for optimal outcomes [22,23].

Common Antibiotic-Related ADRs and Their Symptoms

Table 1: Common Antibiotic related ADRs and their symptoms [24]

ADR Type	Symptoms	Frequency	Severity Level
Gastrointestinal	Nausea, vomiting, diarrhoea, abdominal pain	High	Moderate
Dermatological	Rash, itching, redness, urticaria	Moderate	Mild
Neurological	Dizziness, headache, seizures, confusion	Low	Severe
Haematological	Anaemia, leukopenia, thrombocytopenia	Rare	Severe
Hepatotoxicity	Elevated liver enzymes, jaundice, liver failure	Rare	Severe

MATERIALS AND METHODS

This retrospective observational study was conducted at a tertiary-level facility in Jaipur, Rajasthan, India, spanning six months. The study aimed to investigate adverse drug reactions (ADRs) associated with antibiotic use among hospitalized patients. Data collection utilized both passive and active surveillance methods: prescribers were encouraged to report potential ADRs, while pharmacists proactively identified suspected cases. Included were inpatients of all ages and genders who received antibiotics during their hospitalization. Excluded were ADRs resulting from medication errors, alternative medicine systems, and cases from dentistry and oncology departments, as well as patients nearing end-of-life or those who declined interviews. Comprehensive data were gathered from electronic health records, pharmacy databases, patient case records, investigation reports detailing ADRs, face-to-face interviews with patients or caregivers, and direct consultations with reporting individuals or attending physicians. The Naranjo causality assessment scale was employed to evaluate the likelihood of reported ADRs being attributed to antibiotic usage, categorizing reactions into definite, probable, and possible causal relationships. Additionally, the severity of ADRs was assessed using the modified Hartwig and Siegel Scale, considering parameters such as impact on treatment plans, length of hospital stay, and patient disability. Descriptive statistics were utilized for data analysis, presenting frequencies and percentages of demographic variables, clinical outcomes, antibiotic prescriptions, adverse reactions, contributing factors, and preventability assessments. This methodology ensured a comprehensive evaluation of antibiotic-related ADRs in a hospital setting, aiming to enhance understanding, management, and prevention strategies for optimizing patient safety and healthcare outcomes.

RESULTS

While studying, a comprehensive analysis of ADRs associated with antibiotics was conducted, revealing a total of 46 reported cases among 280 patients receiving antibiotic prescriptions, resulting in an incidence rate of 16.42%. The findings elucidated a predominant occurrence of ADRs among male patients, accounting for 24 cases (52.17%), compared to 22 cases (47.82%) among female patients. Moreover, the distribution of ADRs across different age groups unveiled a notable prevalence among geriatric patients, with 21 cases (45.62%) observed in this geriatrics, followed by 16 cases (34.78%) among adults and 9 cases (19.56%) among other age groups (children). The distribution of ADRs and the demographic traits of the research group are clearly shown by the visual representation of these trends in Fig(s). 1 and 2.

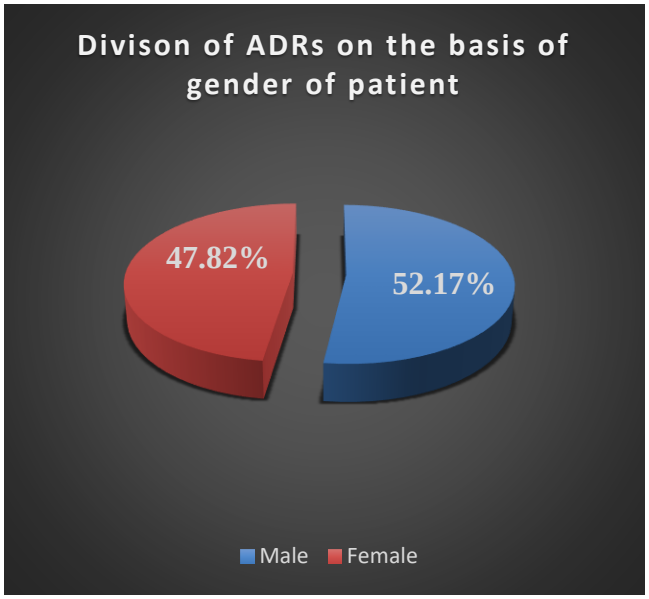

Figure 1: Segmentation of ADRs on the basis of gender of patient

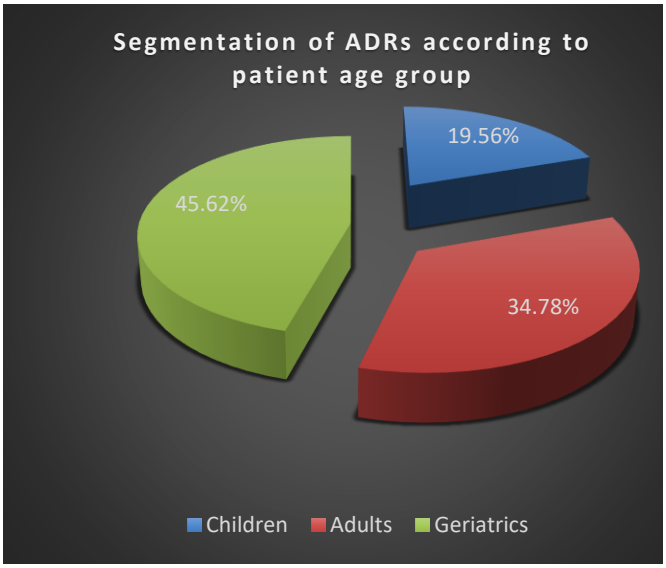

Figure 2: Segmentation of ADRs according to patient age group

The analysis of ADRs about antibiotics delineated the predominant involvement of several organ systems. Specifically, the gastrointestinal tract (GIT) emerged as the most commonly affected system, with 18 cases (39.13%) attributed to ADRs in this anatomical domain. Following closely, the skin exhibited significant involvement, with 15 cases (32.60%) manifesting cutaneous adverse reactions to antibiotic therapy. Furthermore, ADRs affecting the urinary system accounted for 6 cases (13.04%), while respiratory system-related reactions were noted in 4 cases (8.69%). Additionally, a smaller proportion of ADRs were observed in the domains of haematology (4.34%) and cardiovascular system (2.17%). These findings, graphically represented in Fig. 3, elucidate the diverse spectrum of organ system involvement in antibiotic-induced adverse effects, underscoring the need for vigilant monitoring and tailored management approaches to mitigate the risk of complications and optimize patient care.

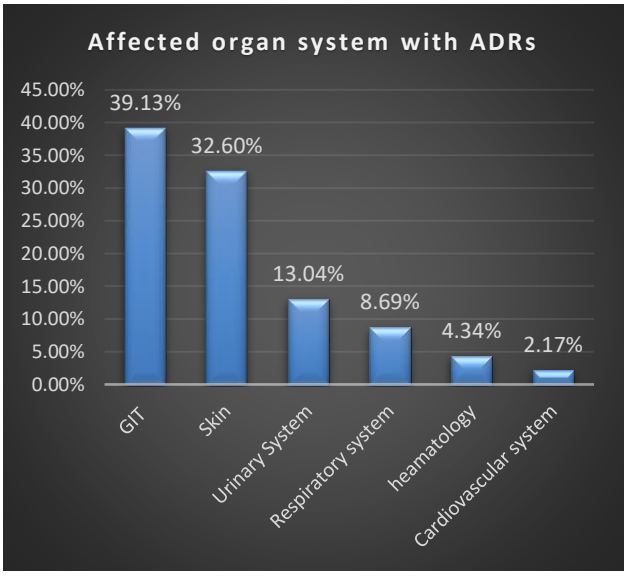

Figure 3: Affected organ system with ADRs of antibiotics

Among the antibiotic classes implicated in adverse drug reactions (ADRs), penicillin emerged as the most frequently associated, constituting 16 cases (34.78%) of reported ADRs. Following closely, cephalosporins were identified in 13 cases (28.26%), underscoring their significant contribution to antibiotic-related adverse effects. Fluoroquinolones represented another notable class, with 9 cases (19.56%) attributed to their use. Additionally, a miscellaneous category accounted for 8 cases (17.39%) of ADRs, reflecting the diverse array of antibiotic agents implicated in adverse reactions. These findings, as depicted in Fig. 4, provide valuable insights into the relative contributions of different antibiotic classes to the overall burden of ADRs, highlighting the need for judicious prescribing practices and vigilant monitoring to optimize patient safety and therapeutic outcomes.

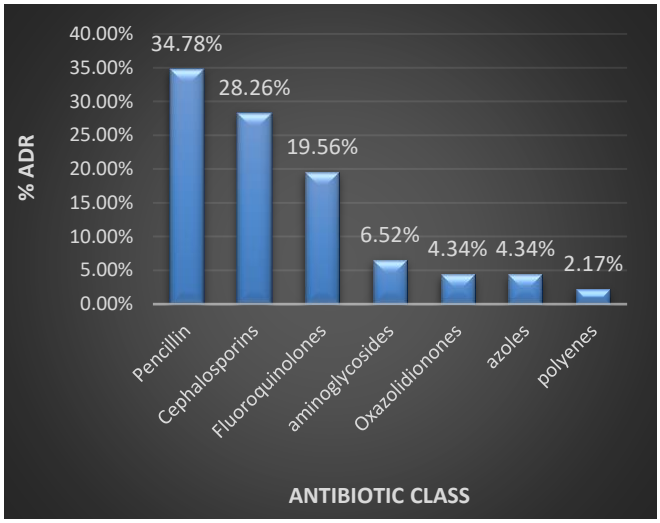

Figure 4: Antibiotic therapeutic classes linked to adverse drug reactions.

The management of ADRs associated with antibiotics encompassed various interventions aimed at mitigating patient discomfort and optimizing therapeutic outcomes. Among the reported cases, the suspected antibiotic was withdrawn in 21 instances (45.65%), reflecting a proactive approach to addressing ADRs by discontinuing the offending medication. Conversely, no changes were deemed necessary in 9 cases (19.56%), suggesting either mild or transient reactions that did not warrant alteration of the treatment regimen. In 16 cases (34.78%), the dose of the antibiotic was modified, indicating a tailored adjustment to minimize the risk of further adverse effects while maintaining therapeutic efficacy.

Encouragingly, the vast majority of patients experienced recovery from ADRs, with 41 cases (89.13%) demonstrating resolution of symptoms. Notably, there were no reported instances of fatal ADRs, underscoring the overall favourable prognosis associated with antibiotic-induced adverse reactions in this cohort. Among the management strategies employed, specific treatment measures were implemented in 16 cases (34.78%), targeting the underlying mechanisms or manifestations of ADRs to alleviate patient discomfort and facilitate recovery. Conversely, symptomatic treatment

was administered in 30 cases (65.21%), focusing on addressing individual symptoms or adverse effects as they arose.

Furthermore, predictability analysis revealed that a significant proportion of ADRs were deemed predictable, with 25 cases (54.34%) exhibiting identifiable risk factors or known associations with antibiotic therapy. Conversely, 21 cases (45.62%) were classified as unpredictable, highlighting the inherent challenges in foreseeing and preemptively mitigating certain adverse reactions. These insights, illustrated in Figure 5, underscore the multifaceted nature of ADR management and the importance of tailored approaches informed by comprehensive risk assessment and clinical judgment.

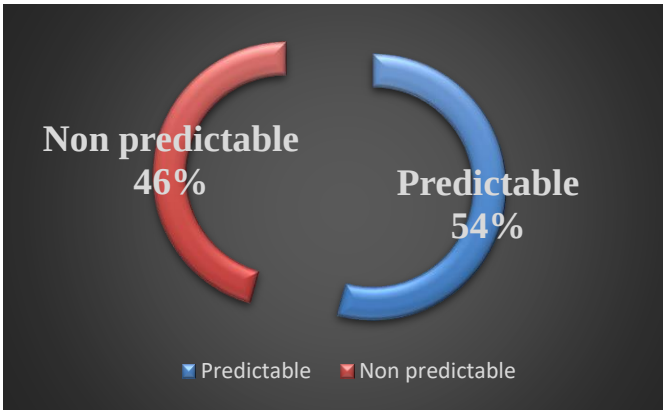

Figure 5: Predictability of reported ADRs

The assessment of ADRs occurring with antibiotics highlighted the predominance of moderate reactions, comprising 29 cases (63.04%), indicating significant clinical impact necessitating intervention. Mild reactions were also documented, albeit to a lesser extent, while severe reactions were relatively uncommon. A notable proportion of reported ADRs, 26 cases (56.52%), were deemed preventable, emphasizing the importance of proactive measures to mitigate risks. Causality assessment revealed that the majority of reactions were probable (32 cases, 69.56%), followed by possible (9 cases, 19.56%) and definite (5 cases, 10.86%), with no reactions deemed unlikely.

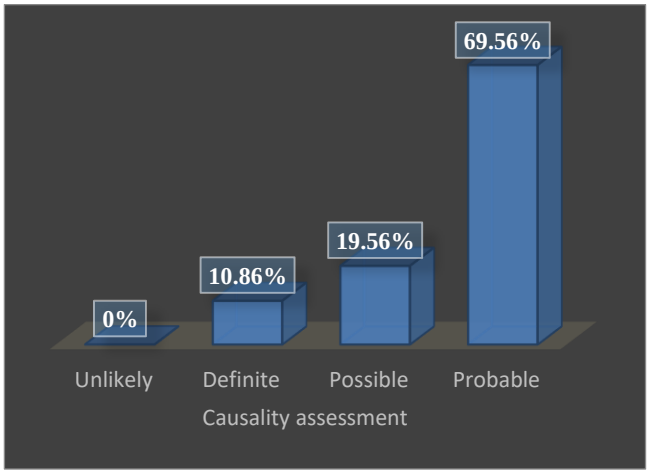

Figure 6: ADR causation evaluation (using the Naranjo Scale)

These findings, depicted in Figure 6, provide insights into the severity, preventability, and causality of antibiotic-related ADRs, guiding targeted interventions for optimizing patient safety.

The severity of reported ADRs associated with antibiotics was evaluated using a modified Hartwig and Siegel scale. Moderate reactions were the most common, accounting for 31 cases (67.39%), indicating a significant clinical impact requiring attention. Mild reactions followed, comprising 11 cases (23.9%), reflecting a less severe but notable manifestation of ADRs. Severe reactions were relatively infrequent, with only 4 cases (8.69%) reported. These findings, depicted in Figure 7, underscore the variable presentation and severity of antibiotic-induced ADRs, guiding clinical management and intervention strategies to optimize patient outcomes.

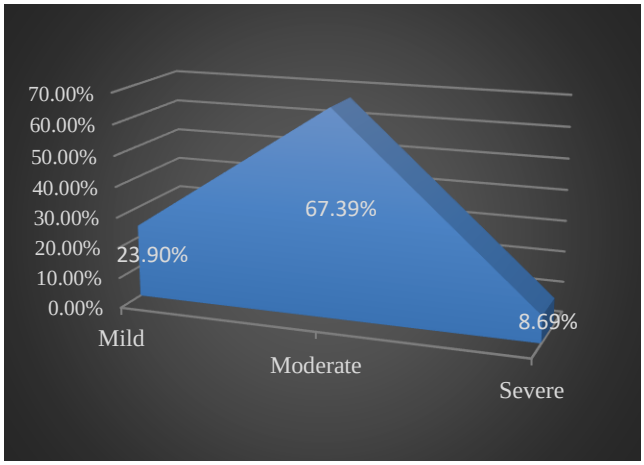

Figure 7: ADRs reported and their severity level (using the modified Hartwig and Siegel scale)

The preventability of reported ADRs associated with antibiotics was evaluated using the modified Shumock and Thornton method. Outcomes indicated that a substantial proportion of ADRs were deemed preventable, with 29 cases (63.04%) classified as definitely preventable, highlighting identifiable factors or interventions that could have mitigated their occurrence.

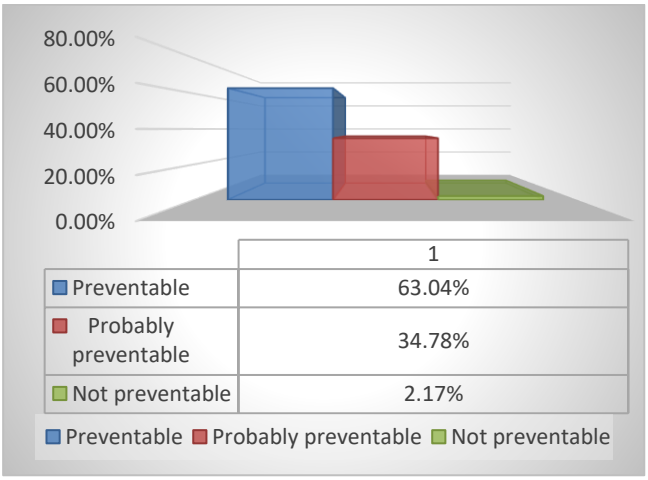

Figure 8: Reportable adverse drug reactions' preventability (using the modified Shumock and Thornton technique)

Additionally, 16 cases (34.78%) were categorized as probably preventable, suggesting potential opportunities for intervention to minimize the risk of ADRs. Only 1 case (2.17%) was deemed not preventable, indicating circumstances where the adverse reaction was unavoidable. These findings, depicted in Figure 8, underscore the importance of proactive measures and risk mitigation strategies in minimizing the incidence and impact of antibiotic-related ADRs, thereby enhancing patient safety and therapeutic outcomes.

DISCUSSION

The investigation into ADRs related to antibiotics in a tertiary-level hospital offers valuable insights into medication safety and patient care practices. The observed predominance of male patients experiencing ADRs aligns with existing literature, suggesting gender disparities in medication responses and healthcare-seeking behaviours, warranting further exploration. The distribution of ADRs across age groups highlights the significant impact of antibiotic therapy, particularly among geriatric patients, who often present with complex medical histories and increased susceptibility to adverse effects. This necessitates comprehensive geriatric assessments and individualized antibiotic prescribing to mitigate ADRs in older adults.

The analysis of ADRs affecting various organ systems underscores the multifaceted nature of antibiotic-related complications, with the gastrointestinal tract being the most frequently affected. However, the involvement of other systems, including skin, urinary, respiratory, haematological and cardiovascular systems, emphasizes the need for vigilant monitoring and prompt management to prevent further complications. Penicillins were the most commonly implicated antibiotic class, followed by cephalosporins, fluoroquinolones, and miscellaneous antibiotics, highlighting the importance of judicious antibiotic selection, appropriate dosing, and vigilant monitoring. Healthcare providers should consider patient-specific factors, antimicrobial resistance patterns, and local epidemiological data when prescribing antibiotics to optimize patient safety and antimicrobial stewardship.

Overall, this study enhances understanding of antibiotic-related ADRs in a tertiary hospital setting, informing targeted interventions, antimicrobial stewardship initiatives, and medication safety practices. These efforts aim to enhance patient care and minimize the burden of antibiotic-related complications, promoting safer antibiotic use and better patient outcomes in tertiary-level healthcare facilities.

CONCLUSION

The investigation into adverse drug reactions (ADRs) associated with antibiotics in a tertiary-level hospital has provided crucial insights into medication safety and patient care. The study analysed patient demographics, ADR characteristics, management strategies, and preventability factors, revealing significant patterns and implications of antibiotic-induced complications. A notable predominance of male patients experiencing ADRs suggests potential gender-related disparities in medication responses and healthcare-seeking behaviours. The distribution of ADRs across different age groups highlights the vulnerability of geriatric patients, emphasizing the importance of tailored medication management and heightened vigilance in this population.

The systemic nature of antibiotic-induced ADRs was evident, with the gastrointestinal tract and skin being the most frequently affected systems. These findings underscore the diverse range of adverse effects associated with antibiotic therapy and the need for comprehensive monitoring and management strategies. Penicillins, cephalosporins, and fluoroquinolones were the most commonly implicated antibiotic classes, underscoring the importance of judicious antibiotic selection, appropriate dosing, and vigilant monitoring. Management of ADRs varied, often requiring drug withdrawal or dose adjustments. While most patients recovered, a significant number of ADRs were deemed preventable, highlighting the need for proactive safety measures.

In conclusion, this study elucidates the prevalence, patterns, and implications of antibiotic-related ADRs in a tertiary hospital setting, providing a foundation for targeted interventions, antimicrobial stewardship, and medication safety practices. Continued efforts to monitor, assess, and address ADRs are essential for ensuring the safe and effective use of antibiotics and optimizing patient outcomes. By leveraging these insights, healthcare providers can implement evidence-based strategies to enhance medication safety and improve care for patients receiving antibiotic therapy.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Coleman JJ, Pontefract SK. ADRs. Clin Med. 2016;16(5):481-9.
2. Giardina C, Cutroneo PM, Mocciaro E, Russo GT, Mandraffino G, Basile G, et al. ADRs in hospitalized patients: results of the FORWARD (Facilitation of Reporting in Hospital Ward) study. Front Pharmacol. 2018;9:350-8.
3. Mohsen S, Dickinson JA, Somayaji R. Update on the adverse effects of antimicrobial therapies in community practice. Can Fam Physician. 2020;66(9):651-9.
4. Chen JJ, Huo XC, Wang SX, Wang F, Zhao Q. Data mining for adverse drug reaction signals of daptomycin based on real-world data: a disproportionality analysis of the US Food and Drug Administration Adverse Event Reporting System. Int J Clin Pharm. 2022;44(6):1351-60.
5. World Health Organization. Tracking universal health coverage: first global monitoring report. World Health Organization; 2015.

6. Venkatesan K, Rajasekhar MB, Gowri MK, Mohapatra MN. An Introduction to Pharmacovigilance. AG Publishing House (AGPH Books); 2022.
7. Bakri HA, Jaly AA, Jaly AA. Antibiotics-Related ADR in a Tertiary Hospital in Saudi Arabia: A Cohort, Retrospective Study. Cureus. 2023;15(5):33-39.
8. Davies EA, O'mahony MS. ADRs in special populations–the elderly. Br J Clin Pharmacol. 2015;80(4):796-807.
9. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, McLaughlin M. A review of antibiotic use in pregnancy. Pharmacotherapy. 2015;35(11):1052-62.
10. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med. 2017;177(9):1308-15.
11. Sello M. Pharmacogenomics of "Core" Essential Medicines. In: Pharmacogenetics. IntechOpen; 2021.
12. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17:1-10.
13. Balaban NQ, Helaine S, Lewis K, Ackermann M, Aldridge B, Andersson DI, et al. Definitions and guidelines for research on antibiotic persistence. Nat Rev Microbiol. 2019;17(7):441-8.
14. Hughes K, Cavell A. The History of Antibiotics and Their Introduction into Modern Medicine. J Antimicrob Chemother. 2020;75(5):1256-61.
15. Spellberg B, Gilbert DN. The Future of Antibiotics and Resistance: A Tribute to a Career of Leadership by John Bartlett. Clin Infect Dis. 2014;59(Suppl 2):40-46.
16. Smith R, Coast J, Millar M. Antibiotics: a global challenge with a complex solution. Lancet Infect Dis. 2018;18(11):1301-2.
17. Weisman JA, Nicholson JC, Tappa K, Jammalamadaka U, Wilson CG, Mills DK. Antibiotic and chemotherapeutic enhanced three-dimensional printer filaments and constructs for biomedical applications. Int J Nanomedicine. 2015:357-70.
18. Yelin I, Kishony R. Antibiotic resistance. Cell. 2018;172(5):1136-6.
19. Giardina C, Cutroneo PM, Mocciaro E, Russo GT, Mandraffino G, Basile G, et al. ADRs in hospitalized patients: results of the FORWARD (Facilitation of Reporting in Hospital Ward) study. Front Pharmacol. 2018;9:350.
20. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2020. Stockholm: ECDC; 2021.
21. Mittal AK, Bhardwaj R, Mishra P, Rajput SK. Antimicrobials misuse/overuse: adverse effect, mechanism, challenges and strategies to combat resistance. Open Biotechnol J. 2020;14(1):22-28.
22. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev. 2020;33(2):45-51.
23. Shipkova M, Jamoussi H. Therapeutic drug monitoring of antibiotic drugs: the role of the clinical laboratory. Ther Drug Monit. 2022;44(1):32-49.
24. Pharmacovigilance: Ensuring the Safe Use of Medicines. 2019. Retrieved from https://www.who.int/news-room/fact-sheets/detail/pharmacovigilance-ensuring-the-safe-use-of-medicines