## Abstract

Background: pharmacovigilance is the science and activities that used to detect, evaluate, understand, and prevent drugs' adverse effects and to ensure that medicines are used safely and effectively. Antimicrobials considered as an important curable medicine for diseases; however, irrational medical prescribing may lead to differing types of adverse drug reactions (ADRs)

Aim of Study: The study aims to summarize besides analyzing data from the pharmacovigilance center in Basrah concerning antibiotic use-related ADR.

Method: This study is a retrospective cohort study of antibiotic used in 2022-2023. The study population consists of patients who received antibiotics during the study period. The outcome of interest is the incidence of antibiotic associated adverse events.

Results: Penicillin and third-generation cephalosporin were the most frequent causes of ADRs, and both were account for 29.00% of the reported cases followed by glycopeptide, and vancomycin about 24.00%. The most common clinical manifestations were skin and subcutaneous tissue disorders, occurred in 80 cases (75.00%), after which difficulty in breathing (8.50%) and with remaining (16.00%) miscellaneous symptoms like hypotension, urticaria, headache, and GIT disorders were come.

Conclusion: Penicillin and third-generation cephalosporin were the most frequent causes of ADRs, skin manifestations were the most frequently reported adverse events. Inappropriate antibiotic prescriptions were common and associated with increased risks of adverse drug events and higher attributable healthcare expenditure and increase need for education programs for rational use of antibiotics.

**Keywords:** pharmacovigilance, antibiotic adverse reaction, adverse drug reaction

## 1. Introduction

Pharmacovigilance is the science and activities used to detect, evaluate, understand, and prevent adverse effects or other problems related to drugs. Pharmacovigilance is an essential motif of drug safety that helps to ensure safe and effective application of medicines [1]. It includes collecting and analyzing data on adverse reactions or other problems related to drug usage plus develop and carry out strategies to prohibit such problems from occurring in the future. The pharmacovigilance's definitive goal is ensuring that patients are receiving the best and possible health care and that medicines are used safely and effectively. This aim can be achieved through the early detection and evaluation of drug safety risks [2]. The world system of pharmacovigilance is specifically based on Adverse Drug Reactions (ADR) spontaneous reports. ADR can lead to severe drawbacks and increase mortality, in addition, most of these drawbacks can be preventable. Globally, antibiotics prescribed widely increases chances for adverse events associated with this extensive use [3].

It is no secret that antibiotics are necessary medications to fight bacteria, but they are not free of side effects, some of which can be serious, and improper use of them can lead to the world's problem ( antimicrobial resistance) [4]. In this study, we will explore the importance of pharmacovigilance for antibiotics and its impact on patient safety. We will discuss the current strategies and systems in place to monitor and manage adverse reactions to antibiotics. Finally, we will propose recommendations for improving pharmacovigilance practices for antibiotics to ensure they’re used safely and effectively in clinical practice.

Safety of drugs is a healthcare important issue that aims to ensure medications' safe and effective use. The drugs' safety can be assessed through various strategies, including preclinical and clinical trials, post-marketing drugs observation, and by reporting the adverse effects [5].

Adverse drug events (ADEs) is referring to any negative or unintended effects that take place on consuming a medication. These events can range from tolerant to serious and can affect a patient's health, life quality, functioning ability [6].

Reporting any dubious ADEs is considered crucial to the professionals of healthcare and regulatory agencies, such as the US Food and Drug Administration (FDA). It helps identifying concerns with potential medications safety, besides it determines whether labeling changes, additional new researches or more educational campaigns are needed [7]. Such reports can be done through MedWatch program by healthcare providers, this program used to collect and analyze reports about ADEs and provide them to the FDA.

Antibiotic safety monitoring

A process in which continuous monitoring and evaluation of antibiotics' safety and effectiveness, it is done to ensure that such drugs do not cause any dangerous side effects or leading to antimicrobial resistance. This can be done by various techniques, like clinical studies, post-marketing surveillance, and adverse effects reporting systems [8].

Agencies such as (FDA) and (EMA) which is the European Medicines Agency oblige drug manufacturers to report on the safety of the drug and its side events, if any, as a condition to approve drugs and post-marketing surveillance [9].

Overall, antibiotic drug safety monitoring is crucial to ensure that antibiotics are safe and effective for use in treating bacterial infections.

**Aim of Study:**

This study aims to summarize and analyze data from pharmacovigilance center in Basrah concerning antibiotic use-related ADR.

## 2. Methods

2.1. Study design

This study is a retrospective cohort study of antibiotic use in 2022-2023. The study population consists of patients who received antibiotics during the study period. The outcome of interest is focusing on antibiotics adverse events associating their use.

2.2 Inclusion and exclusion criteria

All patients with completed data that are officially registered with antibiotic adverse reactions in Basrah pharmacovigilance center were included. Completed documented data within one year from the beginning of the study were included. Patients with uncomplete data about antibiotic adverse reaction and the certain intervention were excluded. Reports about adverse drug

reactions other than antibiotics were also excluded. Patients with uncertain diagnosis were also excluded.

2.3. Data collection

To collect data, electronic medical records were assessed from hospitals and clinics in the study area. Information were collected on patient demographics, diagnosis, antibiotic prescribing practices, and the occurrence of adverse events associated with antibiotic use.

2.4. Data analysis

The data were analyzed using SPSS software. Descriptive statistics were used in order to summarize patient demographics, antibiotic use, and adverse events.

2.5. Ethical considerations

The ethical approval was obtained from institution's ethics committee of college of pharmacy/ University of Basrah before the beginning of the study and the approval number was (EC47).

**3. Results**

This study includes a random sample of 106 reports of antibiotics' adverse effects, about 56 (52.8%) male and 50 (47.2%) female as shown demographic data in table 3.1.

This part of the study shows the reports contents including patients' demographic data, hospitals in which the reports were done, the duration of hospital residence, number of prescribed antibiotics and the severity of the reported adverse events. In addition to the name and categories of antibiotics reported to cause adverse events and the type and severity of the reported side effects, besides, the medical intervention against the reported side effects.

The predominant age group in which antibiotic adverse reactions were reported was 11-20 years old 33.00%, in addition reports from males were somewhat equal to reports from females.

Eighty three percent of patients received antibiotics stay only one-two days in the hospital and 61.30% of them have been received single antibiotic only. Most of them suffer from mild reactions 99.10% as shown in table 3.1.

**Table 3.1: Demographic data for patients included in the study**

| Parameter | No. (%) |
|---|---|
| **Patient age (years)** | |
| **0-10** | 13.0 (12.30%) |
| **11-20** | 35.0 (33.00%) |
| **21-30** | 12.0 (11.30%) |
| **31-40** | 21.0 (19.80%) |
| **41-50** | 18.0 (17.00%) |
| **51-60** | 1.0 (0.90%) |
| **More than 60** | 6.0 (5.70%) |
| **Gender** | |
| **Male** | 56.0 (52.80%) |
| **Female** | 50.0 (47.20%) |
| **Hospital** | |
| **Maternal and children hospital** | 50.0 (47.00%) |
| **Al-Mawani hospital** | 20.0 (19.00%) |
| **Al-Sader hospital** | 14.0 (13.00%) |
| **Al-Fayhaa hospital** | 12.0 (11.00%) |
| **Basra Teaching hospital** | 10.0 (9.00%) |
| **Duration of hospital residence** | |
| **1-2 days** | 88.0 (83.00%) |
| **3-4 days** | 7.0 (6.60%) |
| **5-6 days** | 5.0 (4.70%) |

| | |
|---|---|
| **More than one week** | 6.0 (5.70%) |
| **No of antibiotics were taken at the same time**<br>**Single**<br>**Two**<br>**Three** | <br>65.0 (61.30%)<br>38.0 (35.80%)<br>3.0 (2.80%) |
| **The severity of the reported adverse effect**<br>**Mild**<br>**Severe** | <br>105.0 (99.10%)<br>1.0 (0.90%) |

Table 3.1 shows the demographic data of the included patients, the results were displayed in form of numbers and percentage (%)

The predominant antibiotic groups that cause adverse reactions were pencillins and cephalosporins 29.00% while only one patient suffer from tinidazole adverse reaction as displayed in table 3.2.

**Table3.2: Types of antibiotic-associated with adverse effect**

| **Type** | **No (%)** |
|---|---|
| **Penicillins** | 31.0 (29.00%) |
| **Cephalosporins** | 31.0 (29.00%) |
| **Vancomycin** | 26.0 (24.00%) |
| **Quinolones** | 7.0 (6.60%) |
| **Macrolides** | 4.0 (3.70%) |
| **Aminoglycosides** | 4.0 (3.70%) |
| **Tetracyclines** | 2.0 (1.80%) |
| **Others (tinidazole)** | 1.0 (0.90%) |

Table 3.2 shows that antibiotics that associated with reported adverse events, the results were displayed in the form of numbers and percentages (%)

Vancomycin, amoxicillin and ceftriaxone were the most antibiotics with which adverse reactions were reported in form of 26.00, 24.00 and 24.00 reported case of adverse reaction respectively as displayed in figure 3.1.

**Figure 3.1: The specific antibiotic associated with which adverse effects reported**

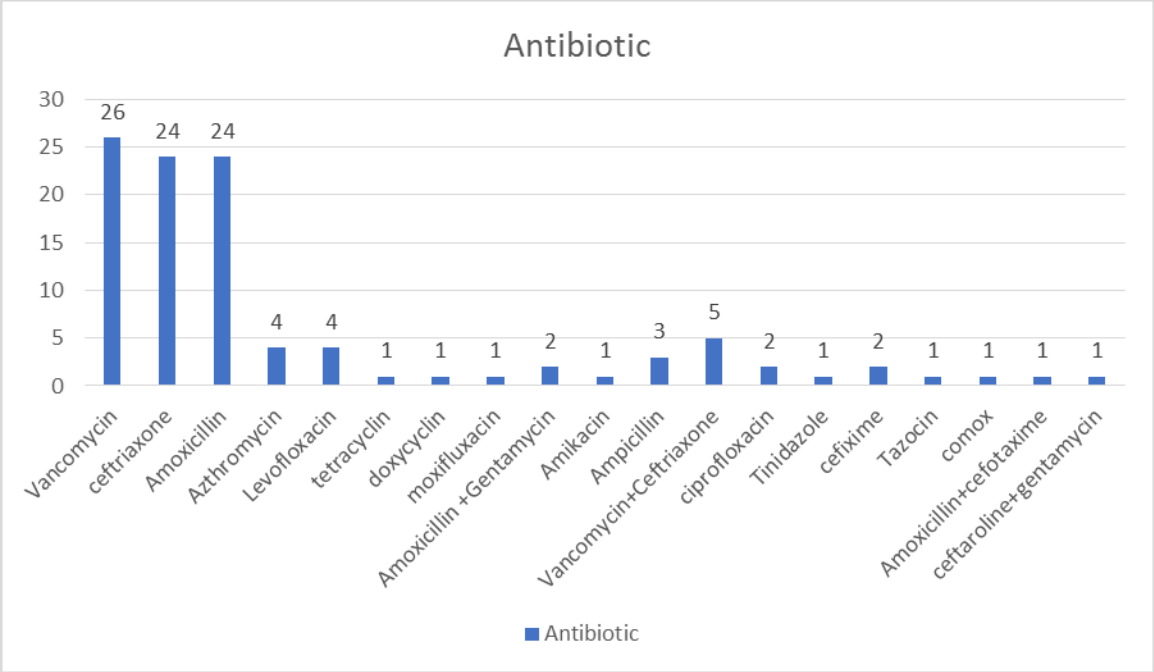


Figure 3.1 shows the exact antibiotics with which adverse events were reported, the results are displayed in form of numbers of reports on the single exact antibiotic.

The major reported adverse drug reaction was skin rash 80.0 case, while only 9.0 reported cases suffer from breathing difficulty as shown in table 3.3 and figure 3.2. Besides, most of these reactions were mild 99.10% as displayed in figure 3.3.

**Table 3.3: Types of the resulted adverse reactions**

| Type of ADR | Severity of ADR | No. (%) |
|---|---|---|
| **Skin rash** | Mild | 80.0 (75.50%) |
| **Breathing difficulty** | Mild | 9.0 (8.50%) |
| **Others (urticaria, hypotension, headache and GIT symptoms)** | Mild | 17.0 (16.00%) |

Table 3.3 shows the type and the severity of the reported ADRs, data displayed in form of numbers and percentages (%).

**Figure 3.2: Types of Adverse drug reactions**

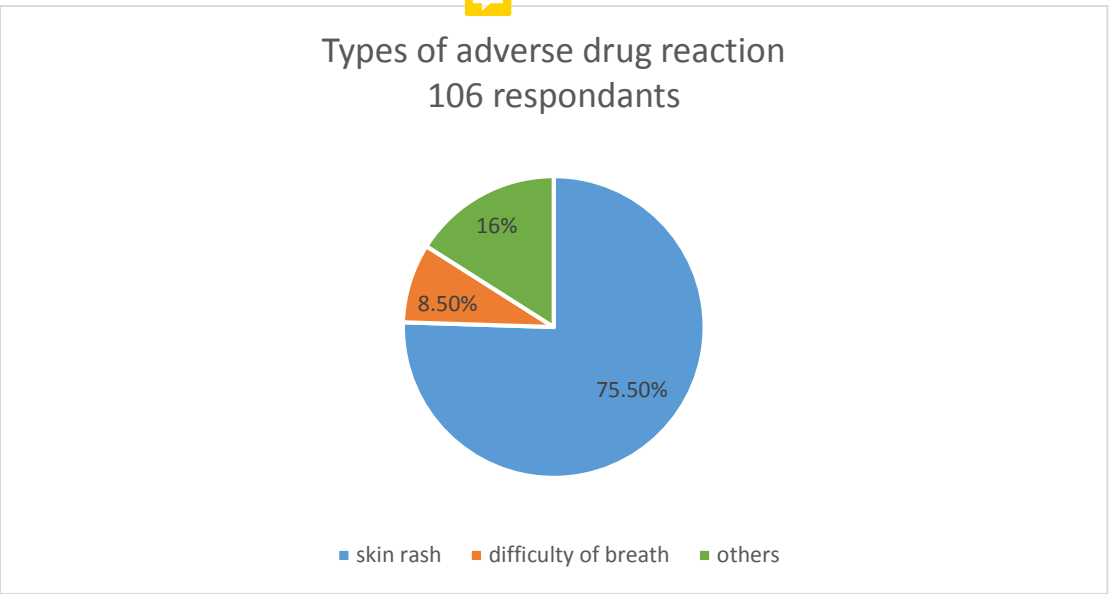


Figure 3.2 displayed the types of reported adverse drug reaction, results displayed in form of percentage %.

**Figure 3.3: Severity of adverse drug effects**

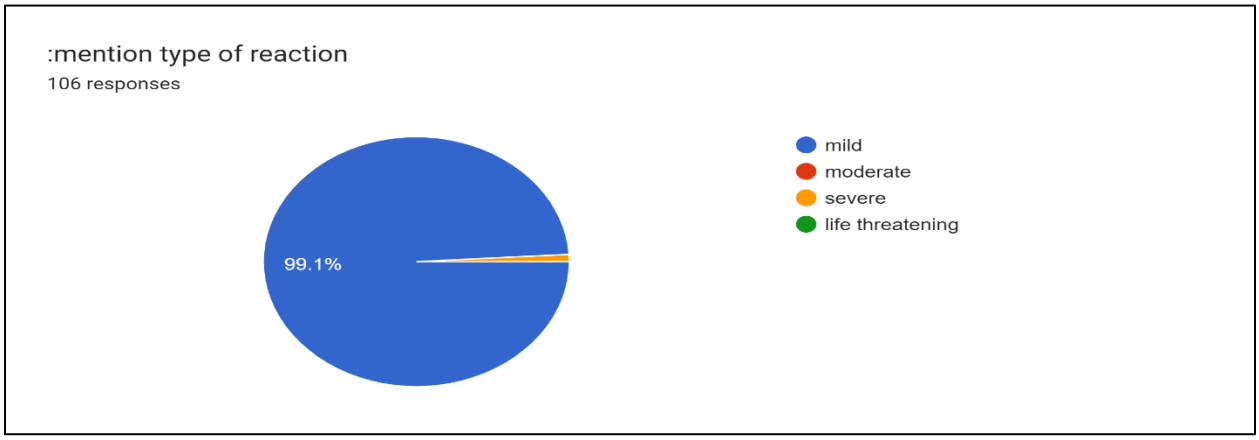


Figure 3.3 displayed the severity of reported adverse drug reaction ranging from mild to life threatening, results displayed in form of percentage %.

The medical staff decided to stop the medicine that cause adverse reaction in most reported cases 69,00 % in addition they decided to treat the adverse drug reactions with hydrocortisone plus diphenhydramine in 39.80% of reported cases as displayed in table 3.4, figure 3.4 and 3.5.

**Table 3.4: Management of the reported adverse drug reactions**

| Response to ADR | Number | Percent |
|---|---|---|
| Medication cessation | 72.0 | 69.00% |
| Keep giving medication | 31.0 | 30.00% |
| **Pharmacological Intervention** | **Number** | **Percent** |
| Hydrocortisone administration | 6.0 | 5.80% |
| Diphenhydramine administration | 1.0 | 1.00% |
| Hydrocortisone plus Diphenhydramine | 41.0 | 39.80% |
| Others | 55.0 | 53.40% |

Table 3.4 shows the managements were done by the medical care providers against reported adverse events, data were displayed in form of numbers and percentages.

**Figure 3.4: Interventions regarding adverse drug reaction**F

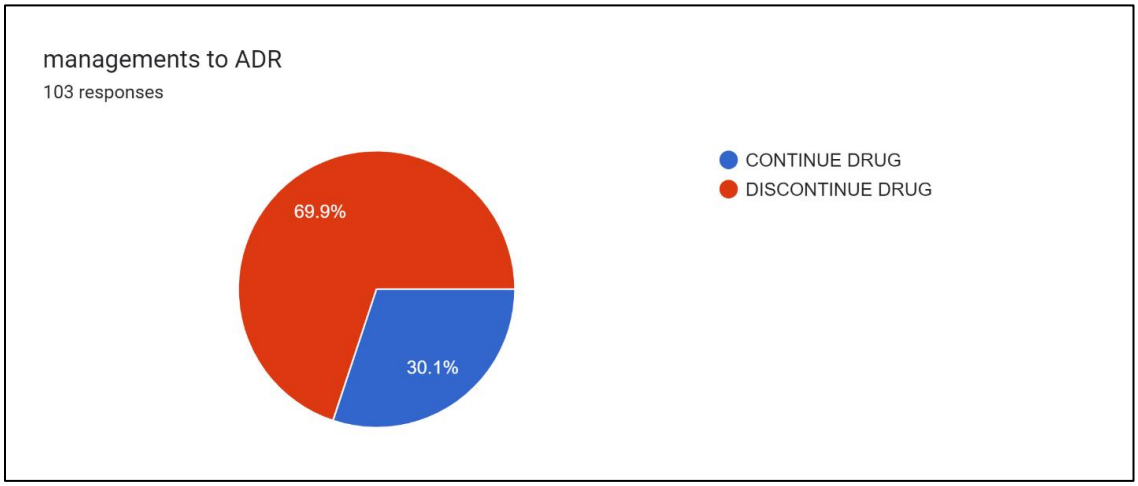


Figure 3.4 displayed the type of medical intervention regarding the adverse drug reaction, results displayed in form of percentage%.

**Figure 3.5: pharmacological interventions regarding ADR**

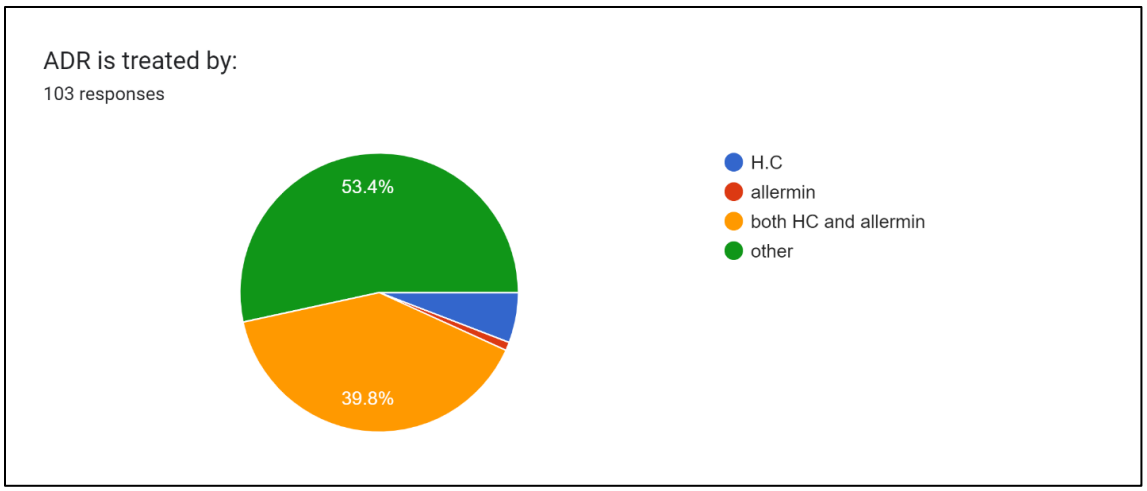


Figure 3.5 displayed the type of pharmacological intervention regarding the adverse drug reaction, results displayed in form of percentage%.

## 4. Discussion

Pharmacovigilance is defined by The World Health Organization (WHO) as the science and activities related to the detection, assessment, understanding, and prevention of adverse events associated drugs use. The aim is to promote the safety and effectiveness during medicines use by the earlier detection and evaluation of drug safety risks [10].

Globally, antibiotics prescribed widely, this extensive use is associated with antibiotic adverse events. Antibiotics relatively have a good safety profile, however, excess or misuse of antibiotics administration increases the incidence for the occurrence of adverse effects as well as increases in antibiotic resistance. The adverse effects of antibiotics range from mild skin reactions to severe life-threatening anaphylaxis reactions.

This study aims to summarize data from the pharmacovigilance center in Basrah concerning reports on adverse events that associate antibiotic use besides, analyzing these reports that have been received from Basra hospitals.

This study includes a random sample of 106 reports of antibiotics' adverse effects, about 56.0 (52.80%) male and 50.0 (47.20%) female as shown in demographic data [Table 1]. Most reports received from Basrah Hospital for Maternal and Pediatrics about (with age groups from (11-20) years and (31-40) years are the highest number of reports about 33.00% and 20.00% respectively. This could be explained by excess and inappropriate administration of antibiotics in children due to their high vulnerability to various types of infection make them at higher risk of adverse effects. This result agrees with other studies that found a high prevalence of antibiotic use among hospitalized pediatrics. Many prescriptions had frequent errors about dose and duration of the treatment. This inappropriate prescription of antibiotics increased the risk of

several drug side effects, including *Clostridioides difficile* infection or severe drug allergy among hospitalized pediatrics [11]. Errors were more frequent with prescription of 3 or more antibiotics or due to short hospitalization [12]. This inappropriate use or prescription of antibiotics will lead to the overgrowth of antibiotic-resistant microorganisms without fail.

In the present study, most reports of adverse effects were recorded for penicillin and cephalosporin (about 30.00% of all ADR of antibiotics) as shown in Table 2. These results could be explained by the fact that Penicillins and cephalosporins are the class of drugs that remain a highly valuable group of antibiotics in primary care. They are considered among the safest, cost effective that are prescribed widely to treat ear infections, skin infections, upper respiratory tract infections and sinusitis [13]. Pencillins and cephalosporins adverse effects range from diarrhea, urticaria, erythema, increased incidence of infection, and hypersensitivity reaction. Hypersensitivity considered among the most important side effect characterized by pruritus, vomiting, urticaria, nausea, wheezy chest, laryngeal edema, and vascular collapse [14]. Even penicillins allergy is more common than cephalosporins, however, 10 percent of patients crossly sensitive with them both [15].

The second antibiotic with highly reported adverse effects is vancomycin about 29.00% of the reports [Table3.2]. Vancomycin is an effective agent against MRSA *(methicillin-resistant Staphylococcus aureus)* plus *enterococci* that resist ampicillin, and other Gram-positive organisms in penicillin allergic patients [16]. Ototoxicity, nephrotoxicity and are the main side effects of vancomycin. Hypersensitivity to vancomycin usually represented as (Red Man syndrome) and anaphylaxis which usually occurs after rapid administration of vancomycin intravenously [17]. Therefore, vancomycin should be chosen as a last option when medical agents are ineffective.

In the present study, a lower number of ADR reports include other types of antibiotics like azithromycin, ciprofloxacin, tetracycline, doxycycline, and gentamycin [figure 1]. This may be explained by a low administration rate of these antimicrobials especially oral ones in hospitalized patients and lower hypersensitivity reactions than B-lactam antibiotics.

In Table 3, the most likely symptom of ADR is skin rash (about 80, 75.50%) followed by difficulties in breathing (8.00, 7.50%) with remaining (17.00, 16.00%) miscellaneous symptoms like hypotension, urticaria, headache, and GIT disorders. Skin manifestations are the most common ADR of antibiotics that resulted mainly after administration of penicillins, third-generation cephalosporins, and glycopeptides. Similar results were seen in other studies where cutaneous ADR is the predominant effect of antibiotics [18, 19].

Regarding the severity of the reported ADR, most symptoms were mild 99.00% and less than 1.00% were severe as shown in Table 3. The medical intervention for most reported cases (about 70.00%) was discontinuation of antibiotics and 30.00% continue the medication with or without administration of antiallergic drugs like corticosteroids alone or in combination with antihistamines. Continuation of causative antibiotics based on the severity of ADR and the medical status of the patients. In the present study, most ADRs were mild and the continuation of antibiotics was reasonable when appropriate intervention and monitoring is done especially in cases where alternative antibiotics were not available.

Finally, Pharmacovigilance reports give an important information about the common ADR of medications and appropriate responses to it, to ensure medications' safety. The pharmacist plays an important role in health systems by keeping rational and safe use of medications since they are drug experts. Improving the outcomes of pharmacotherapy and global health costs lowering can be held by Effective use of pharmacists' workforce.

## 5. Conclusion

The most common antibiotics that cause ADRs were penicillin and third-generation cephalosporin. Besides, the most frequently experienced symptom were skin manifestations. Inappropriate prescription of antibiotic prescriptions are common and increase risks of side effects highly. These findings highlight the individual- and national-level consequences of inappropriate antibiotic prescribing and further support the implementation of outpatient antibiotic stewardship programs.

**Conflict of interest:** none declared.

**This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors OR Conflict of interest: none declared.**

## References

1-Santoro A, Genov G, Spooner A, Raine J, Arlett P. Promoting and protecting public health: how the European Union pharmacovigilance system works. Drug safety. 2017 Oct;40:855-69, doi: 10.1007/s40264-017-0572-8.

2- Mammì M, Citraro R, Torcasio G, Cusato G, Palleria C, di Paola ED. Pharmacovigilance in pharmaceutical companies: An overview. J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1):S33-7, doi: 10.4103/0976-500X.120945.

3- Jiang H, Lin Y, Ren W, Fang Z, Liu Y, Tan X, Lv X, Zhang N. Adverse drug reactions and correlations with drug-drug interactions: A retrospective study of reports from 2011 to 2020. Front Pharmacol. 2022 Aug 22;13:923939, doi: 10.3389/fphar.2022.923939.

4- Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015 Apr;40(4):277-83. PMID: 25859123; PMCID: PMC4378521.

5- Alshammari TM. Drug safety: The concept, inception and its importance in patients' health. Saudi Pharm J. 2016 Jul;24(4):405-12, Epub 2014 May 9, doi: 10.1016/j.jsps.2014.04.008.

6- Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med (Lond). 2016 Oct;16(5):481-485, DOI: 10.7861/clinmedicine.16-5-481.

7-Ventola CL. Big Data and Pharmacovigilance: Data Mining for Adverse Drug Events and Interactions. P T. 2018 Jun;43(6):340-351.

8- Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol. 2012 Jan;73(1):27-36, DOI: 10.1111/j.1365-2125.2011.04080.x.

9- Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. J Gen Intern Med. 2003 Jan;18(1):57-60, DOI: 10.1046/j.1525-1497.2003.20130.x.

10-Magalhães Silva T, Rebelo Gomes E, Ribeiro-Vaz I, Roque F, Teresa Herdeiro M. Prevalence and Significance of Antibiotic-Associated Adverse Reactions. New Insights into the Future of Pharmacoepidemiology and Drug Safety. IntechOpen; 2021, DOI10.5772/intechopen.87642.

11- Butler AM, Brown DS, Durkin MJ, Sahrmann JM, Nickel KB, O'Neil CA, Olsen MA, Hyun DY, Zetts RM, Newland JG. Association of Inappropriate Outpatient Pediatric Antibiotic Prescriptions With Adverse Drug Events and Health Care Expenditures. JAMA Netw Open. 2022 May 2;5(5):e2214153, DOI: 10.1001/jamanetworkopen.2022.14153.

12- Xavier SP, Victor A, Cumaquela G, Vasco MD, Rodrigues OA. Inappropriate use of antibiotics and its predictors in pediatric patients admitted at the Central Hospital of Nampula, Mozambique. Antimicrobial Resistance & Infection Control. 2022 Dec;11(1):1-8, DOI: 10.1186/s13756-022-01115-w .

13-Miller EL. The penicillins: a review and update. Journal of midwifery & women's health. 2002 Nov 1;47(6):426-34, DOI: 10.1016/s1526-9523(02)00330-6.

14- Bhattacharya S. The facts about penicillin allergy: a review. Journal of advanced pharmaceutical technology & research. 2010 Jan;1(1):11.

15-Anderson JA. Cross-sensitivity to cephalosporins in patients allergic to penicillin. The Pediatric Infectious Disease Journal. 1986 Sep 1;5(5):557-61, DOI: 10.1097/00006454-198609000-00013.

.

16-Diaz R, Afreixo V, Ramalheira E, et al. Evaluation of vancomycin MIC creep in methicillin-resistant *Staphylococcus aureus* infections-a systematic review and meta-analysis. *Clin Microbiol Infect* 2018;24:97–104, DOI: 10.1016/j.cmi.2017.06.017.

17-Peng Y, Li CY, Yang ZL, Shi W. Adverse reactions of vancomycin in humans: A protocol for meta-analysis. Medicine (Baltimore). 2020 Sep 18;99(38):e22376, DOI: 10.1097/MD.0000000000022376.

18- Doshi K., Yegnanarayan R., Gokhale N. A Retrospective Study of Drug-Induced Cutaneous Adverse Reactions (CADR) in Patients Attending Tertiary Care Hospital. *Current Drug Safety.* 2016;11(999):1–1, **DOI:** 10.2174/1574886312011702101948 17.

19- Jung IY, Kim JJ, Lee SJ, Kim J, Seong H, Jeong W, Choi H, Jeong SJ, Ku NS, Han SH, Choi JY, Song YG, Park JW, Kim JM. Antibiotic-Related Adverse Drug Reactions at a Tertiary Care Hospital in South Korea. Biomed Res Int. 2017;2017:4304973, DOI: 10.1155/2017/4304973 .