O MUNDO DA SAÚDE

Tool for consultation on adverse reactions to antimicrobials aimed at pharmacists: a literature review

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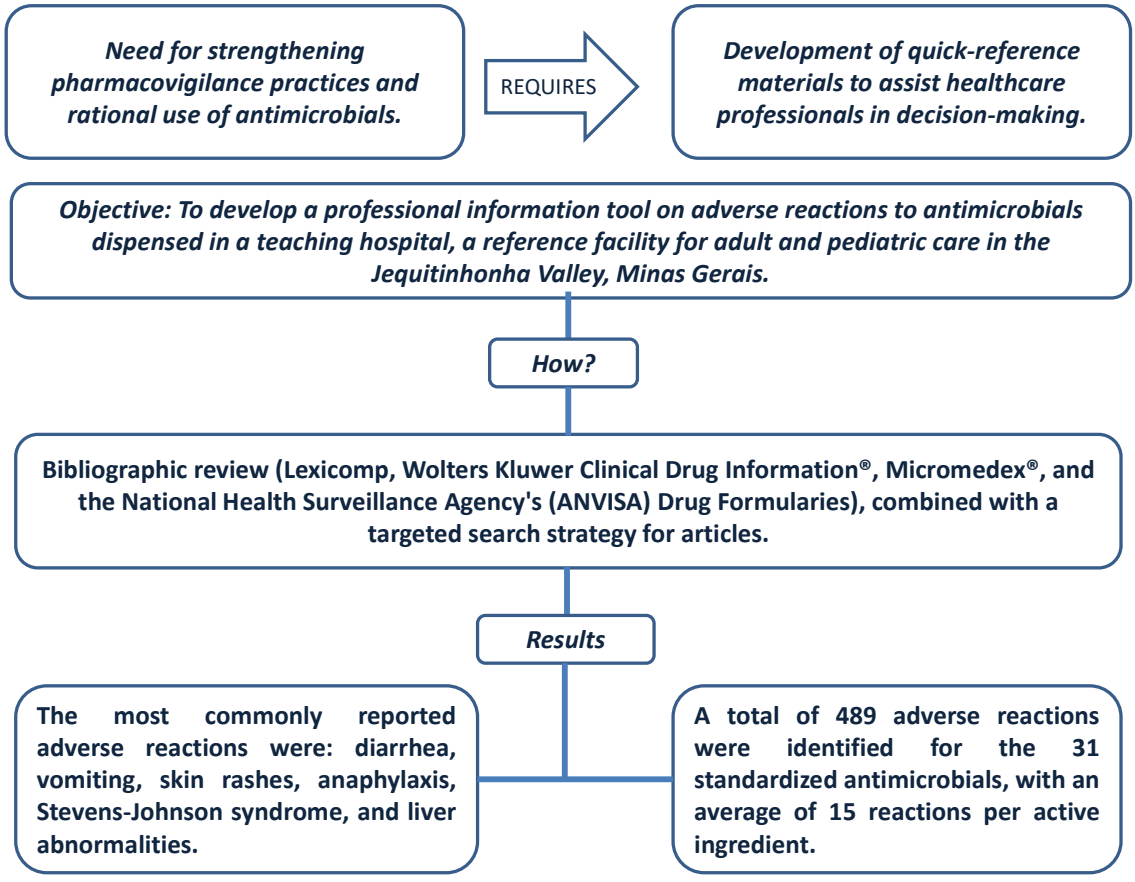
Graphic Abstract



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Abstract

Hospital-acquired infection, also known as nosocomial infection, poses a significant concern for patients and healthcare professionals. This issue is exacerbated by bacterial resistance resulting from the inappropriate use of antimicrobials. Neglect in hospitals and the overprescription of these medications contribute to this scenario, affecting approximately 15% of hospitalized patients globally, according to the World Health Organization. With the aim of promoting safety practices related to the use of antimicrobials in the hospital setting, the present study aimed to develop a professional information tool on adverse reactions to antimicrobials dispensed in a teaching hospital that serves adult and pediatric patients in the Jequitinhonha Valley, Minas Gerais. The methodology involved a bibliographic review conducted using Lexicomp, Wolters Kluwer Clinical Drug Information®, Micromedex®, and the Drug Compendium from the Brazilian Health Regulatory Agency (ANVISA), as well as targeted searches for articles on platforms such as PubMed®, Latin American and Caribbean Health Sciences Literature (LILACS)®, Google Scholar®, Scientific Electronic Library Online (SciELO)®, Medical Literature Analysis and Retrieval System Online (MEDLINE)®, and the Virtual Health Library (VHL)®. In addition to the information obtained from Lexicomp®, Micromedex®, and the Drug Compendium by ANVISA®, 28 articles published in the last 10 years were selected. The most prevalent classes of antimicrobials were penicillins (27%), cephalosporins (20%), aminoglycosides, quinolones, and sulfonamides (7% each). The most commonly reported adverse reactions were diarrhea, vomiting, skin rashes, anaphylaxis, Stevens-Johnson syndrome, and hepatic changes. A total of 489 adverse reactions were identified for the 30 standardized antimicrobials, averaging 15 reactions per active ingredient. Although some reactions are rare, such as red man syndrome, Stevens-Johnson syndrome, and drug-induced liver injury, they carry a high potential for morbidity and mortality. It is concluded that there is a wide variety of adverse reactions, documented in the literature, associated with the use of the antimicrobials studied. Monitoring and reporting of these events through pharmacovigilance are recommended to ensure patient safety in the hospital under study.

Keywords: Antimicrobials. Pharmacovigilance. Adverse Drug Reaction. Hospital Antibiotic.

INTRODUCTION

Hospital-acquired or nosocomial infection, related to healthcare provision, is a major concern for both patients and healthcare professionals. According to regulations established by the Ministry of Health, this infection is acquired after a minimum period of hospitalization or associated with medical procedures performed during the hospital stay. Although 72 hours is the designated timeframe to characterize a hospital-acquired infection, cases diagnosed before this period may also qualify, provided they are related to medical interventions, which represent one of the main challenges faced by healthcare facilities[1,2].

According to the World Health Organization (WHO), healthcare-associated infections are the most frequent adverse incident in the context of global healthcare delivery, affecting approximately 15% of all patients requiring hospitalization[3].

This concerning reality can, in part, be attributed to bacterial resistance a natural selection process in which microorganisms no longer respond to antibiotics previously used to kill or inhibit them. However, hospital negligence and the excessive and improper use of antimicrobials are additional factors that can accelerate this process[4].

According to Mazzeo *et al.*[5], antimicrobials stand out as one of the most frequently prescribed drug groups in hospital settings and are also associated with the occurrence of adverse reactions. In the Brazilian context, it is estimated that one medication error occurs per day in hospitalized patients, with Adverse Drug Reactions (ADRs) accounting for approximately 700,000 emergency visits per year[6]. This underscores the importance of implementing, monitoring, and improving practices related to pharmacovigilance and actions associated with patient safety, especially concerning the use of antimicrobials.

Given this scenario, it is essential to reinforce the role of pharmacovigilance, as it not only bears responsibility for proper guidance on the use of medications, including antimicrobials, but also plays a fundamental role in mitigating

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infections and preventing drug-related adverse events[7]. For effective pharmacovigilance practices, it is believed that the availability of consultation tools can be a key factor in streamlining and ensuring the quality of pharmaceutical activities.

Thus, this study aimed to develop an educational tool for pharmacists, providing guidance on adverse reactions associated with the use of antimicrobials used in a teaching hospital in the Jequitinhonha Valley, Minas Gerais.

METHODOLOGY

This study is a literature review conducted in the Thesis and Dissertation Database of the Coordination for the Improvement of Higher Education Personnel (CAPES)®, as well as on the following academic platforms: PubMed®, Latin American and Caribbean Health Sciences Literature (LILACS)®, Google Scholar®, Scientific Electronic Library Online (SciELO)®, Medical Literature Analysis and Retrieval System Online (MEDLINE)®, and Virtual Health Library (VHL)®. Additionally, the book Lexicomp, Wolters Kluwer Clinical Drug Information®, the Micromedex® website, and the Drug Compendium by the Brazilian Health Regulatory Agency (ANVISA)® were also consulted. The research was conducted using the descriptors: antimicrobials, pharmacovigilance, adverse reactions, and hospital antibiotic, with the boolean operator "AND" applied between terms.

Documents and articles published between 2013 and 2023 were selected, focusing on the identification of adverse reactions related to the human use of at least one of the antimicrobials standardized in 2023 at the teaching hospital where the study was conducted. The antimicrobials studied included: Amoxicillin, Amoxicillin + Clavulanate, Ampicillin Sodium, Ampicillin + Sulbactam, Azithromycin, Cephalexin, Cefalotin Sodium, Cefazolin, Cefotaxime Sodium, Ceftriaxone, Ciprofloxacin, Clindamycin, Chloramphenicol, Cefepime Hydrochloride, Doxycycline Hydrochloride, Gentamicin, Levofloxacin, Meropenem, Metronidazole, Nitrofurantoin, Oxacillin Sodium, Benzathine Penicillin, Potassium Penicillin, Piperacillin + Tazobactam, Polymyxin B, Rifampicin, Sulfadiazine, Amikacin Sulfate, Sulfamethoxazole + Trimethoprim, and Vancomycin. The selection criteria focused on oral or injectable medications, as these are considered the most harmful in relation to ADRs.

The documents were selected based on title and abstract, in English, Spanish, and Portuguese, including studies that addressed the main adverse effects associated with the antimicrobials standardized at the teaching hospital under study. Additional literature searches were conducted by researching the names of the antimicrobials and identifying adverse reactions described on the Google Scholar® platform. These documents were subsequently read in full to decide on their inclusion or exclusion in this study.

Exclusion criteria included publications not available in full, conference abstracts, news articles, and studies that did not address the use of antimicrobials in humans, thus eliminating in vitro and in vivo studies, as well as studies that did not meet all relevant requirements according to the established inclusion criteria.

The selected documents were subsequently subjected to thorough review, with relevant information on standardized antimicrobials and their possible adverse reactions recorded. Ethical approval from the Research Ethics Committee was not required, as the study did not involve humans or animals. Additionally, the list of medications available at the evaluated hospital is freely accessible to the public.

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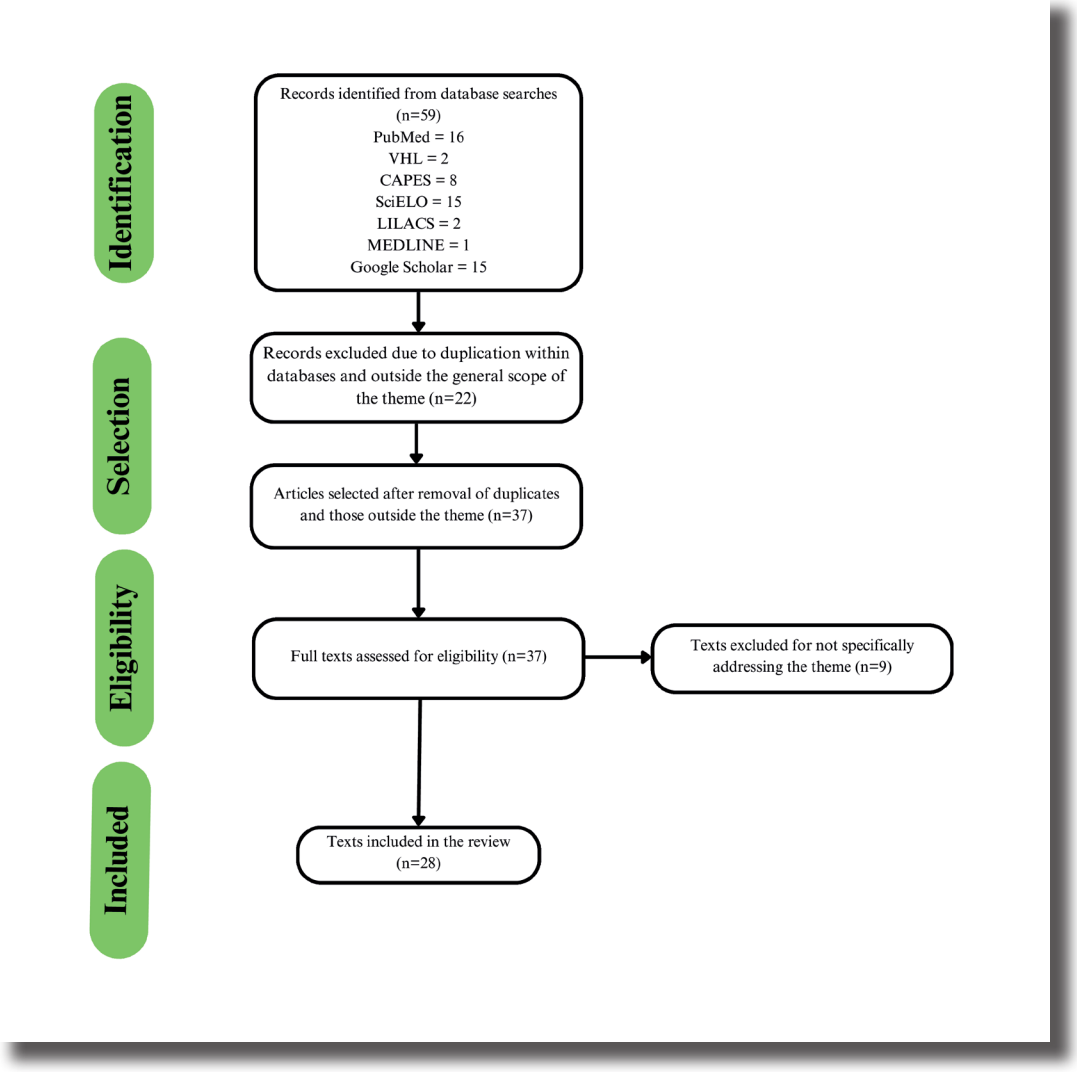
RESULTS

The search for ADRs associated with the use of antimicrobials began with consultations of literature databases. The hospital where the study was conducted has 33 standardized antimicrobials, of which 30 were selected for research.

Following the bibliographic search across various platforms and the application of the pre-established inclusion and exclusion criteria, 28 articles published between 2013 and 2023 were included in this review. Figure 1 outlines the stages of the article selection process for this review.

The antimicrobials with the highest number of reported adverse reactions were amoxicillin with 29 reactions, ampicillin sodium with 28 reactions, rifampicin with 25 reactions, and ceftriaxone and nitrofurantoin, each with 23 reported reactions.



Source: Research data (2023).

Figure 1 - Flowchart of article inclusion and exclusion analysis.

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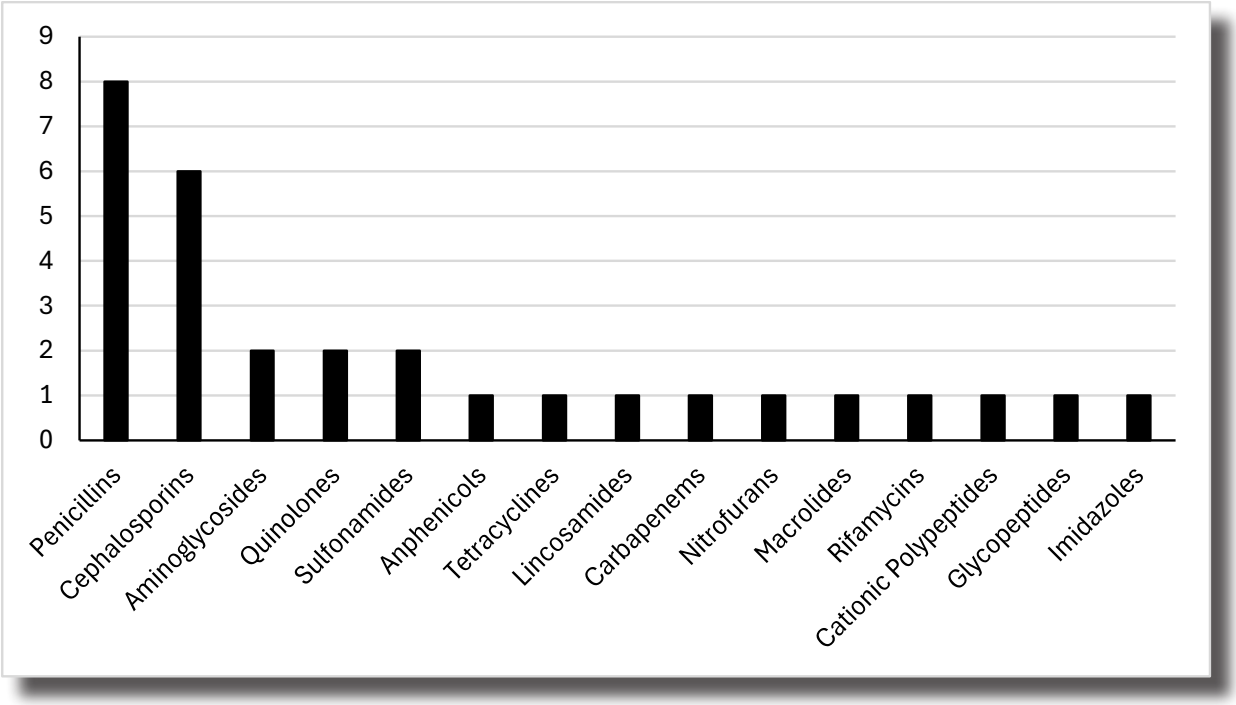
The frequency and type of adverse reactions varied according to the different classes of antibiotics. A total of 489 adverse reactions were reported for the 30 antimicrobials analyzed, compiling data from all sources consulted, with an average of approximately 15 reactions per drug.

As shown in Graph 1, the most prevalent class of antibiotics standardized at the hospital corresponds to beta-lactams, which includes penicillins (8 drugs) and cephalosporins (6 drugs). The aminoglycoside, quinolone, and sulfonamide classes are equally distributed with 2 drugs per class, while the remaining classes included only 1 antimicrobial each.

Graph 1 - Distribution by class of antimicrobial drugs standardized at the teaching hospital studied in 2023 (n=30).



Source: Research data (2023).

The most frequently occurring adverse reactions associated with the use of standardized antibiotics were diarrhea (13%) and vomiting (11%), followed by immune-mediated hypersensitivity reactions, including anaphylaxis, fever, pruritus, skin rash, and Stevens-Johnson syndrome (7% each), toxic epidermal necrolysis (6%), liver enzyme alterations, and urticaria (5%) (Table 1).

Although some reactions are considered rare, such as ototoxicity and cochlear and/or vestibular apparatus damage and nephrotoxicity (2%), agranulocytosis, renal failure, hepatotoxicity, QT interval prolongation (3%), angioedema (4%), kidney injury, and red man syndrome (1%).

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Table 1 - Frequency of adverse drug reactions reported in the evaluated studies. Diamantina, 2023.

Adverse reactions	Frequência
Diarrhea	13%
Vomiting	11%
Pruritus	7%
Fever	7%
Anaphylaxis	7%
Skin rash	7%
Stevens-Johnson syndrome	7%
Toxic epidermal necrolysis	6%
Liver enzyme alterations	5%
Urticaria	5%
Angioedema	4%
Hepatotoxicity	3%
QT interval prolongation	3%
Agranulocytosis	3%
Renal failure	3%
Nephrotoxicity	2%
Ototoxicity	2%
Kidney injury	1%
Red man syndrome	1%

Source: Literature review data (2023).

The majority of the selected articles were case reports (33%), followed by systematic reviews (15%) and narrative reviews (15%), retrospective studies (11%), literature reviews (11%), and other publications (15%) (Table 2).

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Table 2 - Study designs identified in the analyzed articles. Diamantina, 2023.

Study design	Number of publications
Case report	9
Narrative review	4
Systematic review	4
Retrospective study	3
Literature review	3
Cross-sectional study	1
Integrative review	1
Prospective cohort study review	1
Descriptive and cross-sectional observational study	1

Source: Literature review data (2023).

This research enabled the identification of the main adverse reactions associated with different antimicrobial agents, including amoxicillin, amoxicillin with clavulanate, azithromycin, cephalexin, cefalotin sodium, cefazolin, cefotaxime sodium, ceftriaxone, ciprofloxacin, clindamycin, and chloramphenicol (Table 3).

Table 3 - Adverse reactions associated with antimicrobials standardized at the teaching hospital.

CLASS	MEDICINE	SPECIFICATIONS OF ADVERSE REACTIONS	REFERENCES
PENICILLINS	AMOXICILLIN	Urticaria[8,9,10,11], Pruritus[8,9,11], Nausea[8,10,11], Diarrhea[8,10,11], Vomiting[8,10,11], Angioedema[10], Anaphylaxis[8,9,10,11], Hypotension[8], Laryngeal edema[8], Bronchospasm[8], Black and hairy tongue[9,11] Hemorrhagic colitis[9], Pseudomembranous colitis[9], Tooth discoloration[9], Fungal vulvovaginitis[10], Exfoliative palmar rash[8,9,11], Fixed drug eruption[8], Contact dermatitis[8,9,11], Generalized erythema[8,9,11], Linear IgA bullous dermatosis[8,11], Severe maculopapular rash[8,9,10,11], Systemic contact dermatitis[8,9], Urticaria and/or angioedema[8,9,10,11], Stevens-Johnson syndrome[8,9,10,11], Toxic epidermal necrolysis[8,10,11], Rash with eosinophilia[8,11], Generalized bullous fixed drug eruption[8], Acute generalized exanthematous pustulosis[8,9,10], Systemic vasculitis/serum sickness-like reaction[8,11], Clostridium difficile-associated diarrhea[10]	8. ROMANO et al., 2019. 9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011) 10.www.micromedexsolutions.com 11. Bulário da ANVISA.
PENICILLINS	AMOXICILLIN + CLAVULANATE	Fatigue[12], Itch[12], Jaundice[12], Loss of appetite[12], Moniliase[9], Diarrhea[9,10,11], Urticaria[9,10,11], Loose stools[9,10], Nausea[9,10,11], Vomiting[9,10,11], Vaginitis[9,10,11], Anaphylaxis[10,11], Angioedema[10,11], Serum sickness[10,11],Hepatotoxicity[10,11], Rashes[9,10,11], Abdominal discomfort[9,11], Stevens-Johnson Syndrome[10,11], Toxic epidermal necrolysis[10,11], Diarrhea due to Clostridium difficile[10,11], Acute, generalized exanthematous pustulose[10,11], Idiosyncratic drug-induced liver injury (DILI)[12]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com 11. Bulário da ANVISA. 12. deLEMOS *et al*., 2016.

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CLASS	MEDICINE	SPECIFICATIONS OF ADVERSE REACTIONS	REFERENCES
PENICILLINS	AMPICILLIN SODIUM	Odynophagy[13], Liver disease[13], Stomatiti[9,11,13], Hemorrhagic lesions[13], Palpable lymph nodes[13], Acute kidney failure[11,13], Purulent conjunctivitis[13], Painful and bleeding erosive lesions[13], Respiratory tract involvement[13], Multiple bleeding lesions Crusts in the oral cavity[13], Erythema multiforme[9,10,11], Exfoliative dermatitis[9], Rash[9,10,11], Urticaria[9,10], Black and hairy tongue[9], Diarrhea[9,10,11], Enterocolitis[9], Glossite[9], Nausea[9,11], Pseudomembranous colitis[9], Pain in the mouth or tongue[9], Vomiting[9,10,11], Agranulocytosis[9,10,11], Anemia[9], Hemolytic anemia[9,10,11], Eosinophilia[9], Leukopenia[9], Purpura thrombocytopenia[9,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com 11. Bulário da ANVISA. 13. ÁVILA *et al.*, 2019.
PENICILLINS	AMPICILLIN+ SULBACTAM	Fever[14], Lymphadenopathy[14], Acute kidney injury[14], DRESS syndrome[14], Morbilliform rash[11,14], Hematological abnormalities[11,14], Multiple organ manifestations including the kidney[14] , Pain at the injection site (I.M. and I.V.)[9,10,11], Rash[9,10,11], Diarrhea[9,10,11], Thrombophlebitis[9,11], Allergic reaction (may include serum sickness)[9], Urticaria[9], Bronchospasm[9], Hypotension[9], Colitis due to Clostridium difficile[10], Diarrhea due to Clostridium difficile[10], Hepatotoxicity[10], Neutropenia[11], Leukopenia[11], Headache[11], Vomiting[11], Rash[11], Pruritus[11], Fatigue[11], Indisposition[11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 14. TEODORO *et al.*, 2013.
MACROLIDES	AZITHROMYCIN	Diarrhea[9,11,15], Itching[9,10,11,15], Anemia[11,15], QT interval prolongation[10,11,15], Heart diseases and changes[9,10,11,15], Gastrointestinal diseases[9,10,11,15], Skin and subcutaneous tissue diseases[9,10,11,15], Hepatobiliary diseases[10,11,15], Hematological reactions[9,10,11,15], Abdominal pain[9,10], Cramps[9], Vomiting[10,11], Vaginitis[9], Nausea[9,10], Torsades de pointes[10,11], Generalized exanthematous pustulose[10], Stevens-Johnson Syndrome[10], Toxic epidermal necrolysis[10], Congenital hypertrophic pyloric stenosis[9], Liver necrosis[9], Drug reaction with eosinophilia and systemic symptoms[9,11], Eaton-Lambert syndrome[10], Myasthenic crisis[10], Corneal erosion[10]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 15. MELO *et al.*, 2021.
CEPHALOSPORINS	CEPHALEXIN	Eosinophilia[9,11,16], Moderate spongiose[16], Full tense bubbles[16], Crusts and hypochromic macules[16], Blister formation in the stratum corneum[16], Inflammatory infiltrate with eosinophils in the dermis[16], Angioedema[9,10,11], Rash[9,11], Stevens-Johnson syndrome[9,10,11], Toxic epidermal necrolysis[9], Abdominal pain[9,11], Increased ALT[9,11], Increased AST[9,11], Jaundice[9], Cholestatic[9], Arthralgia[9], Dizziness[9], Headache[9,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 16. LONCHIATI *et al.*, 2021.
CEPHALOSPORINS	CEPHALOTHIN SODIUM	Fever[9,11,17], Myalgia[11,17], Arthralgia[7,11], Macular rash[9,11,17], Macular rash[9,11,17], Arthralgia of small joints[9,11,17], Urticaria[9], diarreia[11], Nausea[11], Vomitings[11], Decreased creatinine clearance[11], Serum sickness[11,17]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 17. SEPÚLVEDA-BARBOSA *et al*., 2022.

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CLASS	MEDICINE	SPECIFICATIONS OF ADVERSE REACTIONS	REFERENCES
CEPHALOSPORINS	CEFAZOLIN	Allergy[18], Nephropathy[9,10,11,18], Anaphylaxis[10,11,18], Infection by C. difficile[9,10,11,18], Severe skin reactions[18], Aincrease of ALT[9,11], Increased AST[9,11], Stevens-Johnson syndrome[9,10,11], increased BUN[9], Increased serum creatinine[9], Kidney failure[9] Stevens-Johnson syndrome[9], diarreia[9,11], Nausea[9,11], Vomitings[9,11], Anaphylaxis[9,10,11], Itching[9,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA.. 18. MACY, E.MS, MD, CONTRERAS, R. MS, 2015
CEPHALOSPORINS	CEFOTAXIME SODIUM	Urticaria[11,19], Angioedema[19], Anaphylaxis[19], Skin rash[11,19], Mioclonias[19], Confusion[11,19], Seizures[11,19], Nausea[9,10,11,19], Vomiting[9,10,11,19], Diarrhea[9,10,11,19], Abdominal pain[11,19] Agranulocytosis[9,19], Leukopenia[11,19], Thrombocytopenia[19], Erythema multiforme[9,19], Stevens-Johnson Syndrome[10,11,19] Toxic epidermal necrolysis[9,10,11,19], Increased liver enzymes and jaundice[11,19]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 19. HINCAPIÉ MORALES *et al.*, 2021.
CEFALOSPORINAS	CEFTRIAXONE	Headache[20], Dizziness[20], Oliguria[11,20], Pruritus[20], Exanthema[11,20], Urticaria[20], Edema[20], Tremors[20], Eosinophilia[9,10,11,20], Leukopenia[20], Anaphylactic reactions[11,20], Granulocitopenia[11,20], Hemolytic anemia[20], Thrombocytopenia[9,10,11,20], Allergic dermatitis[20], Erythema multiforme[10,20], Changes in liver enzymes[9,11,20], Calcium sediment in the gallbladder[11,20], Elevated serum creatinine[9,20], BUN increased[9], Newborn kernicterus[10]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 20. ZANONI, R. D. *et al.*, 2023.
QUINOLONES	CIPROFLOXACIN	Fever[9,21], Skin rash[21], Edema[11,21], Eosinophilia[21], Skin lesions with change in color[21], Cardiorespiratory arrest[10], Myocardial infarction[10], Prolonged QT interval[10], Syncope[10], Torsades de pointes[10], Aincrease of ALT[9,11], Increased AST[9,11] Guillain-Barré syndrome[10], Nausea[9,11], Vomiting[9,11], Diarrhea[9,10,11], Hypoglycemia[10]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 21. MENESES *et al.*, 2022.
LINCOSAMIDES	CLINDAMYCIN	Anaphylaxis[11,22], Sweet syndrome[22], maculopapular rash[11,22], Hypersensitivity reactions[9,10,11,22], Acute febrile neutrophilic dermatosis[22], AGEP (acute generalized exanthematous pustulose)[11,22], DRESS reactions (drug reaction with eosinophilia and systemic symptoms)[22], SDRIFE (drug-related symmetric intertriginous and flexural rash) reactions[22], Hypotension[9]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 22. DILLY, M., GENG, B., 2021.
ANPHENICOSIS	CHLORAMPHENICOL	Skin rash[11,23], Anemia[9,10,11,23], Neutropenia[11,23], Nausea[9,11,23], Vomiting[23,9,11],Diarrhea[9,11,23], Hematological side effects[9,10,11,23], Gray syndrome in newborns[10], Aplastic anemia[9], Gray syndrome[9], Hepatotoxicity[10], Anaphylaxis[9,10,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 23. ELIAKIM-RAZ *et al.*, 2015

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CLASS	MEDICINE	SPECIFICATIONS OF ADVERSE REACTIONS	REFERENCES
CEPHALOSPORINS	CEFEPIME HYDROCHLORIDE	Diarrhea[9,10,11,24], Pruritus[9,11,24], Abdominal discomfort[11,24], Rashes[9,10,11,24], Changes in liver enzymes[9,10,11,24], Aincrease of ALT[9,10,11], Increased AST[9,10,11], Hipofosfatemia[9,10], Stevens-Johnson Syndrome[9,10,11], Nausea[9,11], Vomiting[9,11], Diarrhea[9,11], Direct Coombs test positive without hemolysis[9,10]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 24. LEITE *et al.*, 2020.
TETRACYCLINES	DOXYCYCLINE HYDROCHLORIDE	Esophagitis[9,10,11,25], Abdominal pain[9,11,25], Nausea[9,10,11,25], Vomiting[9,11,25], Diarrhea[9,10,11,25] Intracranial hypertension[9], Angioneurotic edema[9], Exfoliative dermatitis[9], Photosensitivity[9,10], rash[9,10], Skin hyperpigmentation[9,10], Urticaria[9,10], increased BUN[9], Stevens-Johnson syndrome[9,10,11], Diarrhea due to Clostridium difficile[10]	29.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 30.www.micromedexsolutions.com. 31. Bulário da ANVISA. 25. ELJAALY *et al.*, 2023.
AMINOGLYCOSIDES	GENTAMICIN	Blush[26], Nausea[11,26], Vomiting[11,26], Diarrhea[11,26], Hypotension[26], Tachycardia[26], Acute kidney injury (AKI)[9,10,11,26], Red man syndrome[26], Transient increase in liver enzymes such as transaminases[11,26], Hypersensitivity reactions such as eosinophilia and rash[11,26], Gait instability[9], Nephrotoxicity[9,10,11], Ototoxicidade[9,10,11], Respiratory tract paralysis[10], Neuromuscular blockade[10], Dizziness[11] , Vertigo[11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 26. HAYWARD *et al.*,2017.
QUINOLONES	LEVOFLOXACIN	Eosinophilia[27], Phototoxicidade[27], Hyperpigmentation[27], Rash[9,10,11,27], Systemic symptoms syndrome[27], Stevens-Johnson Syndrome[10,27], Fixed drug eruption[27], Leucocytoclastic vasculitis[27], Nausea[9,10,11], Vomiting[9,10,11], Diarrhea[9,10,11], Prolonged QT interval[10], Guillain-Barré syndrome[10], Increased intracranial pressure[10], Hypoglycemia[10], Anaphylaxis[9,10,11], Myasthenia gravis[10], Acute renal failure[10,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 27. PATIL *et al.*,2020.
CARBAPENEMS	MEROPENEM	Nausea[9,10,28], Vomiting[9,11,28], Intense itching[9,10,11,28], Erythematous rash[9,10,11,28], Edema around the skin folds of the face and all extremities[28], Increased leukocyte count[11,28], Stevens-Johnson Syndrome[28], Type IV cell-mediated delayed hypersensitivity reactions[28], Anaphylaxis[9,10,11], Hipofosfatemia[9,10], Cholestatic jaundice syndrome[10], Pulmonary hypersensitivity[10], Abdominal pain[9,11], Agranulocytosis[9,10,11], Fever[9,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 28. SAMEED *et al.*, 2019.
NITROIMIDAZOLES	METRONIDAZOLE	Anaphylaxis[11,22], Rashes[9,11,22], Angioedema[22], Stevens-Johnson Syndrome[9,10,11,22], Toxic epidermal necrolysis[10,22], Allergic contact dermatitis[22], Acute generalized exanthematous pustulose (AGEP)[22], Hepatotoxicity[9,10,11], Ototoxicidade[9,10,11], Dizziness[9] Jarisch Herxheimer reaction[10] Nausea[9,10,11], Vomiting[9,10,11], Diarrhea[9,10,11] Thrombophlebitis[10], Cystitis[9], Darkened urine[9]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 22. DILLY, M., GENG, B., 2021.
NITROFURANS	NITROFURANTOIN	Fever[11,29], Cough[9,29], Dyspnea[29], Nausea[9,10,11,29], Vomiting[9,10,11,29], Diarrhea[11,29], Pruritus[11,29], Chills[9,29], Urticaria[29], Liver injury[29], Acute hepatitis[29], Abdominal pain[29], Rashes [9,10,11,29], Hemolytic anemia[10,29], Sensory neuropathy[29], Granulomatous reaction[11,29], Cholestasis or Autoimmune Hepatitis[9,29], Hipofosfatemia[9,10], Rashes[9,10,11], Cholestatic jaundice syndrome[10], Colitis due to C. difficile[9]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 29. ARI *et al.*, 2023.
PENICILLINS	OXACILLIN SODIUM	Fever[9,11,30], Eosinophilia[9,11,30], Atypical lymphocytes[9,10,11,30], Pruritic rash[11,30], Confluent red plaques[30], Leukopenia with eosinophilia[9,11,30], Nausea[9,10,11], Vomiting[9,10,11], Diarrhea[9,10,11], Increased AST[9,10], Acute interstitial nephritis[9], Serum sickness[9], Hepatotoxicity[10]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 30. SHARPE *et al.*, 2019.
PENICILLINS	BENZATHINE PENICILLIN	Headache[31], Myalgia[31], Sweating[31], Hypotension[31], Rash[31], Anaphylaxis[10,11,31], Acute fever spikes[10,31], Hypersensitivity reaction[9,10,11,31], Thrombophlebitis[9,11], Jarisch Herxheimer reaction[10], Direct Coombs test positive[9,10], Acute kidney failure[10,11], Diarrhea by Clostridium difficile[10], Nausea[9,10,11], Vomiting[9,10,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 31. PENHA *et al.*, 2020.

to be continued...

... continuation Table 3

CLASS	MEDICINE	SPECIFICATIONS OF ADVERSE REACTIONS	REFERENCES
PENICILLINS	POTASSIUM PENICILLIN	Urticaria[11,32], Angioedema[32], Maculopapular rash[11,32], Hyperkalemia[10], Tubulointersticial nephritis[10], Fever[11] Nausea[9,10,11], Vomiting[9,10,11], Diarrhea[9,10], Eosinophilia[9,10,11], Pain at the injection site[9], Hemolytic anemia with large intravenous doses[10]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 32.BELTRÁN-SIERRA *et al.*, 2016
PENICILLINS	PIPERACILLIN + TAZOBACTAM	Discomfort[9,10,11,33], Nausea[9,10,11,33], Vomiting[9,10,11,33] Leukocytosis[9,10,11,33], Tachycardia[10,11,33], Progressive fever[9,10,11,33], Extravascular hemolysis[11,33], Immune hemolytic anemia[11,33], Anaphylaxis[9,10,11], Increased transaminases[9], Rashes[9,10,11], Pain at the injection site[9], Stevens-Johnson syndrome[10], Agranulocytosis[9,10,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 33. MARIK, PE., PAREKH, P., 2013.
CATIONIC POLYPEPTIDES	POLYMYXIN B	Diffuse cutaneous hyperpigmentation[11,34], Brownish-brown, non-pruritic patches[9,11,34], Nephrotoxicity due to acute tubular necrosis[9,10,11,34], Neurotoxicity (irritability, drowsiness, ataxia, perioral paresthesia, numbness of extremities and blurred vision)[9], Neuromuscular blockade[9] Diarrhea by Clostridium difficile[10], Respiratory arrest[9,10]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 30.www.micromedexsolutions.com. 31. Bulário da ANVISA. 34. MELO *et al.*, 2022.
RIFAMYCINS	RIFAMPICIN	Fever[9,10,11,35], Chills[9,11,35], Asthenia[25,31], Headache[9,11,35], Myalgia[35], Kidney damage[9,10,11,35], Shock[9,10,11,35], Nausea[9,10,11,35], Diarrhea[24,29,30,31], Vomiting[9,10,11,35], Fever[9,10,11,35], Renal colic[9,11,35], Hepatotoxicity[9,10,11], Thrombocytopenia[11,35], Hemolytic anemia[9,11,35], Pseudoflu Syndrome[9,11,35], Pemphigoid reaction, Agranulocytosis[9,10], Acute renal failure[9,10], Interstical nephritis[9], Increased liver function[9], Edema[9], Myalgia[9], Leukopenia[9], BUN increased[9]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 35. PIRES *et al.*, 2021
SULFONAMIDES	SULFADIAZINE	Porphyria[11,36], Urticaria[9,10,11,36], Rashes[9,10,11,36], Hemolytic anemia[9,10,11,36], Thrombocytopenia[9,10,11,36], Acute pancreatitis[11,36], Strong allergic reaction[9,10,11,36], Urinary tract disorders[11,36], Hematopoietic disorders[9,10,11,36], Stevens Johnson Syndrome [10,11,36], Hypersensitivity reactions[11,36], Fulminant hepatic necrosis[9,10,11,36], Toxic epidermal necrolysis (Lyell syndrome)[11,36], Nausea[9,10,11], Vomiting[9,10], Crystalluria[9], Itching[9,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 36. MATHEWS *et al.*, 2015.
AMINOGLYCOSIDES	AMIKACIN SULFATE	Nephrotoxicity[9,10,11,37], Neuromuscular blockade[10,11,37], Reduced glomerular filtration[11,37], Non-oliguric acute renal failure (ARF)[11,37], Ototoxicity damage to the cochlea and/or vestibular[9,10,11,37], Respiratory arrest[9,10], Fever[11], Hypotension[9]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 37. RIBEIRO, 2017.
SULFONAMIDES	SULFAMETHOXAZOLE + TRIMETHOPRIM	Porphyria[11,36], Urticaria[9,10,11,36], Rashes[9,10,11,36], Hemolytic anemia[9,10,11,36], Thrombocytopenia[9,10,11,36], Acute pancreatitis[11,36], Strong allergic reaction[9,10,11], Urinary tract disorders[11,36], Hematopoietic disorders[9,10,11,36], Stevens Johnson Syndrome[10,11,36], Hypersensitivity reactions[11,36], Fulminant hepatic necrosis[9,10,11,36], Toxic epidermal necrolysis (Lyell syndrome)[11,36], Nausea[9,10,11], Vomiting[9,10], Crystalluria[9], Itching[9,11]	9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 36. MATHEWS *et al.*, 2015
GLYCOPEPTIDES	VANCOMYCIN	RErythematous rash[11,38], Nausea[28,29,30,31], Vomiting[9,10,11,38], Hypotension[10,11,38], Tachycardia[9,10,11,38], Weakness[11,38], Angioedema[28,30,31], Dyspnea[9,10,11,38], Anuria[11,38], Uremia[11,38], Red man syndrome[9,10,11,38], Muscle spasms[11,38], Pain in the chest and/or back[9,11,38], Significant worsening of kidney function[9,10,11,38], Pruritic on the face, neck and back[9,10,11,38], Hypokalemia[9], Hypotension[9], Ototoxicidade[9,10,11], Nephrotoxicity[9,10,11], Anaphylaxis[9,10,11]	_-_-9.Lexicomp. Wolters Kluwer Clinical Drug Information (2011). 10.www.micromedexsolutions.com. 11. Bulário da ANVISA. 38. DAMASCENO *et al.*, 2023.

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DISCUSSION

The incidence of the most common ADRs reported in the reviewed literature included diarrhea, nausea, vomiting, pruritus, and urticaria, with higher prevalence in antimicrobials from the classes of penicillins, macrolides, cephalosporins, anphenicols, tetracyclines, aminoglycosides, quinolones, carbapenems, nitrofurans, rifamycins, sulfonamides, and glycopeptides. The heterogeneity of this incidence may be associated with different characteristics of the studied populations or the profile of the antimicrobials.

As some publications did not provide the exact number of patients studied[8, 19, 20, 22, 26, 29, 36, 37] data standardization was not achieved, which complicated result interpretation regarding the exact patient count in each study. Thus, the incidence of adverse reactions was estimated based on the number of ADRs reported for each antimicrobial.

According to the systematic review by ROMANO *et al.*[8] on the use of amoxicillin, immediate hypersensitivity responses to this drug occur within 1 to 6 hours after exposure and include symptoms such as urticaria, angioedema, and bronchospasm. On the other hand, non-immediate reactions, such as maculopapular rash, pustulosis, and vasculitis, may appear more than 72 hours after contact. It is worth noting that anaphylaxis is a rare event with amoxicillin use but should not be disregarded.

Adverse reactions in patients are considered high-risk and low-risk. For high-risk, with immediate manifestations, anaphylactic reactions, hypotension, laryngeal edema, bronchospasm, and immediate skin manifestations have been described, as well as non-immediate reactions such as Stevens-Johnson syndrome, epidermal necrolysis, and specific organ manifestations. Low-risk reactions include localized skin reactions and isolated gastrointestinal symptoms[8].

In line with other authors, prevalent reactions manifest on the skin, presenting as rash or urticaria, while the remaining reactions were predominantly gastrointestinal, particularly diarrhea. Penicillins are prescribed for infections such as pharyngitis, sinusitis, cutaneous anthrax, ear infections, and gastrointestinal tract infections caused by Helicobacter pylori, among others. Penicillin toxicity can lead to confusion and hallucinations, which may occur with the intravenous administration of massive doses of penicillins[9,10,39].

ADRs such as fatigue, loss of appetite, itching, and jaundice are symptoms of cholestatic hepatitis resulting from the use of amoxicillin with clavulanate. Cases of liver injury and mild to moderate hepatic alterations have also been observed in patients using this antibiotic[12].

The use of amoxicillin with clavulanate has shown that drug-induced liver injury (DILI) can affect patients, leading to elevated liver enzymes or even severe liver failure, potentially resulting in death. This condition is more common among older men, with a noted higher vulnerability among Caucasians. Clinical manifestations of DILI can occur in three forms: hepatocellular, cholestatic, or mixed. The hepatocellular pattern is characterized by blood alanine transferase (ALT) levels that are twice the normal limit. The cholestatic type occurs when blood alkaline phosphatase levels exceed twice the upper normal limit or when the ALT-to-alkaline phosphatase ratio is equal to or greater than two. The mixed type is characterized by an ALT ratio greater than two but less than five. Anaphylactic shock and renal damage, including renal failure, are rare adverse reactions associated with the use of this antibiotic[12,40].

Stevens-Johnson syndrome is a rare mucocutaneous hypersensitivity reaction that begins within 4 to 28 days after ingestion of the causative drug or its withdrawal, in the case of drugs with a long half-life. In this context, AVILA *et al.*[13] reported a case of a male patient who developed the syndrome, with lesions appearing 2 days after completing treatment with ampicillin sodium, affecting 27% of the body surface. Manifestations may include hepatopathy, stomatitis, hemorrhagic lesions,

palpable lymph nodes, acute renal failure, purulent conjunctivitis, painful and bleeding erosive lesions, and involvement of the respiratory tract. These findings align with similar research results, as this syndrome can also occur with the use of other antibiotics such as amoxicillin, azithromycin, cefazolin, cefotaxime sodium, doxycycline hydrochloride, levofloxacin, meropenem, piperacillin with tazobactam, sulfadiazine, amikacin sulfate, and sulfamethoxazole with trimethoprim[8, 15, 19, 25, 34].

Although cases of Stevens-Johnson syndrome are considered rare, monitoring affected patients is crucial, given that the symptoms of this reaction can be fatal. This syndrome affects individuals across various age groups and ethnic backgrounds, with higher prevalence among men. The incidence of this condition tends to increase with age, especially in groups considered more vulnerable, such as those with associated comorbidities, genetic predisposition, or immunosuppression[9, 10, 22, 27, 36].

The DRESS syndrome was highlighted in 3 studies, associating it with the use of ampicillin and sulbactam combined, ciprofloxacin, and clindamycin. This syndrome can cause skin rash, lymphadenopathy, hematological abnormalities, and multi-organ manifestations, including kidney enlargement in patients with acute renal injury. Despite common mucocutaneous involvement, this syndrome differs from Stevens-Johnson syndrome in the clinical presentation of lesions and disease course. Adverse reactions to the use of ampicillin + sulbactam include severe renal manifestations and laboratory abnormalities such as anemia, moderate leukocytosis with eosinophilia without atypical lymphocytes, elevated creatinine, and urinalysis showing hematuria. Additionally, injection site pain is very common in these patients, affecting about 10% of the population[14, 21, 22] .

The study by Melo *et al.*[15] analyzed reports of adverse drug reactions in patients with COVID-19, finding a higher frequency of QT interval prolongation in 33.6% of cases. This was the most reported ADR associated with azithromycin, with a mean QT prolongation of 513 ms. QT interval prolongation increases the risk of developing cardiac arrhythmias, ventricular fibrillation, torsades de pointes, and sudden cardiac death. Other ADRs highlighted in this context include diarrhea, skin, and liver manifestations related to azithromycin use[34].

Cephalexin was highlighted as one of the antibiotics that can induce bullous pemphigoid, the most common autoimmune dermatosis that can be triggered by drugs, along with ciprofloxacin and levofloxacin. In many cases, pharmacological etiology may induce ADRs, posing risks to patients using these medications[16].

Cefazolin is widely used as pre-surgical prophylaxis to reduce the likelihood of surgical site infections. Its use can lead to allergy, anaphylaxis, nephropathy, and Clostridium difficile infections. Cephalosporins have the potential to induce mental status effects, manifesting through myoclonus, confusion, seizures, and other nervous system disorders, especially in individuals with impaired renal function. Notably, renal dysfunction plays a significant role in this context, as cephalosporins exhibit high cerebrospinal fluid penetration capability. Both cefazolin and ceftriaxone have the potential to induce acute renal failure, particularly in individuals with predisposing factors such as diabetes and hypertension[18, 19, 41].

Adverse reactions associated with beta-lactams, particularly piperacillin/tazobactam, may include fever, tachycardia, malaise, and neurological effects such as abnormal behavior, confusion, delirium, and disorientation. Additionally, the risk of acute renal failure is heightened when these drugs are used in conjunction with other nephrotoxic agents, and further disorders may arise. Among these manifestations are hematologic and lymphatic system disorders, hepatobiliary system conditions, as well as issues affecting skin and subcutaneous tissues, gastrointestinal disturbances, and complications in musculoskeletal and connective tissue conditions[33,42,43,44,45].

Gentamicin, amikacin sulfate, and vancomycin are considered pharmacovigilance markers at the hospital under study and have the potential to impair hearing and kidney function in susceptible individuals, particularly in neonates or elderly patients, given that these drugs are

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primarily excreted through the kidneys. When no alternatives to gentamicin and amikacin sulfate are available, it is essential to rigorously monitor patients' renal function and serum levels during gentamicin use[46, 47].

Regarding gentamicin and amikacin sulfate, aminoglycoside-associated nephrotoxicity leads to non-oliguric acute renal failure as well as a decrease in glomerular filtration rate. These effects typically appear after approximately seven days of treatment. Neurotoxicity (vertigo, ataxia), gait instability, ototoxicity (auditory and vestibular), nephrotoxicity, and decreased creatinine clearance are characteristic ADRs of these antibiotics. Gentamicin is more commonly associated with vestibular damage and increased excretion of sodium, calcium, and magnesium, whereas amikacin is linked to cochlear damage. For neurological reactions, which may be associated with neuromuscular blockade, patients with conditions impacting the neuromuscular junction and those under medications that prolong neuromuscular blockade, particularly calcium channel blockers, should exercise caution when using aminoglycosides[26, 37].

Vancomycin has a significant incidence of ADRs, including nephrotoxicity, ototoxicity, thrombocytopenia, acute tubular necrosis, neutropenia, phlebitis, and a histamine release-related condition known as red man syndrome, which can be triggered by rapid infusion of this drug. In certain situations, this condition may be accompanied by potentially dangerous signs and symptoms, such as nausea, vomiting, hypotension, tachycardia, weakness, angioedema, muscle spasms, shortness of breath, and chest and/or back pain. Additionally, this reaction may be associated with worsening renal function, manifested by anuria and uremia, potentially leading the patient to hemodialysis[38,48].

Whenever possible, the use of vancomycin should be avoided in elderly patients, especially those over 80, due to its minimal metabolism; only a small portion of the administered dose (approximately 5%) undergoes metabolic processes, with excretion primarily via the kidneys 75% to 90% through glomerular filtration. Vancomycin dosing intervals should be adjusted in patients with renal insufficiency, and it is important to note that the optimal infusion rate for this drug is ≤ 5 mg/mL at a rate of < 15 mg/min and < 1 g per hour[47].

The results of this study align with previous findings in the literature on the use of antimicrobials and ADRs, where cutaneous adverse reactions are the most frequent manifestations associated with antibiotic use. Maculopapular eruptions, urticaria, and pruritus were the most commonly reported types by authors in the cases analyzed. Other commonly described symptoms included diarrhea, nausea, and vomiting, along with hematological reactions such as anemia, leukopenia, and other cytopenias. Renal failure and hepatotoxicity were also identified as significant adverse reactions to be monitored[9, 10].

In this regard, it is essential to remain vigilant for possible reactions to ensure patient safety during treatment. The reaction-to-drug table serves as a valuable reference source for healthcare professionals and others interested in studying ADRs to antimicrobials, allowing for a more comprehensive and specific understanding of the challenges associated with the use of these medications.

The active ingredients of these drugs are potential triggers for ADRs, but excipients although considered inert should also be taken into account, as they can contribute to adverse reactions associated with medications. Currently, it is understood that excipients are compounds that can directly influence the safety profile of medications, potentially playing a significant role in the occurrence of various adverse effects. Therefore, a comprehensive evaluation of substances used in drug formulations is essential for a complete understanding of potential adverse reactions, considering not only active ingredients but also excipients[49].

Pharmacovigilance can significantly contribute by preventing and detecting ADRs associated with antimicrobial use, ensuring the prevention of bacterial resistance and supporting the assessment, identification, and mitigation of medication-related issues, such as drug interactions and appropriate antibiotic use. Moreover, the presence of diverse types of reactions including hepatic manifestations, severe syndromes, hypersensitivity reactions, and other conditions highlights the importance of

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pharmacovigilance for monitoring and reporting these events. The diversity of authors and sources in the articles underscores the global scope of safety challenges, emphasizing the importance of a collaborative approach to understanding and reducing these risks[16, 18].

The pharmacist plays a fundamental role in active participation in pharmacovigilance to ensure safe and effective healthcare. Their involvement contributes not only to the identification of medication-related issues but also to the implementation of preventive and educational measures that positively impact the quality of care provided to patients[50].

CONCLUSION

Healthcare-associated infections represent a serious public health issue, affecting many patients. This reality is particularly concerning, not only because of the direct impact on patient health but also due to the costs associated with treating these infections. Excessive antimicrobial use has contributed to the rise of bacterial resistance and the occurrence of adverse reactions to these medications.

Through a literature review, this study highlighted the multiple adverse reactions associated with antimicrobials, forming an educational tool. The most prevalent reactions in the studies were gastrointestinal symptoms such as diarrhea, nausea, and vomiting, hypersensitivity reactions, and skin-related reactions, including rashes, pruritus, and urticaria.

Rare syndromes that severely affect patients should be monitored to improve treatment management. Creating consultation tools, like the one developed in this study, aligns with the goal of building preventive strategies against these conditions and can significantly enhance medication safety.

Author CRediT statement

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