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ORIGINAL ARTICLE

# Adverse drug reactions in a high-complexity pediatric hospital: a six-year experience

## Reacciones adversas a medicamentos en un hospital pediátrico de alta complejidad: 6 años de experiencia

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**What do we know about the subject matter of this study?**

Adverse drug reactions in pediatrics represent an important cause of morbidity and mortality, particularly among hospitalized pediatric patients. The high proportion of off-label prescriptions, especially in patients with risk factors such as concomitant diseases or polypharmacy, increases the risk of adverse drug reactions.

**What does this study contribute to what is already known?**

This study describes the epidemiology of adverse drug reactions in a high-complexity pediatric hospital over six years, identifying the most frequent drugs, their severity, and the units affected. The findings support the implementation of strategies for the detection and management of adverse drug reactions, with the aim of improving care in the pediatric population.

## Abstract

Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality in the pediatric population, particularly due to the frequent use of medications in off-label indications. **Objective:** To characterize the epidemiology of ADRs in a high-complexity pediatric hospital. **Patients and Method:** A descriptive, observational, and retrospective cohort study was conducted at the *Hospital Dr. Exequiel González Cortés* (HEGC) between 2018 and 2023. HEGC is a high-complexity, teaching, and self-managed pediatric hospital, and is one of the seven hospitals of the Southern Metropolitan Health Service. It has 168 beds and provides coverage to an estimated pediatric population of 254,000 children. Hospitalized and outpatient patients with reported ADRs were included. Demographic variables, involved drugs, causality (Naranjo algorithm), severity (WHO criteria), and affected physiological systems were analyzed. **Results:** A total of 787 ADR reports were recorded in 718 patients, with a median age of 8 years. The highest incidence occurred in the Critical Care Unit. The main therapeutic groups involved were antibacterials (18.6%), antineoplastics (18.4%), and psycholeptics (9.7%). The most affected systems were the immune system (35.7%), nervous

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system (15%), and digestive system (7%). Regarding severity, 63.5% of ADRs were moderate, 26.7% were severe, with no fatal events reported. **Conclusion:** This study shows that ADRs are frequent in pediatric patients, with a higher incidence in the critical care setting. It highlights the need for improving ADR reporting and developing pharmacovigilance strategies to optimize the safety of drug prescribing in pediatrics.

## Introduction

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "any harmful, unintended, and undesirable effect that occurs after the administration of a drug, at doses normally used in humans, to prevent, diagnose, or treat a disease, or to modify a biological function"[1]. Recently, ADRs have been observed to be a significant cause of morbidity and mortality in the population, which has prompted the development of pharmacovigilance (PV)[2].

PV is a set of activities related to the detection, evaluation, understanding, and prevention of adverse effects associated with the use of drugs, according to the provisions of Supreme Decree 3 of 2010[3,4]. In our country, the proper reporting of ADRs is required by General Technical Standard No. 140 on the National Pharmacovigilance System for Pharmaceutical Products for Human Use[5].

Futhermore, the pediatric population is at greater risk for developing ADRs, mainly due to the off-label use of medications. Off-label use is understood to be the prescription of drugs for indications, doses, or routes of administration other than those approved by the regulatory authority, but it should be noted that, in many cases, scientific evidence support such use. To understand the magnitude of the issue, it has been estimated that approximately 75% of medication used in pediatric units are prescribed off-label[6].

Regarding the incidence of ADRs in pediatrics, the results are mixed. A meta-analysis conducted by Impicciatore et al. determined an incidence of ADRs in hospitalized pediatric patients of 9.5%, while Aagaard et al. found an average prevalence of 24.0% (range: 1-72%)[7,8]. Similarly, Smyth et al. found an ADR incidence rate between 0.6% and 16.8% in children exposed to a drug during hospitalization[9]. In the outpatient setting, the incidence of ADRs is lower. Clavenna and Bonati conducted a systematic review of prospective studies in pediatric outpatients between 2001 and 2007, determining 1% incidence of ADRs[10]. It has been shown that, of all hospital admissions in pediatric patients, between 1.8% and 5% are due to ADRs, with a mortality rate of around 1.1%[11,12].

As mentioned above, the pediatric population is at greater risk of ADRs. Therefore, given the variability of information and the scarcity of data at the national level, it is important to understand the epidemiology of ADRs in a high-complexity pediatric center. These data are essential to develop strategies for the detection, management, and prevention of ADRs in order to improve safety and medical care in pediatric patients.

The *Hospital Exequiel Gonzalez Cortes* (HEGC) is a highly complex pediatric center and a reference in various specialties, serving an estimated population of 254,000 children. Since 2018, it has had a multidisciplinary pharmacovigilance team with nine health professionals, seven physicians, and two pharmaceutical chemists. The objective of this study is to characterize the epidemiology of ADRs in a high-complexity pediatric hospital.

## Patients and Method

### Study design

Descriptive observational study with a retrospective cohort design.

### Population

Patients hospitalized in the medical-surgical wards (MSW) and in the critical care unit (CCU) were included. Patients seen in the specialty outpatient clinic (SOPC) and in the emergency department were also considered. All patients were required to have had at least one reported ADR between January 1, 2018, and December 31, 2023. ADR reports lacking complete information at the time of analysis were excluded from the study.

### Variables and data sources

Patients were categorized according to their age group: neonates (0 to 28 days), infants (1 to 24 months), preschoolers (2 years to 5 years 11 months 29 days), schoolchildren (6 years to 11 years 11 months 29 days), and adolescents (12 years to 19 years 11 months 29 days). The demographic variables of sex and age were evaluated. The number of ADR reports and suspected drugs was recorded, identified by their International Nonproprietary Name (INN), and categorized up to the second level of the Anatomical, Therapeutic, Chemical (ATC) classifica-

tion. ADR reports were categorized according to the suspected drug, causality (Naranjo ADR Probability Scale), seriousness (WHO criteria), severity (WHO criteria), and affected physiological system (System Organ Class, SOC).

According to the methodology proposed by Naranjo et al., the probability that an ADR is causally related to a drug can be classified into the following categories, based on the score obtained on a 10-item scale:

- Definite (score ≥ 9): There is a reasonable temporal relationship between drug administration and ADR, the response pattern is recognized, improvement is observed upon discontinuation of the drug, and recurrence of the ADR upon re-administration.
- Probable (score between 5 and 8): Same definition as above; however, there is no evidence of recurrence after re-exposure.
- Possible (score between 2 and 4): The temporal relationship is consistent, the clinical pattern may be related to the drug, but it may also be explained by the patient's underlying clinical condition.
- Doubtful (score < 2): The ADR is more likely attributable to factors other than the administered drug[13].

To ensure consistency in the application of the algorithm, inter-rater validation was performed among members of the pharmacovigilance team.

**Information sources**

The information came from the coded records of the HEGC Pharmacovigilance team, which were systematically updated. It was supplemented with data from the patient's physical or electronic medical record. For this study, the confidentiality of each patient was maintained through a code assigned to each case.

The ADRs from hospitalized patients correspond to the MSW, CCU, and pediatric oncology inpatient units, which are included within the Med-Surg patients.

The incidence of ADRs was calculated to compare the ADR reporting density between the MSW and CCU. The metric used was the incidence per 1,000 bed-days, defined as:

$$\text{ADRs incidence per 1000 bed-days} = \frac{\text{No. of ADRs in the Clinical Unit} \times 1000}{\text{Bed occupancy}}$$

**Statistical analysis**

For our study, we used an encrypted Excel database to subsequently perform a descriptive statistical analysis according to the type and scale of the variables. For quantitative variables, we used means, standard deviation, or median and interquartile range; for qualitative variables, we used absolute and relative frequencies.

**Ethical considerations**

This study was approved by the ethics committee of the HEGC and the South Metropolitan Health Service.

## Results

During the study period, from January 1, 2018, to December 31, 2023, a total of 787 ADR reports were recorded for 718 patients. The median age was 8 years (0.08-20). The number of annual reports was 173 in 2018, 146 in 2019, 179 in 2020, 119 in 2021, 115 in 2022 and 55 in 2023. Table 1 shows the demographic characteristics.

Of the 787 ADR reports, 71 occurred in the emergency department, 324 in the SOPC, and 392 in hospitalized patients. Among the latter, 25.3% were recorded in Oncology, 28.8% in the CCU, and 44.3% in the MSW. Figure 1 shows that the incidence of ADR was systematically higher in the CCU, almost double that of the MSW in 2019.

Globally, the most involved therapeutic groups were systemic antibacterials (18.6%), followed by antineoplastic agents (18.4%) and psycholeptics (9.7%) (Figure 2). In hospitalized patients, systemic antibacterials were the most common (30.1%), followed by antineoplastic agents (18.9%) and psycholeptics (8.2%). In the SOPC, antineoplastic agents (21.9%), immunosuppressants (15.7%), and psycholeptics (10.5%) predominated. In the Emergency Unit, reports focused on systemic antibacterials (19.7%), followed by anti-inflammatory and antirheumatic drugs (8.5%) and psycholeptics (7.0%). Figure 3 details the specific drugs by unit.

In hospitalized patients, the distribution varied according to the unit. In the MSW, systemic antibacterials predominated (52.9%), followed by psycholeptics (9.0%) and antiepileptics (5.8%). In Oncology, antineoplastic drugs predominated (65.6%), followed by antibacterial drugs (13.5%), and systemic antifungal drugs (4.1%). In the CCU, reports focused on psycholeptics (15.1%), systemic antibacterials (14.4%), and anesthetics (11.1%) (Figure 4).

Figure 5 shows the physiological systems affected during the study period. The immune system was the most compromised (35.7%), followed by the nervous system (15%) and the digestive system (7%). Within the immune system, hypersensitivity reactions predominated (93.6%), mainly maculopapular/urticarial rash (a term used in the medical records to group both

cutaneous presentations) with 65.5%, anaphylaxis (24.6%), and DRESS syndrome (2.5%). In the nervous system, the most frequent were withdrawal syndrome (21.5%) and drowsiness (11.6%). In the digestive system, nausea/vomiting (30.2%) and diarrhea (20.8%) stood out.

According to the Naranjo ADR Probability Scale, 54.9% of ADRs were classified as probable, 38.1% as possible, and 7.0% as definite. When analyzing the defined ADRs, most corresponded to hypersensitivity reactions such as maculopapular/urticarial rash (31.5%) and anaphylaxis (14.8%). Dystonia, nephrotoxicity, diarrhea, encephalopathy, and irritability were observed in smaller proportions (3.7% each).

In terms of severity, 63.5% of ADR reports were moderate, 9.8% were mild, 26.7% were severe, and no fatal ADRs were recorded. Of the total number of severe ADR reports, most corresponded to hospitalized patients (16.3%), followed by outpatient clinics (6.9%) and emergency rooms (3.6%). Among hospital units, the proportions were similar, although Oncology had a slightly higher frequency of serious ADR reports (41.4%) compared to CCU (31.9%) and the MSW (28.3%). Regarding severity, 26.7% of reports were classified as serious according to WHO criteria, mostly in hospitalized patients (61.0%). Table 2 summarizes the drugs involved in 4 or more reports of serious ADRs, presented in descending order according to the number of reports. The most frequent were asparaginase and pegaspargase (anaphylaxis), followed by midazolam (hypotension).

**Table 1. Demographic characteristics of the patients**

| | |
|---|---|
| Sex | Male: 54,9%<br>Female: 45,1% |
| Median age (range) | 8 years (0,08-20) |
| Age group (n) | School-age children: 33,9% (267)<br>Adolescents: 33,4% (263)<br>Preschool children: 19,3% (152)<br>Infants:13,2% (104)<br>Newborn: 0,1% (1) |

## Discussion

This descriptive cohort study shows that the three most frequently used therapeutic groups throughout the hospital were systemic antimicrobials, followed by antineoplastic agents and psycholeptics. This distribution could be influenced by the prescribing patterns observed in the pediatric population. Several studies have reported that antibiotics, psychotropic drugs, and corticosteroids are among the most commonly used drugs in pediatrics, both in outpatient and inpatient settings[14,15]. According to an international systematic review, which analyzed data from more than 35 million pediatric patients in 11 OECD member countries, systemic antibacterials were identified as the most commonly prescribed drugs, followed by drugs for obstructive respiratory diseases and systemic corticosteroids[16].

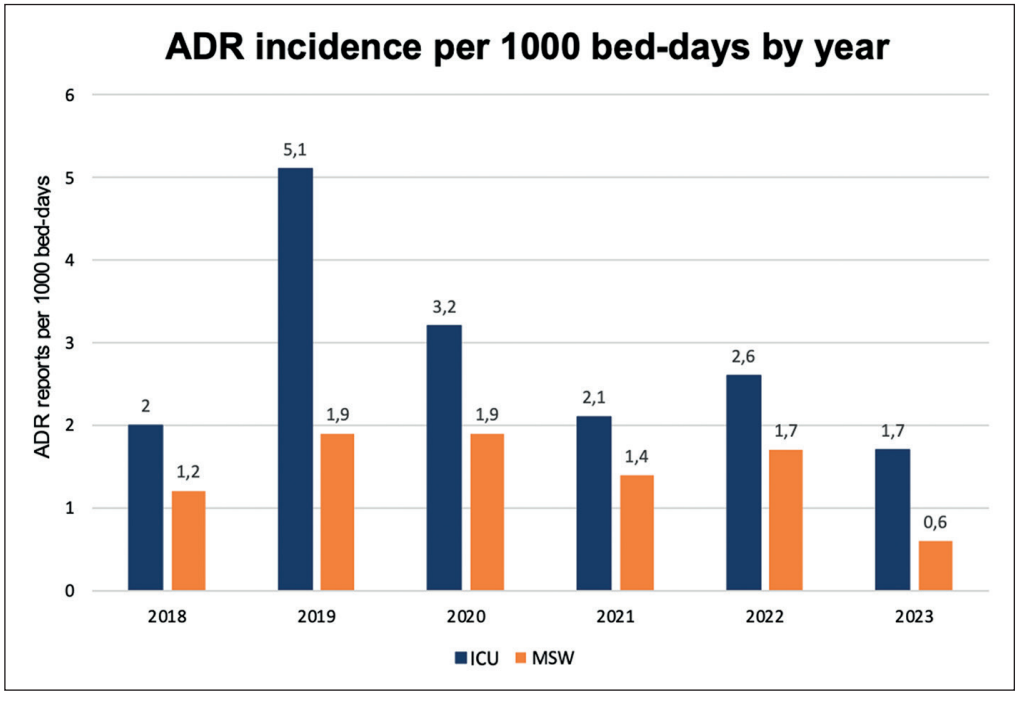


**Figure 1.** Annual incidence of ADRs per 1,000 bed-days in the medical–surgical wards (MSW) and the critical care unit (CCU), 2018–2023. ADR: adverse drug reaction; MSW: medical-surgical wards; ICU: Intensive care unit.

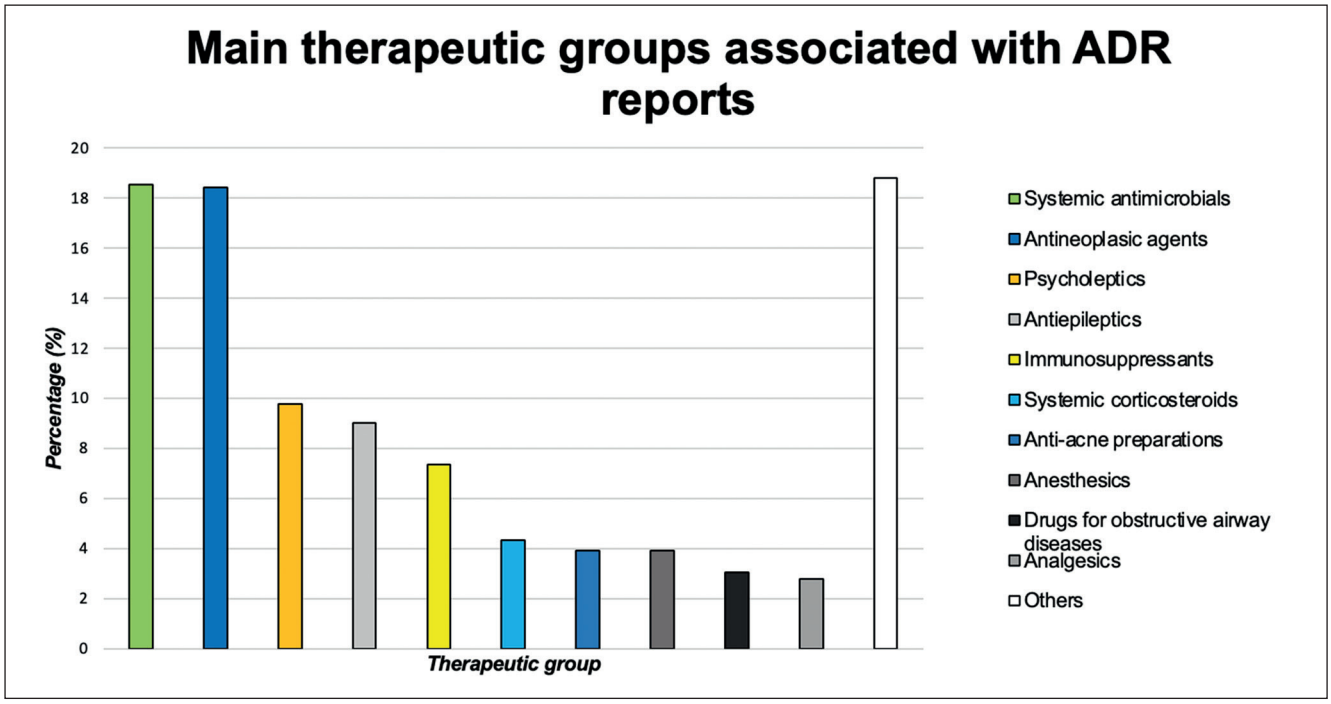


**Figure 2.** Therapeutic groups most frequently associated with ADR reports at Hospital Exequiel González Cortés. ADR: adverse drug reaction.

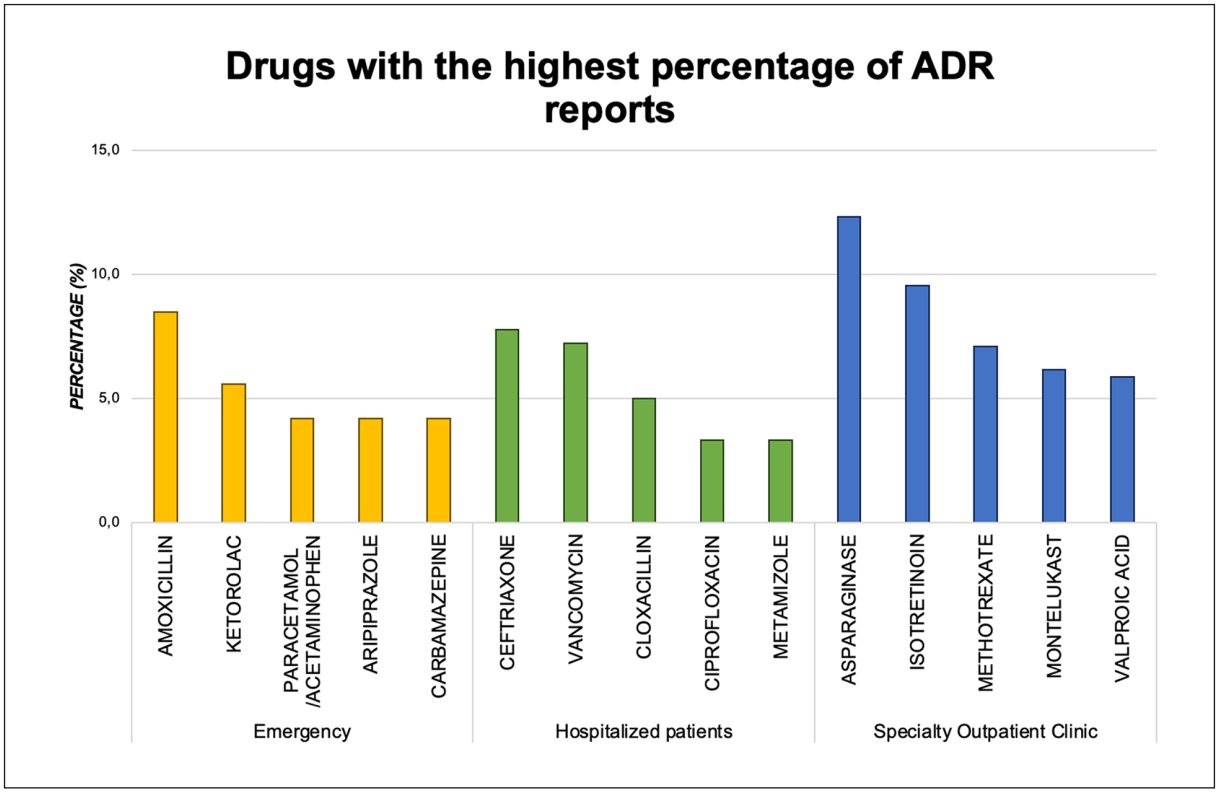


**Figure 3.** Drugs involved in the highest number of ADR reports according to hospital units at Hospital Exequiel González Cortés. ADR: adverse drug reactions.

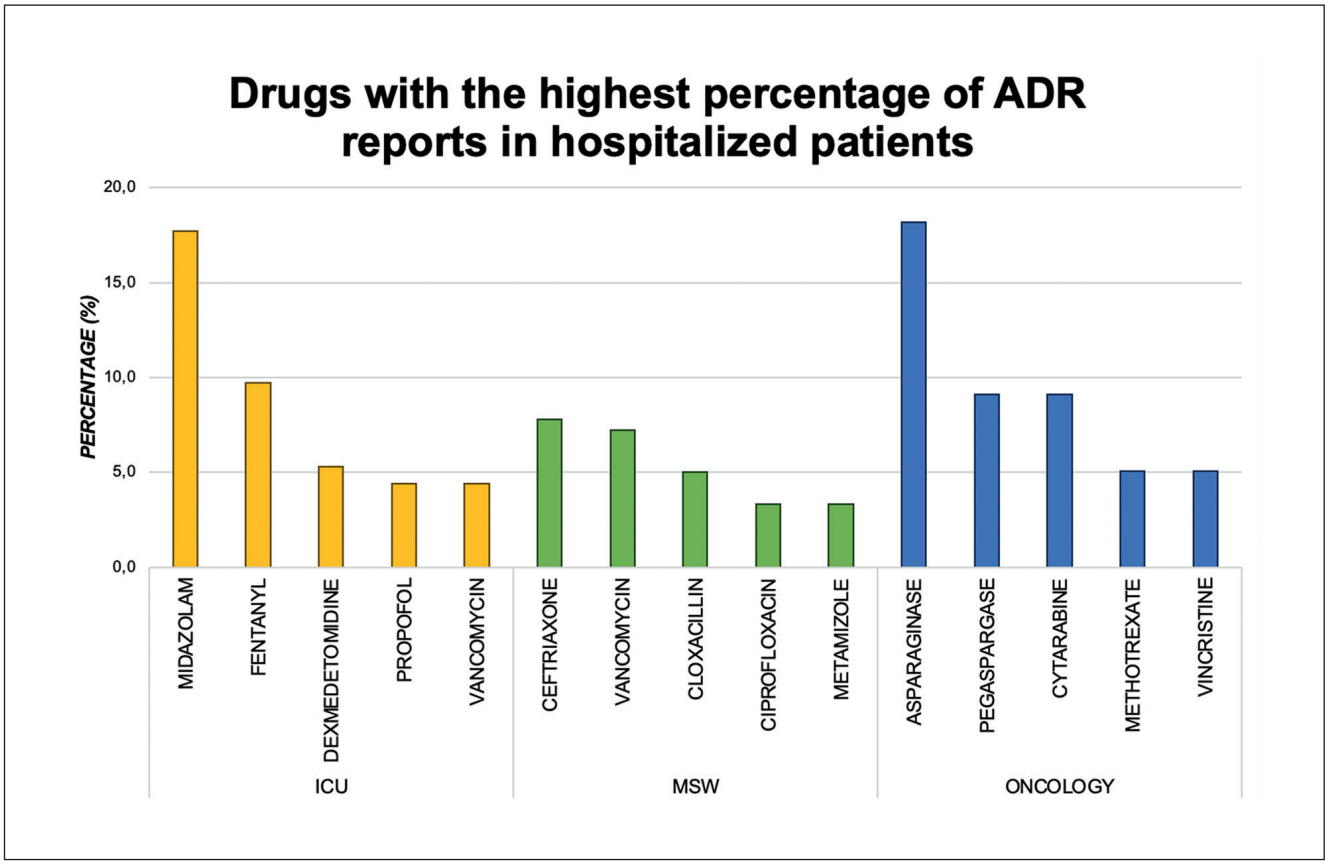


**Figure 4.** Drugs involved in the highest number of ADR reports according to inpatient hospital units. ADR: adverse drug reactions.

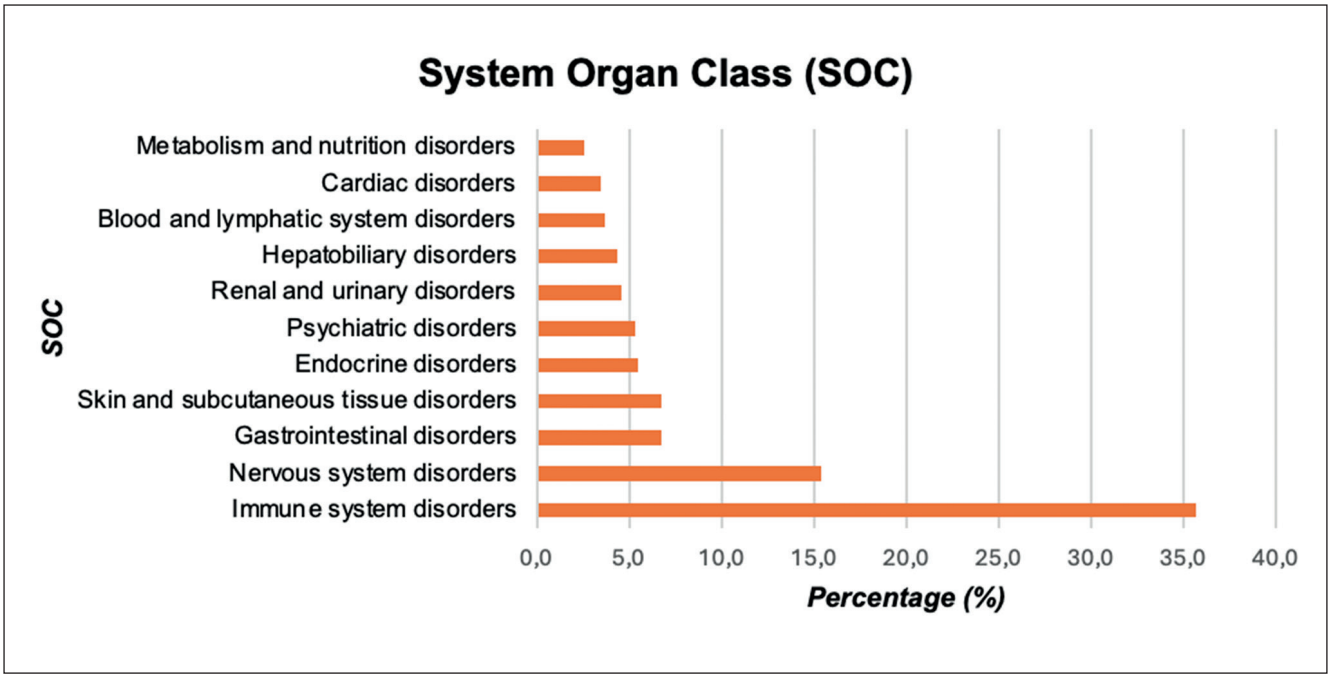


**Figure 5.** System organ classes affected in ADR reports. ADR: adverse drug reactions.

**Table 2. Drugs involved in four or more reports of serious ADRs and their most frequent drug-ADR association**

| Drug | N° of serious ADR reports | % of total serious ADRs | Most frequent drug-ADR association |
|---|---|---|---|
| Asparaginase | 36 | 17.1% | Anaphylaxis (27/36) |
| Pegaspargase | 13 | 6.2% | Anaphylaxis (10/13) |
| Midazolam | 10 | 4.8% | Hypotension (4/6) |
| Vincristine | 6 | 2.9% | Peripheral neuropathy (3/6) |
| Amoxicillin | 5 | 2.4% | Cutaneous hypersensitivity (5/5) |
| Ibuprofen | 5 | 2.4 % | Nephrotoxicity (2/5) |
| Carbamazepine | 5 | 2.4% | Cutaneous hypersensitivity (2/5) |
| Dexmedetomidine | 5 | 2.4% | Bradycardia (4/5) |
| Methotrexate | 4 | 1.9% | Seizures (3/4) |
| Inmunoglobulin | 4 | 1.9% | Hypotension (2/4) |

ADR: Adverse drug reaction.

Although the latter two ranked seventh and ninth in this study, respectively, their high prescription rate globally highlights the need for strict clinical monitoring during their use.

Furthermore, data collected from pediatric hospitals in the United States show that antibacterials, antineoplastics, and psychotropics are also among the main groups associated with adverse drug events[17]. Although adverse drug events include both ADRs and medication errors and other incidents related to drug use, these findings reinforce that there is a close relationship between the frequency of use of certain therapeutic groups and the likelihood of clinically relevant events occurring in hospitalized patients.

The study by De las Salas et al., which described the epidemiology of ADRs in children under 6 years of age admitted to the national hospital in Barranquilla, found that 70% of ADRs were caused by antimicrobials, with ampicillin, amikacin, and clarithromycin being the main agents involved. In this study, the systemic antibiotics responsible for the highest number of ADR reports included vancomycin, ceftriaxone, and cloxacillin. The differences could be associated with differences in sensitivity and, therefore, the frequency with which they are prescribed, to antimicrobials between the two countries[18].

Our study shows that the incidence of ADR in the CCU is higher than in the MSW during the study period. In the CCU, the mean ADR incidence reports per 1,000 bed days was 2.8 ± 7.8, while in the MSW, the mean ADR incidence reports per 1,000 bed days was 1.5 ± 1.3 (p-value of 0.048). This result may be related to the fact that critically ill patients are exposed to a greater number of medications (7.5 drugs per patient on average) versus patients hospitalized at the MSW (3.6 drugs per patient on average). Exposure to a greater number of medications is a well-known risk factor for drug-drug interaction, which can precipitate the onset of ADRs[19-21].

The high frequency of reports of ADRs affecting the immune system is consistent with what is described in the pediatric literature. These reactions, mainly cutaneous, are more easily recognizable and are reported more frequently[22]. Their high incidence is related to high exposure to antibacterials, interaction with viral infections that favor rashes[23], and the use of drugs with a high risk of immunological reactions, such as asparaginase in pediatric oncology[24], where in the pediatric oncology unit, the sensitization of nursing staff in pharmacovigilance favors greater detection and reporting of events associated with asparaginase and pegaspargase. These findings reflect both exposure and susceptibility factors in the pediatric population and are consistent with international guidelines that highlight the prevalence of immune reactions and the need for diagnostic confirmation through allergy testing[25].

Regarding the assessment of causality using the Naranjo algorithm, 93% of ADR reports were classified as probable and possible. This result is mainly because most patients were not re-exposed to the drug, which is necessary for causality to be classified as definite. In the study by De Salas et al., 98.1% of ADRs were categorized as probable, while in the study by Vallejo et al., 68% of ADRs were classified as possible[18,26]. It is difficult to compare the causality of ADRs in pharmacovigilance studies due to the different definitions and algorithms used. Furthermore, in some circumstances, when studies are retrospective, not all the data are available to perform a proper assessment of causality.

Regarding the temporal evolution of reports, a con-

siderable decrease was observed in 2023. This decline is interpreted as a reporting phenomenon and not necessarily as a lower occurrence of ADRs. During the 2023 winter campaign, the hospital faced an overload of care associated with an increase in pediatric consultations and hospitalizations, with prioritization of immediate clinical care and redistribution of staff. In this context, the capacity for recording and reporting ADRs was likely reduced, suggesting underreporting linked to healthcare conditions rather than a true reduction in the incidence of ADRs.

The main weaknesses of our study are that, as the study was conducted in a single center, it reflects the reality of a group of pediatric patients whose pathologies may differ from those at other centers. In addition, the retrospective design of the study generates some biases, especially in the analysis of the causality of ADRs. Furthermore, given that ADR reports were predominantly investigated through spontaneous notification, underreporting plays an important role. The study by Sánchez et al. established that up to 93.5% of ADRs in a hospital were underreported[27].

The strengths of the study include the availability of a database with multiple parameters and the participation of a multidisciplinary team, which allowed for a detailed analysis of ADR reports. In addition, the epidemiology of ADRs in all units comprising the HEGC is described.

Based on the findings, this study proposes specific institutional improvements to strengthen pharmacovigilance in the hospital: These include the implementation of continuing education for healthcare professionals in the detection and reporting of ADRs, the incorporation of trigger drugs as an improvement strategy, understood as drugs that, when prescribed to treat a possible ADR, serve as indirect indicators of its occurrence and prompt reporting[28]; and the optimization of the reporting and documentation system through more streamlined processes integrated into the electronic medical record. Together, these actions could improve timely detection, reduce underreporting, and increase the safety of pediatric drug use.

## Conclusions

Given the limited evidence available on pharmacovigilance in pediatrics, this study provides relevant data on the epidemiology of ADRs in different pediatric care services, including hospitalization, emergency, and outpatient areas. The findings show that immunological reactions are the most prevalent category and that their proper identification requires strengthening clinical pharmacovigilance. This information may assist healthcare teams to develop strategies aimed at improving detection, reporting, and allergy testing, in order to optimize safety in pediatric prescribing and promote more rational use of medications.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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