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Potential drug interactions in the pediatric inpatient unit: a retrospective study

Potenciais interações entre medicamentos na unidade de internação pediátrica: estudo retrospectivo

Potenciales interacciones entre medicamentos en la unidad de hospitalización pediátrica: estudio retrospectivo

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ABSTRACT

Objective: to identify potential drug interactions and their respective severity levels in prescriptions from a pediatric unit. **Method:** quantitative investigation conducted in a public hospital between August and September 2023. Prescriptions containing two or more drugs were included, and those unavailable or with incomplete data were excluded. Prevalence ratios and 95% confidence intervals were calculated. Drug interactions were analyzed using the Drugdex-Micromedex® and WeMEDS® applications. **Results:** a total of 628 prescriptions were analyzed, comprising 3,030 prescribed drugs, with a mean of 4.8 drugs per prescription. Potential drug interactions were identified in 21.3% (*n*=134) of the children, with major severity predominating, accounting for 65.8% (*n*=129) of occurrences. These interactions were significantly more prevalent among children aged three to five years, with 47% (PR=1.47; 95%CI=1.26 – 1.71), and six to 12 years, with 74% (PR=1.74; 95%CI=1.48 – 2.06). **Conclusion:** a considerable number of potentially interactive combinations were identified, and the predominance of these interactions was classified as major, which could pose a risk to the patient's life.

Descriptors: Pediatric Nursing; Drug Interactions; Drug-Related Side Effects and Adverse Reactions.

RESUMO

Objetivo: identificar interações medicamentosas potenciais e os respectivos graus de severidade contidos nas prescrições de uma unidade pediátrica. **Método:** investigação quantitativa, desenvolvida em um hospital público, entre agosto e setembro de 2023. Foram incluídas prescrições contendo dois ou mais medicamentos e excluídas aquelas indisponíveis ou com baixa completude de dados. Realizados cálculos da razão de prevalência, intervalo de confiança de 95%. As interações medicamentosas foram analisadas nos aplicativos *Drugdex-Micromedex®* e *WeMEDS®*. **Resultados:** foram analisadas 628 prescrições, com 3.030 medicamentos prescritos, em média 4,8 medicamentos por prescrição. 21,3% (n=134) crianças apresentaram interação medicamentosa potencial, sendo a gravidade maior predominante, com 65,8% (n=129) ocorrências. Essas interações foram significativamente prevalentes entre as crianças de três a cinco anos, com 47% (RP=1,47; IC95%=1,26-1,71), e de seis a 12 anos com 74% (RP=1,74; IC95%=1,48-2,06). **Conclusão:** evidenciou-se um número considerável de combinações potencialmente interativas e, a predominância dessas interações foi classificada como maior, podendo resultar em risco à vida do paciente.

Descritores: Enfermagem Pediátrica; Interações Medicamentosas; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos.

RESUMEN

Objetivo: identificar interacciones medicamentosas potenciales y sus respectivos grados de severidad presentes en las prescripciones de una unidad pediátrica. **Método**: investigación cuantitativa desarrollada en un hospital público entre agosto y septiembre de 2023. Se incluyeron prescripciones que contenían dos o más medicamentos y se excluyeron aquellas no disponibles o con baja completitud de datos. Se realizaron cálculos de la razón de prevalencia y del intervalo de confianza del 95%. Las interacciones medicamentosas fueron analizadas mediante las aplicaciones Drugdex-Micromedex® y WeMEDS®. **Resultados**: se analizaron 628 prescripciones, con un total de 3.030 medicamentos prescritos, con un promedio de 4,8 medicamentos por prescripción. El 21,3% (n=134) de los niños presentó interacciones medicamentosas potenciales, siendo la gravedad mayor la predominante, con un 65,8% (n=129) de los casos. Estas interacciones fueron significativamente más prevalentes entre los niños de tres a cinco años, con un 47% (RP=1,47; IC95%=1,26-1,71), y entre los de seis a 12 años, con un 74% (RP=1,74; IC95%=1,48-2,06). **Conclusión**: se observó un número considerable de combinaciones potencialmente interactivas, y la predominancia de estas interacciones se clasificó como de gravedad mayor, ya que pueden representar un riesgo para la vida del paciente.

Descriptores: Enfermería Pediátrica; Interacciones Farmacológicas; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos.

INTRODUCTION

The safety of hospitalized patients has been a constant topic of discussion. In this context, the multidisciplinary team plays a crucial role in promoting and maintaining safe care, which is influenced by factors that may increase the likelihood of adverse events and hinder the clinical recovery of assisted patients[1].

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In 2004, the World Health Organization established the World Alliance for Patient Safety with the aim of disseminating knowledge about patient safety in healthcare institutions of member countries and contributing to the definition of research priorities in the field. In 2017, the third global patient safety challenge was launched under the theme "Medication Without Harm," aiming to reduce by half the number of severe and preventable medication-related harms over five years through the development of safer and more efficient health systems at every stage of medication use[2–4].

The medication system involves actions carried out by healthcare providers to promote health through the use of medications, encompassing processes from prescription to administration to the patient. In this context, physicians are responsible for prescribing medications, pharmacists for pharmacotherapeutic follow-up, and nursing professionals for preparing and administering them. Proper execution of these stages is essential to prevent medication therapy errors[5–6].

Medication use is a widely employed form of health intervention that contributes to the symptomatic, curative, or palliative treatment of many diseases. However, adverse reactions are common, particularly in children, who are in continuous development and exhibit different physiological responses at each stage. Factors such as age, height, weight, comorbidities, hereditary aspects, and concurrent medications must be considered. Pharmacokinetic particularities during childhood influence the efficacy and safety of the administered drug, making this group more vulnerable to developing adverse drug reactions (ADR), such as Drug Interactions (DIs)[7].

The heterogeneity of medication use, regarding type, quantity, dosage, population characteristics, and medical prescriptions, constitutes a strategic factor for studying PDIs, especially in the pediatric population. This phenomenon occurs when the effect of a drug is altered by the presence of food, another drug, or idiosyncratic factors, and it is of clinical interest due to its association with pharmacotherapeutic success or failure[8].

Potential Drug Interactions, which are the focus of this study, refer to events identified in drug prescriptions and reported in the literature but without clinical manifestation investigation. Understanding the occurrence of PDIs is important because of their relationship to clinical manifestations, indicating that potential risk is directly associated with the true occurrence of a DI. Drug interactions are linked to longer hospital stays, higher hospitalization costs, and increased mortality[9].

Drug interactions may be harmful or beneficial, depending on factors such as the drug involved, patient characteristics, and the circumstances of the combination. They may be intentional when beneficial or clinically irrelevant when no special measures are needed. However, they can also cause temporary or permanent harm and increase mortality[9]. Even desired interactions require observation and monitoring of possible clinical effects, as they may reduce therapeutic efficacy, increase adverse effects, and raise treatment costs, thereby posing a risk to the patient's life[10].

Identifying and analyzing PDIs in hospitalized pediatric populations is essential for therapeutic safety, as medication-related problems are the most common adverse events in this setting, accounting for 3% to 5% of preventable ADRs. Moreover, children are particularly susceptible to medication-related adverse events.

A study conducted in pediatric hospitals in Mexico showed that approximately 61% of prescriptions contained at least one PDI, most of which were classified as of major or contraindicated severity, indicating significant risks to patient health and reinforcing the need for systematic pharmacological surveillance in this context. Another study, conducted in the state of Rio de Janeiro, corroborated this finding by examining children hospitalized in a pediatric intensive care unit, identifying a high prevalence of PDIs of major severity, which directly increased hospital length of stay. These findings highlight the need for systematic monitoring of pediatric prescriptions, even outside the intensive care setting, given that the concomitant use of multiple drugs is also common in general inpatient units[11].

Such interactions in the therapeutic context constitute preventable adverse events that may occur following medication therapy or medical procedures and may or may not be related to the signs or symptoms of the underlying disease[12,13]. Although early detection of PDIs favors the prevention, reduction, or elimination of outcomes associated with pharmacotherapeutic failure and adverse reactions, studies on medication use in children remain limited, despite their importance for improving medical prescriptions, planning pharmaceutical services, and identifying medication-related problems[14]. Therefore, the development of this study is justified to expand healthcare providers' understanding of this field.

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In the medication therapy system, prescribing is crucial to patient safety and requires rigorous attention to minimize errors. Nurses are responsible for scheduling the administration of prescribed drugs and share accountability for the care provided, preventing risk situations for pediatric patient safety, in accordance with the recommendations of the Ministry of Health's Protocol for Safety in Medication Prescription, Use, and Administration[15]. Therefore, a detailed understanding of PDIs not only supports the prevention of adverse events but also contributes to optimizing clinical practice and developing more effective safety protocols. Based on the above, the research question was formulated: "What are the potential drug interactions and their respective severity levels contained in prescriptions from a pediatric inpatient unit?"

This study aimed to identify potential drug interactions and their respective severity levels contained in prescriptions from a pediatric inpatient unit.

METHOD

Descriptive study, quantitative in nature and with a cross-sectional design, using the retrospective documentary technique, conducted in a public hospital located in the interior of the state of Rio de Janeiro, Brazil, with a description guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[16].

The study setting was a public hospital of municipal authority, intended for care under the Brazilian National Health System (*Sistema Único de Saúde,* SUS). The institution was selected due to its high patient turnover, serving not only the population of the municipality where it is located but also neighboring regions, acting as a gateway for referring units, as it is a large facility and has a maternity ward that serves as a regional reference. Furthermore, it has a nursery, pediatric emergency department, and pediatric inpatient unit. It has two wards with three beds each and two beds for isolation. However, it does not have a pediatric or neonatal intensive care unit; in such cases, it relies on the central regulation system for referring children with greater severity. It serves children from zero to twelve years of age with a wide variety of clinical diagnoses, allowing for the study of potential drug interactions.

The collection of medication prescriptions specifically dispensed in the pediatric inpatient unit was carried out using medical records from the medical records department of the institution. Data collection took place from August to September 2023 and covered the period from May 2022 to May 2023. The period was chosen randomly to describe the reality of PDIs that occurred in the last year prior to the research protocol design.

Prescriptions containing two or more drugs, regardless of the route of administration, were included if available in the medical records of children and scheduled by nurses after approval by the attending physician for each hospitalized child. Records with prescriptions unavailable for access at the time of data collection and/or those with incomplete data were excluded to minimize potential information bias. The sampling was intentional and non-probabilistic, without sample size calculation, aiming to collect the maximum number of medical records available within the defined time frame and criteria.

The data were organized in a spreadsheet structured in Microsoft Excel® by two data entry clerks, both undergraduate students under the supervision of the advisor and co-advisor. The spreadsheet was divided into two parts: the first containing variables related to the characterization of the sociodemographic profile of the children, including sex, age, race, weight at admission, and medical diagnosis; and the second containing variables related to the pharmacological therapy, namely: drug name, number of drugs prescribed, dosage, route, and administration schedule. The spreadsheet built by the researchers was previously tested on three medical records that were not included in the sample to verify whether the study objectives would be met.

To obtain information on the PDI and the degree of severity among the drugs identified in the prescriptions, a systematic bibliographic search was carried out to identify, analyze, and synthesize information about the interactions and their respective severity levels. The search used the "generic/commercial name" of each drug described in a highly reliable information resource, Drugdex-Micromedex®, a clinical reference platform providing drug-related information available only in English, as it is an American application.

In Drugdex-Micromedex®, the variables of pharmacological interest were consulted, considering dose, routes of administration, side effects, precautions, and the classification of the severity of the PDI, categorized as contraindicated when concomitant use is not indicated; major when concomitant use poses a life threat to the patient and/or requires medical intervention to minimize or prevent serious health damage; moderate when the interaction may result in exacerbation of the patient's condition and/or requires a change in therapy; and minor

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when the interaction is expected to have limited clinical effect[15]. This database can be accessed free of charge on the Drugdex-Micromedex® platform through the link: https://www.micromedexsolutions.com/home/dispatch or downloaded from mobile app stores.

As it is an American database, some drug formulations specifically used in Brazil and not marketed in other countries, including the United States of America (USA), such as dipyrone, bromopride, salbutamol sulfate, zinc oxide, tenoxicam, dienogest, Zirvit, Enterogermina, vitamin K, Sucrafilm, Biozinc, sodium carboxymethylcellulose, Despacilin, and ambroxol hydrochloride, were not found, making it impossible to study PDIs among these drugs and their respective severity levels, as this informational resource was not designed for them[17]. To identify the effects of PDI, clinical management, and probable mechanism of action, a search was conducted on the WeMEDS Portal, developed by Universidade de São Paulo (USP), Unicamp, Universidade Federal do Paraná (UFPR), among others. Among the available resources, detailed information on PDI, as well as toxicological and pharmacological data, stands out[18]. The WeMEDS Portal can also be downloaded from the Play Store for Android devices and the App Store for iOS, or accessed free of charge at: https://play.google.com/store/apps/details?id=com.wemeds.

In addition, the Anatomical Therapeutic Chemical (ATC) Classification System was used to identify the most prescribed drugs. This classification was developed to establish an internationally uniform system for drug classification. It is a tool recommended by the World Health Organization (WHO) for comparing patterns of drug use in different contexts. In this system, drugs are allocated into different groups according to their sites of action and therapeutic and chemical characteristics.

In the data analysis, proportions and measures of central tendency that comprise basic statistics were calculated. Bivariate analyses between sex, age group, and severity level of interaction were performed using prevalence ratio (PR) and respective confidence interval (CI = 95%), analyzed using IBM SPSS program, v.23.0.

For pharmacoepidemiological analysis, all drugs prescribed between the first and third day of hospitalization were considered, as this is the period of greatest therapeutic adjustment, and to minimize the possibility of information bias due to the variable half-life of different prescribed drugs, mainly depending on the patient's pathological condition[17]. Likewise, for the purposes of analysis in this study, PDIs with two or more occurrences were considered.

The study complied with Resolution No. 466 of 2012 of the National Health Council and was approved by the Research Ethics Committee of the proposing institution.

RESULTS

A total of 664 medical records were selected, with 36 excluded due to incomplete data or medications discontinued during hospitalization. A total of 628 prescriptions were analyzed, comprising 3,030 prescribed medications. The mean number of medications per prescription was 4.8, ranging from 2 to 14, with the intravenous route being the most frequently used, accounting for 71.7% of the analyzed documents (*n*=450).

During the study period, the ages of the hospitalized patients ranged from one day of life to 12 years. The highest frequency of hospitalization occurred among those aged 29 days to 2 (+3.2) years (*n*=329; 52.4%), with a predominance of boys (*n*=336; 53.5%). Diseases of the respiratory system were the most frequent medical diagnoses (*n*=360; 57.1%), followed by diseases of the skin and subcutaneous tissue (*n*=69; 10.9%). Regarding the hospitalization period, most children remained hospitalized for approximately three days (*n*=374; 59.3%). As for clinical outcomes, most children were discharged from the hospital (*n*=570; 90.4%).

Among the prescribed medications, dipyrone and antimicrobials were widely used (*n*=590; 93.9%). Among the most prescribed antimicrobials, third-generation cephalosporins (ceftriaxone) were the most prevalent (*n*=199; 31.7%), followed by penicillin (amoxicillin with potassium clavulanate) in 21.3% of cases (*n*=134). According to the ATC classification, the most prescribed classes were anti-infectives for systemic use (*n*=25; 18.8%) and nervous system drugs (dipyrone), followed by drugs for the alimentary tract and metabolism (*n*=21; 15.8%), with notable use of combination therapy with other medications. Table 1 presents the PDIs with two or more occurrences.

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Table 1: Most frequent potential drug interactions in the pediatric inpatient unit (*n*=134). Niterói, RJ, Brazil, 2024.

Drugs	*n*	*f* (%)	Severity of PDI
Ampicillin × Gentamicin	54	27.5	Minor
Methylprednisolone × Clarithromycin	19	9.7	Major
Clarithromycin × Hydrocortisone	9	4.6	Major
Ondansetron × Tramadol	7	3.6	Major
Ondansetron × Azithromycin	5	2.6	Major
Metronidazole × Ondansetron	5	2.6	Major
Hydrocortisone × Ibuprofen	5	2.6	Major
Fentanyl × Midazolam	4	2.0	Major
Clarithromycin × Ondansetron	3	1.5	Major
Furosemide × Gentamicin	3	1.5	Major
Other interactions	82	41.8	All types
Total	**196**	**100**	

Legend: PDI – Potential Drug Interactions

Regarding the occurrence of PDIs per patient, most did not present any PDI (*n*=496; 79%). However, 21.3% of the children exhibited some type of PDI (n=134), totaling 196 interactions, with the severity classified as major being the most predominant (*n*=129; 65.8%) of the occurrences. Additionally, 82 children presented other interactions corresponding to drug combinations that appeared only once (41.8%).

Data indicate that the combination of antimicrobials, particularly between ampicillin and gentamicin, was the most prevalent interaction (*n*=54; 27.5%). The combined use of clarithromycin with other drug classes, such as corticosteroids and antiemetics, was also identified (*n*=31; 15.8%).

Table 2 presents the findings related to the associations between the degree of PDI and the variables sex and age of the patients.

Table 2: Association between sex and age and the degree of drug interaction in the pediatric inpatient unit (*n*=328). Niterói, RJ, Brazil, 2024.

	Degree of drug interaction				
	Minor	Moderate		Major	
	n (%)	*n* (%)	PR(95%)	*n* (%)	PR(95%)
Sex					
Female	33(31.1)	3(2.8)	2.72(0.30-24.82)	70(66.0)	1.01(0.83-1.23)
Male	29(32.6)	1(1.1)	1.0	59(66.3)	1.0
Age					
Up to 29 days					
PDI (Yes)	11(78.6)	0(0.0)	-	3(21.3)	**0.30(0.11-0.82)**
PDI (No)	51(28.2)	4(2.2)	-	126(69.6)	1.0
29 days to 2 years					
PDI (Yes)	46(51.7)	1(1.1)	0.13(0.02-1.21)	42(47.2)	**0.56(0.45-0.71)**
PDI (No)	16(15.1)	3(2.8)	1.0	87(82.1)	1.0
3 to 5 years					
PDI (Yes)	2(6.7)	2(6.7)	**15.50(2.89-83.09)**	26(86.7)	**1.47(1.26-1.71)**
PDI (No)	60(36.4)	2(1.2)	1.0	103(62.4)	1.0
6 to 12 years					
PDI (Yes)	3(4.8)	1(1.6)	5.17(0.68-39.14)	58(93.5)	**1.74(1.48-2.06)**
PDI (No)	29(28.2)	3(2.9)	1.0	71(68.9)	1.0

Legend: PR – Prevalence Ratio

No significant associations were identified between sex and interaction severity. However, the prevalence of major interactions was lower among newborns (PR=0.30; 95%CI=0.11–0.82) and children aged 29 days to 2 years (PR=0.56; 95%CI=0.45–0.71). Conversely, major interactions were significantly more prevalent among older children, particularly in the 3- to 5-year age group, with 47% (PR=1.47; 95%CI=1.26–1.71), and in the 6- to 12-year segment, with a 74% higher prevalence (PR=1.74; CI95% = 1.48–2.06) compared to younger children.

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Figure 1 presents the most frequent PDIs identified in the prescriptions from the pediatric inpatient unit, according to the documentation, severity level, interaction effect, probable mechanism in the context of combined drug use, and the respective therapeutic management in potentially interactive conditions.

Drugs	Documen-tation	Severity of PDI	Interaction effect	Probable mechanism	Therapeutic Management
Ampicillin x Gentamicin	Good	Minor	Concomitant use may result in loss of aminoglycoside efficacy.	Chemical inactivation of antimicrobials.	Monitor patients for efficacy and consider alternative drug options.
Methylprednisolone x Clarithromycin	Good	Major	Simultaneous use may result in an increased risk of methylprednisolone adverse reactions.	Inhibition of methylprednisolone metabolism by the CYP3A4 enzyme.	Monitor for adverse reactions caused by the corticosteroid. If necessary, consider dose adjustment or the use of antimicrobials from another class.
Hydrocortisone x Clarithromycin	Fair	Major	Same as for the methylprednisolone × clarithromycin combination.	Same as for the methylprednisolone × clarithromycin combination.	Same as for the methylprednisolone × clarithromycin combination.
Ondansetron x Tramadol	Fair	Major	Concomitant use may result in an increased risk of serotonin syndrome, defined as a potentially fatal drug reaction that tends to cause elevated body temperature, muscle spasms, and anxiety or delirium.	Potentiation of serotonergic effects.	If concomitant use is necessary, monitor the patient, especially at the beginning of treatment, and adjust the dose. Symptoms such as fever, muscle spasms, and anxiety may occur within hours or days after use.
Ondansetron x Azithromycin	Fair	Major	Ventricular tachycardia, ventricular arrhythmias, and ventricular fibrillation resulting from QT interval prolongation.	Additive prolongation of the QT interval.	If concomitant therapy is necessary, ECG monitoring is recommended.
Metronidazole x Ondansetron	Fair	Major	Simultaneous use may result in an increased risk of QT interval prolongation.	Additive prolongation of the QT interval.	Susceptible patients may require ECG monitoring.
Hydrocortisone x Ibuprofen	Fair	Major	Concomitant use may result in an increased risk of gastrointestinal ulcer or bleeding.	Potentiation of drug-induced bleeding.	If concomitant administration is necessary, monitor for signs of bleeding.
Fentanyl x Midazolam	Fair	Major	Concomitant use may result in an increased risk of profound sedation, respiratory depression, hypotension, coma, and death.	Additive CNS depression.	Reserve concomitant prescription of these drugs for patients for whom alternative treatment options are inadequate. Inform and educate patients and/or caregivers about the signs and symptoms of respiratory depression (including sedation).
Clarithromycin x Ondansetron	Fair	Major	Concomitant use may result in increased ondansetron exposure and increased risk of QT interval prolongation.	Inhibition of ondansetron metabolism; additive prolongation of the QT interval.	If simultaneous use is indicated, ECG monitoring is recommended. Consider dose adjustments, when possible, and closely monitor serum drug concentrations.
Furosemide x Gentamicin	Good	Major	Concomitant use may result in increased plasma and tissue concentrations of gentamicin, as well as additive ototoxicity and/or nephrotoxicity.	Additive or synergistic toxicity caused by the combination of two or more medications.	Avoid concomitant administration of the drugs, especially in patients with renal impairment. If not possible, change the antimicrobial, and monitor for signs of ototoxicity and nephrotoxicity.

Legend: QT interval prolongation – corresponds, in the electrocardiographic tracing, to the time of activation and recovery of the ventricular myocardium; CNS – Central Nervous System; ECG – Electrocardiogram.
Figure 1: Most frequent Potential Drug Interactions identified in prescriptions from the pediatric inpatient unit. Niterói, RJ, Brazil, 2024.

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DISCUSSION

A total of 196 interactions were identified in the prescriptions dispensed in the pediatric inpatient unit, with major severity being predominant among older children. Among the prescribed drugs, dipyrone and antimicrobials were the most prevalent, with cephalosporin and penicillin classes being the most common. However, the most prevalent interaction occurred between ampicillin and gentamicin.

Based on the characterization of hospitalized children, it can be seen that the profile of the pediatric inpatient unit studied is similar to that of other studies, with a predominance of males (53.5%)[19,20]. Most children were between 29 days and two years of age, consistent with other studies conducted in pediatric units[21,22].

Regarding medical diagnoses, respiratory system disorders were the most frequent. This result may be explained by the immaturity of the immune system, which makes children more susceptible to hospitalizations and, in some cases, the development of systemic complications, leading to the combined use of medications to resolve the clinical condition, as reported in another study[23].

Numerous drug classes were also prescribed, with anti-infectives for systemic use and drugs acting on the central nervous system (dipyrone) being the most frequently used in the inpatient unit. In this regard, another study found a similar result, reporting that the prevalent use of these medications may be related to the previous finding concerning respiratory diseases as the most common among conditions treated in neonatal intensive care units. Furthermore, researchers have consistently shown that antimicrobials are among the most prescribed drugs in pediatric units[23].

Studies have correlated the widespread prescription of antimicrobial agents with high hospital costs. It is estimated that in 50% of cases, there is inappropriate use of antimicrobials, which may lead to the development of microbial resistance and an increased risk of ADRs[10,24]. This finding reinforces the importance of raising awareness among the multidisciplinary team involved in the rational use of medicines, particularly antimicrobials, as well as the need to identify and appropriately manage PDIs. Therefore, the identification of PDIs should occur during prescription, dispensing, and administration of drugs to minimize the occurrence of those that can cause harm to patients' health[9].

Although few studies have been conducted in Brazil, this study observed a 27.5% prevalence of DI in the combined use of antimicrobials, particularly the association between ampicillin (beta-lactams) and gentamicin (aminoglycosides), which are widely prescribed for the empirical treatment of respiratory infections[24]. The combination of antimicrobials can result in beneficial or desirable DIs, with synergistic effects in mono- and polymicrobial infections, improved treatment adherence, prevention of bacterial resistance, and reduced dosages, with fewer toxic effects. However, attention must be paid to the possibility of chemical antagonism, as evidenced by the concomitant use of beta-lactams and aminoglycosides, which may inactivate the aminoglycoside[24,25].

Another prevalent drug was dipyrone (analgesic/antipyretic), whose indiscriminate use is associated with adverse reactions and side effects, in addition to potential drug interactions[26]. Regarding the combined use of dipyrone and ibuprofen, UpToDate indicates that the simultaneous use of more than one nonsteroidal anti-inflammatory drug (NSAID) should be avoided, classifying this type of drug interaction in category "X", for which the recommendation is to avoid such a combination, since the risks associated with the concomitant use of these agents generally outweigh the benefits and are therefore contraindicated[7].

Another example involves hydrocortisone, whose plasma concentration is reduced when administered concomitantly with dipyrone, making it necessary to increase the corticosteroid dose to achieve the desired effect[7]. Although these PDIs were not identified in this study, it is worth noting that both ibuprofen and hydrocortisone are commonly combined with dipyrone in pediatric clinical practice, with ibuprofen alternated in cases of persistent fever, and hydrocortisone used to improve respiratory conditions, depending on the dose, due to its anti-inflammatory and/or immunosuppressive action. This highlights the need for strict control and monitoring in the use of these medications, as the combination is not recommended in the literature.

The concomitant use of furosemide in prescriptions has been reported in several studies as one of the drugs most associated with severe DI, as identified in this research. Furosemide combined with aminoglycoside antimicrobials increases the risk of nephrotoxicity when used together, in addition to the possibility of causing irreversible damage, such as ototoxicity. Therefore, the prescriber must assess the risk–benefit ratio for each patient when faced with this interaction[23].

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Regarding PDIs, most children did not present interactions. However, the short hospital stay, approximately three days, may have contributed to this finding, differing from other studies where the length of stay was longer, increasing the risk of adverse events[9]. Although this study was conducted in a low-complexity unit, where hospital stays are shorter, the children still presented potentially interactive combinations with major severity. It can be inferred, therefore, that if the length of stay of the children involved in this study were longer, it would likely have contributed to a higher number of potentially interactive combinations.

Concerning the severity level of PDIs, major severity predominated. This result is similar to that of studies that analyzed DI in prescriptions for pediatric patients in burn treatment centers and dermatological units, where PDIs pose a life-threatening risk and/or require medical intervention. Therefore, the analyses demonstrated that this setting is vulnerable to the occurrence of DIs that require careful assessment of the risks and benefits[27].

This reinforces the need for studies that monitor the safety of hospitalized patients, particularly those in conditions involving severe alterations in drug metabolism, such as severe dehydration or pediatric patients[28]. This finding is noteworthy because, according to the literature, the frequency of PDIs is directly related to the hospital sector involved, being more common in intensive care due to the greater number of prescribed drugs[10], unlike the setting of this study (a low-complexity unit), where major DIs are not expected.

Regarding documentation, the high prevalence of PDIs with fair documentation was also found in other studies, reaffirming the need for further research on the PDIs identified, since this documentation indicates that, although there is no consensus in the literature, there are pharmacological considerations that raise suspicion about their existence. This type of analysis is relevant, as it allows assessing how accurate the information on drug interactions is[13,29].

Due to the difficulty in establishing a relationship between the clinical manifestations observed and DI, the scientific literature has relied on the study of PDIs that are already well known and documented, highlighting the risks to which patients are exposed[19]. Nevertheless, despite information on PDIs and drug characteristics being widely available in applications and reputable sources consulted for this study, inadequate practices regarding pharmacotherapy are still observed in hospital settings, resulting in the occurrence of PDIs with higher severity levels, as observed in this study. This underscores the need for ongoing training and guidance on updated knowledge of DI for nursing and multidisciplinary teams.

It should be emphasized that both ADRs and therapeutic inefficacy may result from DI. Among the patients studied, the predominant age groups were three to five years and six to twelve years, with a higher prevalence of DI. One study indicates that the high rate of interactions highlights the need to expand healthcare providers' knowledge about the risks and benefits of interactions and clinical management of such events, as well as access to information systems such as Micromedex®[10]. Therefore, when healthcare providers involved in pharmacotherapy processes have greater knowledge, the care delivered to patients becomes safer and less likely to cause harm, particularly for children.

Accordingly, it is understood that healthcare providers play an indispensable role in pharmacotherapy and in preventing adverse events resulting from undesirable drug interactions, and that it is not enough for a medication to be safe in its intrinsic sense; its safe use process must also be ensured[30]. It is imperative to equip nurses, who must have specific knowledge about each drug used, often without the support of scientific evidence, revealing the need to restructure processes and create safety strategies to reduce avoidable risks and harms associated with care[31].

Study limitations

Study limitations include the lack of analysis of the effects of the PDIs and the fact that the study was conducted in a low-complexity unit and in only one center, without including other hospital units. These settings may have different health indicators based on their local realities and social contexts, which underscores the need for further research.

CONCLUSION

A considerable number of prescriptions with PDIs were identified in the studied setting, with a predominance of interactions classified as major in severity. Therefore, depending on the patient's condition, the risk-benefit ratio and the necessity of such combinations must be carefully considered. When necessary,

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these events should be identified using validated tools to enable continuous monitoring and ensure patient safety.

In addition, it is essential to raise awareness among the multidisciplinary team involved in the rational use of medications, especially in inpatient units. Anticipating the risk of potentially interactive combinations at the time of prescription is crucial to minimizing the occurrence of PDIs that may cause harm to hospitalized children, extend hospital stays, increase healthcare costs, and heighten the risk of adverse drug reactions, ultimately resulting in potential harm to the patient's life.

Conducting studies of this nature in a pediatric inpatient unit of a public hospital in a municipality located away from large urban centers aims to provide insight into the magnitude and risks of potentially interactive combinations and the respective degrees of severity present in medical prescriptions, thereby supporting better-targeted actions to address and mitigate this problem. This study reinforces the importance of local investigations to improve prescribing practices and ensure patient safety.

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Use of artificial intelligence tools

Authors declare that no artificial intelligence tools were used in the composition of the manuscript "*Potential drug interactions in the pediatric inpatient unit: a retrospective study*".