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Drug-related problems among pediatric intensive care units: prevalence, risk factors, and clinical pharmacists' interventions

Nasrin Shirzad-Yazdi[1,2], Sajjad Taheri[1†], Afsaneh Vazin[2†], Eslam Shorafa[3], Seyedeh Narjes Abootalebi[3,4], Katayoon Hojabri[3], Fatemeh Javanmardi[5] and Mojtaba Shafiekhani[2*]

Abstract

Background Drug-related problems (DRPs) are frequently observed in intensive care units, resulting in a higher occurrence of drug side effects and increased treatment expenses. This study aimed to assess the prevalence of DRPs in pediatric patients admitted to the most prominent surgical and medical pediatric intensive care units (PICUs) in southern Iran, given the susceptibility of children to the effects of DRPs.

Method This cross-sectional study was conducted at Namazi Hospital, which is affiliated with Shiraz University of Medical Sciences in Shiraz, Iran, from June 2022 to March 2023. The research focused on identifying and detecting drug-related problems (DRPs) among pediatric patients during their hospital stays across three medical wards, two pediatric intensive care units, and a surgical intensive care unit. The identification process occurred concurrently with patient treatment and utilized the Pharmaceutical Care Network of Europe's data collection form for DRPs version 8.01. Before any documentation, all cases were thoroughly reviewed and validated by a professional focus group. The data gathered were then statistically analyzed using SPSS to evaluate the study's outcomes.

Result During the study, 323 pediatric patients were involved, of whom 57% experienced at least one DRP. The primary issues identified during the study were suboptimal drug treatment, accounting for 41.13% of cases, followed by concerns related to treatment safety, which constituted 38.53% of cases. Drug-drug interactions were found to be the leading cause of DRPs, accounting for 36.26% of cases. Two significant factors associated with DRP occurrence were the number of prescribed drugs and the number of prescribed anticonvulsants. Out of all clinical pharmacist interventions, 97% were accepted.

Conclusion Patients admitted to the PICUs experience a high occurrence of DRPs. It is essential to consider optimal dosage adjustment, particularly for pediatric patients with impaired kidney function.

Keywords Drug -related problems, Clinical pharmacist, Pediatrics, PCNE classification

[†]Sajjad Taheri and Afsaneh Vazin contributed equally to this work.

*Correspondence:
Mojtaba Shafiekhani
mojtabashafiekhani@gmail.com
Full list of author information is available at the end of the article

Background

Medication errors and their consequences remain a significant concern for healthcare providers, insurance organizations, and policymakers worldwide. A landmark report by the Institute of Medicine estimates that in the United States alone, drug-related problems (DRPs) result in 44,000 to 98,000 fatalities each year, primarily due to adverse drug reactions (ADRs) and avoidable medication errors [1]. Studies indicate that medication errors can lead to one death for every 131 outpatients and one for every 854 inpatients [2]. DRPs are defined as events or circumstances that disrupt the intended health outcomes from the appropriate use of medications, rather than arising from the underlying illness itself [3]. These issues not only incur significant costs but also contribute to various forms of morbidity and mortality for patients seeking to restore their health through medication.

Currently, various classification systems have been developed to analyze and categorize DRPs, aiding in the identification of their nature, causes, and necessary strategies to prevent future occurrences in hospital environments. One effective system is the classification model proposed by the Pharmaceutical Care Network of Europe (PCNE) [3]. Implementing pharmaceutical care departments staffed by clinical and hospital pharmacists in healthcare facilities can significantly enhance medication safety services and streamline drug supply processes. This proactive approach aims to prevent and reduce DRPs while promoting the responsible use of medications [4].

The incidence of DRPs in the pediatric population is a significant concern, as children are at a higher risk of experiencing these issues, including ADRs, compared to adults [5]. This increased vulnerability is attributed to several factors: the lack of sufficient safety data for pediatric use during clinical testing, the absence of appropriate pharmaceutical dosages and formulations tailored to children, and the variable and often unpredictable metabolism of drugs in this demographic [6, 7].Given these challenges, pediatric patients require special consideration in pharmacotherapy due to differences in drug pharmacodynamics and pharmacokinetics [8]. This study aims to examine the prevalence of DRPs among children in the Pediatric Intensive Care Unit (PICU) at Namazi Hospital in southern Iran, categorizing these problems based on their characteristics and underlying causes.

Method

Study design

A cross-sectional study took place in the children's special care departments of Namazi Hospital, a distinguished educational referral center in southern Iran, from June 2022 to March 2023. This hospital is associated with Shiraz University of Medical Sciences in Shiraz, Iran. Within the pediatric ICU of this facility, there are two medical units and one surgical unit, totaling 30 beds. The patients in these intensive care units were visited and assessed by three Specialists in pediatric intensive care alongside a clinical pharmacist. The study focused on pediatric patients who were under 18 years old, had been hospitalized in the PICU for more than 24 h, and were prescribed a minimum of two medications. Before participation, the patients' parents provided informed written consent. The study received approval from the Medical Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1401.385) and followed the ethical guidelines outlined in the Declaration of Helsinki (1975) [9].

DRP identifications and data collection

Demographic information, diagnosis, medication details (including name, dosage form, drug class, indication, dosage, and interval), and laboratory data were collected by a pharmacy student under the guidance of a clinical pharmacist. This information was obtained through a review of patient medication charts, clinical notes, medical records, and the electronic hospital database. The data was gathered from admission to discharge from the PICUs. Clinical outcomes like ICU length of stay, mechanical ventilation duration, mortality, and any DRP-related outcomes were documented. The PCNE version 8.01 was used for documenting DRPs [3]. The PCNE guidelines help identify and categorize the type and number of DRPs based on five areas. These areas include "Problems," which can fall into three categories ("treatment efficacy," "treatment safety or ADR," and "other cases"); "Causes," which identifies the reasons behind the DRPs under eight sub-areas, such as "Drug Selection," "Drug Form," "Dose Selection," "Treatment Duration," "Drug Administration Process," "Patient-related," and others. "Planned interventions" are also documented to specify the level of pharmacist interventions. The acceptance or rejection of these interventions by the relevant parties is noted under "Intervention acceptance." Finally, the "DRP Status" describes the outcome of the identified DRPs.

Drug-drug interactions (DDIs) were analyzed using the Lexi-comp® online database (https://online.lexi.com/loc/action/home) [10], where we identified both the nature of the interactions and the severity of their clinical impacts. These interactions were categorized into five groups based on their clinical relevance: A, B, C, D, and X (see Table 1). For cases involving severe DDIs (classified as D or X), healthcare providers, including physicians and nurses, were notified, and a clinical pharmacist responsible for the study initiated appropriate interventions.

Table 1 The Lexi-Comp software risk rating classifications for drug interactions

Risk Rating	Description	Action
A	There is no evidence of pharmacodynamics or pharmacokinetic interactions between the specified agents	No interaction
B	Data shows that the specific agents may interact with each other, but there is minimal evidence of clinical concern arising from their simultaneous use	No action needed
C	Data shows that these specific agents may interact with each other in a clinically significant way 2. The benefits of using these two medications together typically outweigh the risks	Monitor therapy
D	Conduct a patient-specific assessment to determine if the benefits of concomitant therapy outweigh the risks	Modify regimen
X	The risks of using these agents together are typically greater than the benefits	Avoid combination

Furthermore, the Naranjo probability scale was utilized to evaluate all adverse drug reactions. This algorithm comprises 10 questions that consider factors such as the timing of the reaction and previous exposures. Each question is assigned a score ranging from -1 to + 2 based on the response. The cumulative score determines the likelihood of an adverse drug reaction: a score of > 9 indicates a definite reaction, 5–8 suggests a probable reaction, 1–4 indicates a possible reaction, and a score of zero implies doubt regarding the drug's role in the adverse event [11].

Sample size estimation

The required sample size was calculated using the Single Population Proportion formula, based on the following assumptions: a drug-related problem proportion (P) of 80.4% [12], a 95% confidence level, and a 5% margin of error (absolute level of precision).

$$n = (Z\alpha/2)2p(1 - p)/d2$$
$$z = 1.96$$
$$P = 80.4\%(0.804)$$
$$d = 0.05$$
$$n = (1.96)2(0.196)(0.804)/(0.05)2 = 301$$

Where; n = sample size, P = Proportion of drug related problems (p) = 86%

Z = Z is standardized normal distribution value at the 95% CI: 1.96.

d = the margin of sample error tolerated = 5%

During the study period, we anticipated a total population size (N) of 255, which was derived from the average number of patients visiting the hospital over a three-month timeframe. To determine the adjusted sample size (nf), we employed a correction formula as outlined below:

$$nf = (n * N)/(n + N)$$
$$nf = (185 * 255)/(185 + 255)$$
$$nf = 138$$

When a 15% contingency is applied, this total rises to 158. A consecutive sampling method was employed to select the participants for the study.

Clinical pharmacist interventions

The clinical pharmacist carefully examined the medications prescribed to each patient daily to check for any potential drug interactions or adverse drug reactions. They used resources such as The Harriet Lane Handbook, [13] UpToDate® [14] to ensure the chosen drugs were appropriate for each individual. Additionally, the clinical pharmacist considered factors such as kidney and liver function and the patient's laboratory and clinical conditions to adjust the medication doses when necessary. The pharmacist collaborated with healthcare professionals in prescribing medications to provide recommendations on addressing drug-related problems. The summary of clinical pharmacist interventions is shown in Fig. 1.

Statistical analysis

Statistical analysis was conducted using SPSS Version 22.0 (Armonk, NY, USA: IBM Corp.). Descriptive statistics were utilized to assess the frequency of each type of DRP and to calculate the acceptance rate of prescribers. Continuous variables were presented as mean ± standard deviation (SD), while categorical data were expressed as percentages or frequencies. To evaluate the potential risk factors associated with DRPs, both univariate and multivariate logistic regression analyses were employed. The results are presented as odds ratios (ORs) along with 95% confidence intervals (CIs). A p-value of less than 0.05 was deemed statistically significant.

Results

Demographic data

The study involved 323 patients, with 194 (60.1%) boys and 129 (39.9%) girls. The patients' ages ranged from 1 to 219 months, and pediatric patients older than 60 months were the majority in both groups. Of these patients, 216 (66.8%) were admitted to the pediatric medical ICU and 107 (33.12%) to the pediatric surgical ICU. The main

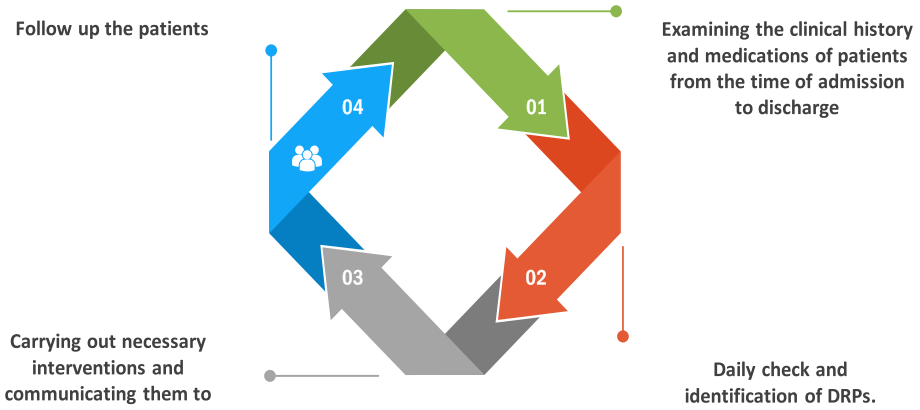

Fig. 1 The trend of clinical pharmacist interventions

reasons for hospitalization were pneumonia (35.6%), gastroenteritis problems (10.8%), and trauma (9.6%). Notably, the significant underlying diseases were diabetes mellitus (DM), glucose-6-phosphate dehydrogenase (G6PD) deficiency, and central nervous system (CNS) disorders. On average, all patients stayed in the ICU for 8.85 ± 7.84 days, ranging from 1 to 63 days. Each patient received an average of 15.24 ± 9.48 prescription drugs, varying between 2 and 58. The most commonly prescribed drug classes were antibiotics (53.47%), proton pump inhibitors (PPIs) (29.06%), and anticonvulsants (18.56%). Further information can be found in Table 2.

DRPs

During the study, it was observed that out of the 323 patients, 184 patients (56.96% of patients) had at least one DRP based on PCNE. The total number of DRPs in these patients was 423. In the medical PICU, there were 140 patients with 335 DRPs (78.27%), while in the surgical PICU, 44 patients with 88 DRPs (20.56%). The likelihood of experiencing DRPs was 2.63 times higher in patients hospitalized in the medical PICUs than in the surgical PICUs, which was statistically significant (P-value < 0.001). Furthermore, the Medical PICU had a significantly higher number of prescribed medications and anticonvulsants than the surgical PICU (P-value < 001). The most commonly used anticonvulsants in both units were Levetiracetam, phenobarbital, and sodium valproate, with Levetiracetam having the highest usage rate at 14.2%. Similarly, vancomycin was the most commonly prescribed at a rate of 22%, followed by Meropenem at 20.9%.

The distribution of DRPs in different age groups and both sexes was checked based on Pearson's chi-square test, and no significant difference was observed in the occurrence of DRPs in other age groups and genders. Using multivariable logistic regression, we identified a significant association between the number of prescribed anticonvulsants and the occurrence of DRP. Table 3 provides a summary of the DRP risk factors. According to Table 4, the main type of DRP was non-optimal drug therapy (174 prescriptions, 41.13%) and treatment safety (163 prescriptions, 38.53%). Non-optimal drug therapy arises from not adjusting the drug dosage, particularly antibiotics, in patients with reduced kidney function (low GFR). Furthermore, the significant causes for these problems are an incorrect combination of medications resulting in drug-drug interactions (153 prescriptions, 36.26%) and inappropriate selection of drug dosage (126 prescriptions, 29.86%).

Moreover, based on our results, no significant differences were observed between the occurrence of DRP and risk factors such as age, gender, weight, prematurity, underlying diseases, cause of hospitalization, and positive history of drug sensitivity.

According to Table 5, a study was conducted to examine how quantitative and qualitative factors contribute to the occurrence of DRPs. The analysis revealed that two significant factors associated with the occurrence of DRP were the number of prescribed drugs (95% CI of 1.17—1.56) and the number of prescribed anticonvulsants (95% CI of 1.07—4.64). These results were obtained using multivariate logistic regression analysis. Additionally, other variables, such as the reason for hospitalization, underlying disease, number of comorbidities, and number of opioid drugs, were found to also impact the occurrence of DRPs based on the results of univariate regression analysis.

Furthermore, potential drug-drug interactions (categories D and X) were evaluated. One hundred twenty-seven interactions were identified within the D category, while the X category yielded 39. The most frequent drugs associated with class D interactions included

Table 2 Baseline demographic and clinical characteristics of pediatric admitted to the ICUs (N: 323)

variable				DRP ($n=184$)	Non-DRP ($n=139$)	*P*-value
Age (month)	1–3			29 (15.8%)	15 (10.8%)	0.15
	4–6			16 (8.7%)	5 (3.6%)	
	7–9			11 (6.0%)	5 (3.6%)	
	10–12			6 (3.3%)	7 (5.0%)	
	13–24			19 (10.30%)	10 (7.2%)	
	25–60			29 (15.8%)	27 (19.4%)	
	More than 60			74 (40.2%)	70 (50.4%)	
Sex	Boy			107 (58.2%)	87 (62.6%)	0.42
	Girl			77 (41.8%)	52 (37.4%)	
Cause of admission	DKA			2 (1.1%)	18 (12.9%)	< 0.001
	Pneumonia			77 (48.1%)	38 (27.3%)	
	Trauma			19 (10.3%)	12 (8.6%)	
	GE			14 (7.6%)	21 (15.1%)	
	Renal failure			8 (4.3%)	4 (2.9%)	
	Liver failure			3 (1.6%)	10 (7.2%)	
	CNS disorder			18 (9.8%)	8 (5.8%)	
	Cardiovascular disease			7 (3.8%0	4 (2.9%)	
	Bite			2 (1.1%0	4 (2.9%)	
	Poisoning			7 (3.8%)	8 (5.8%)	
	Convulsion			19 (10.3%)	6 (4.3%)	
	Others			8 (4.3%)	6 (4.3%)	
Number of narcotics Prescribed	$N=0$			104 (56.5%)	114 (82.0%)	< 0.001
	$N=1$			65 (35.3%)	22 (15.8%)	
	$N=2$			15 (8.2%)	3 (2.2%)	
Number of comorbid diseases	$N=1$			98 (53.23%)	95 (68.3%)	0.02
	$N=2$			80 (43.5%)	41 (29.5%)	
	$N=3$			6 (3.3%)	3 (2.2%)	
Underlying disease	At least one disease			84 (45.7%)	58 (41.7%)	0.48
Number of prescribed medicine				20.53 ± 9.15	8.24 ± 3.46	< 0.001
Number of antibiotics				3.67 ± 1.22	2.10 ± 1.06	< 0.001
Number of anticonvulsants				1.03 ± 1.05	0.25 ± 0.6	< 0.001
Number of sedative drugs				0.57 ± 0.61	0.14 ± 0.35	< 0.001
Length of antibiotic therapy(day)				9.27 ± 8.15	2.71 ± 1.36	< 0.001
Length of ICU stay(day)				11.46 ± 10.26	3.05 ± 1.58	< 0.001
Length of hospital stay(day)				31.35 ± 30.92	19.24 ± 30.33	< 0.001
Length of mechanical ventilation(day)				1.35 ± 3.10	0.15 ± 0.63	< 0.001
Ward			Medical PICU	140 (76.1%)	76 (54.7%)	< 0.001
			Surgical PICU	44 (23.9%)	63 (45.3%)	
Patients status		Expire		49 (26.6%)	11 (7.9%)	< 0.001
		Alive		135 (73.4%)	128 (92.1%)	
History of prematurity				23 (12.5%)	161 (87.5%)	0.11
History of allergy				51 (27.7%)	133 (72.3%)	0.42

ICU Intensive Care Unit, *PICU* Pediatric Intensive Care Unit, *DKA* Diabetic Keto-Acidosis, *GE* Gastroenteritis, *CNS* Central Nervous System

meropenem + valproate sodium and Methadone + Linezolid. Class X interactions included linezolid + morphine, and ciprofloxacin + Tizanidine. More details are shown in Table 5.

Result of clinical pharmacists' interventions

The clinical pharmacist assessed 4924 medication orders. It is essential to mention that clinical pharmacist consultation services are only provided in the medical PICU. Among these interventions, 97% were accepted. The most

Table 3 Determinants of drug-related problems (DRPs) among Pediatrics admitted to PICUs, using logistic regression

variable		Univariate logistic regression		Multiple logistic regression	
		Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*P*-value
Age (month)	1–3	1.82 (0.9 – 3.69)	0.09	0.72 (0.19 – 2.66)	0.62
	4–6	3.02 (1.05 – 8.70)	0.04	0.60 (0.1 – 3.49)	0.6
	7–9	2.08 (0.68 – 6.29)	0.19	0.55 (0.09 – 3.23)	0.51
	10–12	0.81 (0.26 – 2.53)	0.71	1.97 (0.37 – 10.27)	0.42
	13–24	1.79 (0.78 – 4.13)	0.16	1.82 (0.39—8.56)	0.44
	25–60	1.01 (0.54—1.88)	0.96	0.57 (0.15 – 2.10)	0.39
Cause of admission	DKA	0.083(0.014—0.5)	0.007	0.015(0.00—2.18)	0.098
	Pneumonia	1.52 (0.49 – 4.69)	0.46	1.23 (0.19—7.87)	0.82
	Trauma	1.18 (0.33 – 4.27)	0.79	0.40(0.036—4.49)	0.45
	GE	0.5 (0.14 – 1.75)	0.27	0.91(0.10–8.11)	0.93
	Renal failure	1.50 (0.3 – 7.43)	0.61	0.40 (0.023 – 7.21)	0.53
	Liver failure	0.22 (0.04–1.19)	0.08	0.26 (0.02—3.31)	0.29
	CNS disorder	1.68(0.43—6.48)	0.44	0.91 (0.096 – 8.67)	0.93
	Cardiovascular disease	1.31(0.25—6.64)	0.74	0.21 (0.009 – 5.19)	0.34
	Poisoning	0.65(0.15—2.84)	0.57	0.08 (0.004—1.83)	0.08
	Convulsion	2.37(0.58 – 9.64)	0.22	0.31 (0.026 – 3.70)	0.11
Number of narcotics prescribed	*N* = 1	0.18 (0.05—0.64)	0.009	2.2 (0.21–22.56)	0.5
	N = 2	0.59 (0.15—2.23)	0.43	1.65 (0.15 – 18.29)	0.68
Number of comorbid diseases	*N* = 1	0.51 (0.12—2.12)	0.35	_____	_
	N = 2	0.97 (0.23—4.10)	0.97	_____	_
Underlying diseases	At least one disease	1.17 (0.75—1.83)	0.48	1.35 (1.17 – 1.56)	0.35
Number of anticonvulsants prescribed		3.42 (2.36—4.94)	< 0.001	2.23 (1.07 – 4.64)	0.03
Length of antibiotic therapy (day)		2.45 (1.97—3.05)	< 0.001	1.25 (0.73—2.16)	0.4
Length of ICU stay(day)		2.16 (1.78—2.61)	< 0.001	1.33 (0.78 – 2.27)	0.28
Length of hospital stay(day)		1.01 (1.00 – 1.02)	0.001	0.98 (0.97—1.00)	0.23
Length of mechanical ventilation(day)		1.65 (1.27—2.14)	< 0.001	1.02 (0.63 – 1.65)	0.91
History of prematurity		1.84(0.84—4.01)	0.12	_____	_
History of allergy		0.81 (0.48—1.34)	0.42	_____	_
ward(PICU Vs Surgical ICU)		2.63 (1.63 – 4.24)	< 0.001	_____	_

OR Odds ratio, *CI* Confidence interval, *DKA* Diabetic Keto-Acidosis, *GE* Gastroenteritis, *CNS* Central Nervous System, *ICU* Intensive Care Unit, *PICU* Pediatric Intensive Care Unit

frequent interventions were dose adjustments of antibiotics, particularly Meropenem and Vancomycin, according to renal function. More details are shown in Table 6.

Clinical outcomes

The time spent in the ICU for patients in the DRP and non-DRP groups was 11.46 ± 10.26 and 3.05 ± 1.58 days, respectively. This difference was statistically significant (*P*-value < 0.001). An increase in the duration of antibiotic treatment, ventilator use, hospitalization, and ICU stay by one day is associated with a respective increase of 2.453, 1.653, 1.016, and 2.161 in the likelihood of experiencing DRPs.

Out of 184 patients with DRPs, 135 died. The incidence of mortality in patients with DRPs was significantly higher (*P*-value < 0.001). Based on the odds ratio calculation, the likelihood of death in patients with DRPs is 4.22 times higher compared to those without DRPs (*P*-value < 0.001).

Discussion

This is the first study that describes the problems and causes of DRPs and the use of the PCNE classification in a pediatric medical and surgical ICU in a referral hospital in southern Iran. The prevalence of DRP in the present study was reported as 56.95%. Additionally, the study revealed that patients, on average, experienced 1.3 DRPs, which is a lower rate compared to the previous research that reported 1.7 DRPs [12]. Based on pediatric studies worldwide, the prevalence of DRPs has reported a

Table 4 Drug-related problems (DRPs), causes, and interventions by clinical pharmacist according to the PCNE classification

Classification for Drug related problems		N (%)
Problems	P1.1: Treatment effectiveness	10 (2.36%)
	P1.2:Effect of drug treatment not optimal	174 (41.13%)
	P1.3: Untreated symptoms or indication	33 (7.80%)
	P2.1: Adverse drug event (possibly) occurring	163 (38.53%)
	P3.2: Problem with cost-effective treatment	41 (9.69%)
	P3.3: Dose timing instructions wrong, unclear, or missing	2 (0.47%)
Causes	C1.1Inappropriate drug according to guidelines/formulary	7 (1.66%)
	C1.2: Inappropriate drug (within guidelines but otherwise contra-indicated)	24 (5.69%)
	C1.3: No indication for drug	12 (2.84%)
	C1.4: Inappropriate combination of drugs or drugs and herbal Medication	153 (36.26%)
	C1.5: Inappropriate duplication of therapeutic group or active Ingredient	2 (0.47%)
	C1.6 No drug treatment in spite of existing indication	23 (5.45%)
	C1.7 Too many drugs prescribed for indication	16 (3.79%)
	C2.1: Inappropriate drug form	6 (1.42%)
	C3.1: Drug dose too low	126 (29.86%)
	C3.2: Drug dose too high	30 (7.11%)
	C3.3: Dosage regimen not frequent enough	12 (2.84%)
	C3.4: Dosage regimen too frequent	5 (1.18%)
	C3.5: Dose timing instructions wrong, unclear or missing	1 (0.24%)
	C5: Dispensing causes	1 (0.24%)
	C6: The drug use process causes	1 (0.24%)
	C8: Other causes	2 (0.47%)
Interventions	No intervention	247 (76.47%) 108(58.7%)
	Intervention	76 (41. 3%)
	Intervention accepted	74 (97.37%)
	Intervention not accepted	2 (2.63%)
Status	Problem solved	61 (33.33%)
	Problem partially solved	13 (7.10%)
	Problem not solved	109 (59.56%)

variable ranging from 21 to 89.89% [15–23]. In this study, as mentioned above, the prevalence of DRPs was found to be 56.95%, significantly exceeding the 6.8% reported in a Brazilian study [20]. However, this figure was lower than the findings from a study at Jimma University Medical Center, which reported rates of 74.3%, [16], and Dessie Referral Hospital, where the rate was 87.7% [15]. Additionally, research by Nguyen et al. in Vietnam indicated that 65.7% of pediatric outpatients experienced DRPs with their prescriptions [24]. The occurrence of these issues was also similar to a study conducted in a general pediatric ward in Malaysia, which found a prevalence of 52.9% [25].

The discrepancies in the reported rates of DRPs can be attributed to variations in the study population, sample size, number of prescriptions, prescribed medications, presence of a clinical pharmacist, and different classifications. Different versions of classification systems (such as PCNE 6, 8, and 9) and reference sources are utilized to identify and assess DRPs.

For instance, the study conducted by Jafarian et al. analyzed a population of 250 children, including both the pediatric and neonatal departments [12]. Neonates and Infants have a higher likelihood of experiencing DRPs compared to children for various reasons. These include variances in body weight and structure, the efficiency of drug-metabolizing enzymes, and the maturation and functioning of organs like the kidney and liver [26, 27]. These factors result in disparities in drug exposure and response, specifically among children below the age of 2. According to the findings of Moore et al., approximately 7,000 out of 500,000 reported instances of adverse drug reactions involved infants and children under the age of two [28]. Another study in Saudi Arabia in 2016 reported a DRP occurrence rate of approximately 36%. Notably, this study differed from the current research in several

Table 5 Potential drug- drug interactions (categories D and X) among pediatrics admitted to PICUs ($N=323$)

Interactions drugs	Interaction category	The cause of the interaction	The result of interaction	Clinical pharmacist intervention
Meropenem + Sodium Valproate	D	Carbapenems may decrease the serum concentration of sodium valproate	The patient may experience convulsions due to the decrease in sodium valproate concentration	1. Avoid concurrent use of carbapenem antibiotics with valproate products 2. Consider alternative antimicrobial agents 3. If a carbapenem must be used concurrently, consider additional anti-seizure medication 4. Monitor valproate concentrations closely when using a carbapenem with valproic acid and derivatives
Methadone + Diazepam	D	BZDs may increase the CNS depressant effect of methadone	It may increase neurological complications (confusion, speech disorder, movement disorder, etc.)	1. Avoid concurrent use of methadone and benzodiazepines whenever possible 2. Exercise caution if the benefits of methadone treatment outweigh the risks of the combination 3. Evaluate the potential risks and benefits carefully before considering the long-term use of low doses of both medications together
Methadone + Fluconazole	D	Fluconazole may increase the serum concentration of methadone	Methadone may increase the QT-prolongation of fluconazole and fluconazole may increase the adverse effects of methadone	1. Watch for signs of respiratory depression and QT prolongation/torsades de pointes 2. Consider methadone dose reductions if necessary
Amikacin + Vancomycin	D	Vancomycin may increase the adverse effects of aminoglycosides (Amikacin)	It may increase the nephrotoxic, neurotoxic effect of aminoglycosides	1. Monitor for increased nephrotoxic effects of aminoglycoside when administered with vancomycin 2. Carefully monitor aminoglycoside serum concentrations and adjust dosing as needed
Amphotericin B + Colistin	D	Amphotericin B may increase the adverse effects of Colistin	It may increase the nephrotoxic effect of Colistin	Closely monitor patients' renal function
Methadone + Linezolid	D	Methadone may increase the serotonergic effects of monoamine oxidase inhibitors	It can lead to serotonin syndrome	1. Discontinue serotonin modulators at least 2 weeks before administering linezolid 2. Consider alternative agents and interventions if urgent initiation of linezolid is necessary 3. If the benefit of linezolid outweighs the risk of serotonin toxicity, discontinue the serotonin modulator immediately and monitor closely for signs of serotonin syndrome 4. Resume serotonin modulator treatment 24 h after the last dose of linezolid
Posaconazole + Alprazolam	D	CYP3A4 inhibitors (posaconazole) may increase the serum concentration of alprazolam	It may cause an increase in skin, sexual, and digestive complications	Consider alternatives instead of Alprazolam
Linezolid + Methylphenidate	X	Linezolid (monoamine oxidase inhibitor) increases the effect of methylphenidate	May increase the hypotensive effect of methylphenidate	Do not use methylphenidate during or within 14 days of discontinuing a monoamine oxidase inhibitor
Ciprofloxacin + Tizanidine	X	Ciprofloxacin may increase the serum concentration of tizanidine	It may cause an increase in gastrointestinal, urinary, genital, and liver complications	Avoid using Ciprofloxacin and Tizanidine together
Desmopressin + Dexamethasone	X	Corticosteroids may increase the hyponatremic effect of desmopressin	May increase hyponatremia and gastrointestinal side effects of desmopressin	1. Wait at least 3 days or 5 half-lives (whichever is longer) after discontinuing the glucocorticoid before initiating intranasal desmopressin

Table 5 (continued)

Interactions drugs	Interaction category	The cause of the interaction	The result of interaction	Clinical pharmacist intervention
Linezolid + Morphine	X	Linezolid (a monoamine oxidase inhibitor) may increase the adverse effects of morphine	It may cause an increase in cardiac, skin, digestive,… morphine side effects	1. Avoid using morphine with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping an MAOI 2. Be cautious of the potential for CNS/respiratory depression and potentiation of morphine-related anxiety and confusion
Erythromycin + Fluconazole	X	Fluconazole may increase the serum concentration of erythromycin	Fluconazole may increase the QT-prolongation of erythromycin	Avoid using fluconazole and systemic erythromycin together

BDZ Benzodiazepine, *CNS* Central Nervous System, *CYP3A4 inhibitors* cytochrome P450 family 3 subfamily A member 4 inhibitors

Table 6 The most frequent DRPs and interventions performed by the clinical pharmacist

Clinical pharmacist's suggestions		Cause	DRP	Frequency (%)	Acceptance (%)
Meropenem	**Change in drug dose based on kidney function** **Change in drug dose based on disease** **Change in route of administration**	C3.1/C3.2	Non-optimal dose	40.9	100%
Meropenem	**administration (Extended or continues infusion vs intermittent bolus)**	C3.3	Treatment effectiveness	9.4	100%
Vancomycin	**Change in drug dose based on kidney function**	C3.1/C3.2	Non-optimal dose	20.8	100%
Cessation of Methadone and Addition another of non-opioid agonist		C1.4	Interaction between Methadone and Linezolid	10.9	0%
Cessation of Sodium Valproate and Addition of another anticonvulsant		C1.4	Meropenem and Sodium Valproate drug interaction	9.7	0%
Discontinue of antibiotic therapy		C1.3	no need to prescribe or continue vancomycin	8.3	100%

C3.1 Drug dose too low, *C3.2* Drug dose too high, *C1.4* inappropriate combination of drugs or drugs and herbal medication, C1.3: No indication for drug

aspects. Firstly, the sample size of the Saudi Arabian study was more significant, including 655 patients. Secondly, it examined the NICU department, whereas the current study examined different children's departments. Lastly, a considerable disparity lay in the study criteria, with the Saudi Arabian study employing PCNE version 7, while the present study relied on the more precise and comprehensive version 8. In version 7, the definition of DRP is not as concise and thorough as in version 8 [29]. Furthermore, our research findings have surpassed those of a previous study conducted in 2017 by Mequanent Kassa Birarra et al. Their research, conducted in general pediatric departments, reported an overall incidence rate of DRP of 31.6% [17]. The increase in DRP incidence can be attributed to various factors. Patients in the PICU and NICU often have more complex medical conditions and frequently experience multiple organ failure, which is not as common in the general wards. This compels the need for stronger medications to support the functioning of vital organs. However, the use of these medications also increases the likelihood of toxicity and potential interactions with other drugs. Therefore, it is crucial to consider these factors when exploring possible reasons for the elevated prevalence of DRP.

Our results showed that the most common type of DRPs found were related to the effectiveness of treatment. This problem often occurs due to insufficient medication prescriptions and inadequate dosage. Meropenem was consistently identified as the drug most commonly associated with DRPs among the medications studied. However, the study conducted in Ethiopia revealed the most errors in determining the dose of ampicillin [17].

Inappropriate dosage adjustment of antibiotics like Meropenem or vancomycin based on kidney function can lead to a higher risk of under-dosing in some patients. Studies have shown that kidney dysfunction is common among children admitted to the ICU, [30] particularly in older children receiving sepsis treatment, ventilator support, and vasoactive agents [31]. Children in the ICU are also at risk of polypharmacy and drug-drug interactions due to multiple co-morbidities and organ dysfunction [32]. Previous studies [18, 22, 25, 33–37] have highlighted incorrect dose selection in pediatric patients [38]. A study conducted in Saudi Arabia found that the most common medication errors in children were related to incorrect dosages and drug interactions [35]. Therefore, it is crucial to closely monitor medication dosages based on kidney function and appropriately adjust antibiotic doses to ensure optimal treatment outcomes. However, determining the ideal dosage for children of different ages is challenging due to limited pharmacokinetic studies [39]. In addition to kidney function, other factors such as weight, age, and body surface area are crucial in pediatric patients' dose adjustment [40]. Therefore, educating and training pediatricians to prevent under-dosing of these medications is necessary.

The DRPs we frequently encountered after the most common type were associated with ensuring treatment safety, notably by addressing both evident and potential side effects of medications. Notably, we came across a significant interaction between methadone and linezolid.

As previously stated, most DRPs occur in the medical PICU rather than the surgical PICU. This disparity could be attributed to factors such as the higher number of

beds in the medical PICU (18 compared to 8 in the surgical PICU), a more significant amount of prescribed drugs in the medical PICUs (especially anticonvulsants), and longer stays in the medical PICU compared to the surgical PICU. Previous research also demonstrated a correlation between an increase in drug prescriptions and the occurrence of medication errors, which aligns with our research findings [34]. Levetiracetam, phenobarbital, and sodium valproate are frequently prescribed anticonvulsants in our study. By adding just one anticonvulsant to a patient's medication record, the occurrence of DRPs doubled. A survey conducted by Malfará et al. in a PICU unit in Brazil found that anticonvulsants were identified as the main contributors to DRP. Specifically, anticonvulsants accounted for 13% of all drugs associated with these issues [41]. This high occurrence may be attributed to various drug-anticonvulsant interactions [42], especially with older-generation anticonvulsants like phenytoin and phenobarbital [43, 44].

We also examined the effect of demographic information on the occurrence of DRPs. Similar to previous studies, gender does not play a significant role in the prevalence of DRP in children [12, 37]. The age variable played a substantial role in the development of DRP in the Isfahan study, [12] which differs from our research findings. In our study, participants of a particular age group comprised 44.5% of the total sample. Additionally, our results indicate that factors like BMI, previous drug or food allergies, prematurity, and other existing medical conditions do not significantly increase the chances of experiencing DRP. Al-Azmi et al. also discovered no notable association between the occurrence of DRPs and age, gender, or weight in children [29].

Our study's primary causes of hospitalization were pneumonia, trauma, and neurological issues such as seizures. The data was collected mainly during autumn when respiratory illnesses like pneumonia are more prevalent. However, we couldn't find any significant relationship between the causes of admission and DRP occurrence.

Given the recent development of the clinical pharmacy service in the PICUs of Namazi Hospital, the rate at which our recommendations were accepted was extremely high, reaching 97%. Compared to previous studies conducted in the same facility [45] and elsewhere [12, 34, 46, 47] this disparity can be attributed to our extensive clinical knowledge and experience in pediatric drug therapy. Kelly J. Cunningham highlighted the significant influence of pediatric pharmacists in decreasing the incidence of medication errors. Patients have experienced merely 0.2% of medication errors, underscoring the crucial contribution of pharmacists in minimizing medication errors and enhancing safety [48]. So, the clinical pharmacist's role within the medical team will be increasingly important in reducing DRP and patient expenses. Additionally, the clinical team should adhere more closely to treatment guidelines to prevent the inappropriate prescribing of drugs for this specific group.

Our study had several limitations, including a short duration and a limited number of wards examined. While this is the first study conducted at our center, which is the largest pediatric referral center in southern Iran, it is important to recognize that it is a small-scale study focused on a single institution. The primary aim of our research was to identify and document (DRPs) in children admitted to Namazi Hospital, and as such, the findings may not apply to other hospitals. To gain a more comprehensive understanding of DRPs, particularly the economic impact of medication errors in pediatrics, larger and multicenter studies are needed.

Conclusion

According to the present study's findings, a significant percentage (56.9%) of children experienced DRP. Furthermore, the prevalence of DRP was higher among patients who were on multiple medications and those using anticonvulsant drugs compared to the rest.

Certainly, to effectively identify, prevent, and resolve Drug-Related Problems (DRP), a clinical pharmacist is a critical healthcare team member who encourages smooth collaboration between clinical pharmacists and physicians.

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Authors' contributions

N. Sh. Y: design of the work, acquisition, and analysis of data, assisting with the creation and editing of the manuscript, S.T, and A. V: Analysis and interpretation of data; revising the manuscript E. Sh, N. A, and K.H: assisting with the creation and editing of the manuscript F.J: data analysis, drafting, and revising the manuscript M. Sh: Conception, design of the work, acquisition, supervision, analysis, and interpretation of data, as well as assistance with the creation and editing of the manuscript.

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Data availability

The datasets produced and/or examined in this study are not publicly accessible due to the inclusion of sensitive information that could jeopardize the privacy of the participants. However, interested individuals may obtain access to these datasets by contacting the corresponding author and making a reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the clinical Ethics Committee of Shiraz University of medical Sciences (approval code: IR.SUMS.REC.1401.385). Written consent was obtained from the pediatric guardian or parent after thoroughly explaining the study's purpose and objectives before data collection.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran. [2]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran. [3]Department of Pediatrics, Division of Intensive Care Unit, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [4]Department of Biostatics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [5]Biotechnology Research Center, Shiraz University of Medical Science, Shiraz, Iran.

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