Original Article

Use in Hospitalized Children: A Middle Eastern Experience

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Abstract

Objective: We aimed to detect and report the frequency of occurrence of drug-related problems (DRPs) in a Middle Eastern University Children's Hospital (Isfahan, Iran) and classify them in terms of their nature and cause to clarify the responsibility of clinical pharmacists for the safe utilization of medications in hospitalized children. **Methods:** In this cross-sectional study which was carried out in Imam Hossein Children's University Hospital affiliated with Isfahan University of Medical Sciences (Isfahan, Iran) from September 2017 to May 2018, DRPs during the hospitalization of pediatric patients in three medical wards, the pediatric intensive care unit, and two neonatal intensive care units were detected and identified concurrently with the treatment process using Pharmaceutical Care Network of Europe data gathering form for DRPs v. 8.01. All cases were verified and validated in a professional focus group before documentation. **Findings:** We detected 427 DRPs in 201 out of 250 randomly included hospitalized children in which 86% of them were directly reported by the hospital's clinical pharmacist. The highest frequency of DRPs (47.3%) was observed in the age range of 1 month–2 years. Safety of treatment was the most frequently reported as the nature of the problem (43.5%), followed by effectiveness issues (36.8%). The most frequent cause of DRPs was dose selection issues (34.2%), followed by drug-type selection (25.5%), and unavailability of appropriate dosage forms (13.6%). Ninety-eight interventions were proposed by the clinical pharmacist, in which 59.2% of them were accepted. **Conclusion:** This study confirms the necessity for the active role of clinical pharmacists before, during, and after drug therapy in hospitalized pediatric patients for the safety and proper utilization of drugs in this vulnerable population.

Keywords: *Adverse drug events, clinical pharmacists, drug-related problems, hospitalized child, medication errors*

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Introduction

Medication errors and their related outcomes are still among the major concerns for health care, providing institutions, insurance bodies, and policymakers of the health sector in the world. According to the report of the seminal institute of medicine, in the United States, drug-related problems (DRPs) cause 44000–98000 cases of death per year mostly due to adverse drug reactions (ADRs) and theoretically preventable medication errors.[1] It is estimated that

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medication errors or a problem caused by drug utilization during a medical prophylaxis or treatment regimen may lead to the death of 1 individual per 131 outpatients and also one individual per 854 inpatients.[2] DRPs refer to those events or conditions which interfere with the desired health outcome through the legitimate use of medications, rather than the illness itself. These problems are the cause of significant costs and various types of morbidity and mortality[3] for the patients who are seeking recovery of their health using them. ADRs are among the top 10 most prevalent causes of death in the United States[4] which affects annually about 3.4 million people both for the nature of the consequent medical problem and also the need for another remedial action to resolve these undesirable effects of the medications.[5]

Nowadays, different classification systems are introduced to describe and explore DRPs[6] which can help to identify the nature of the problem, its causes, and the needed intervention to prevent the occurrence of further DRPs in hospital settings.[7] The classification which is presented by the Pharmaceutical Care Network of Europe (PCNE) classification[3] is a good and functional example of them.

Establishing pharmaceutical care departments by clinical and hospital pharmacists in hospitals which provides medication safety services as well as drug supply in routine hospital pharmacies is an effective measure to prevent, minimize, and document DRPs and to promote the optimal use of medications.[8] Providing this type of health service with a history of 60 years in some North American medical centers[9] and about 20 years in some university hospitals in Iran has dramatically helped to have a better assessment of DRPs in drug therapy and resulted in the suggestion of practical strategies of pharmacists on these issues.[10,11] For example, in a recent study conducted by Tasaka *et al*. in 20 hospitals in Japan, it was shown that 2376 interventions by hospital pharmacists prevented ADRs for 1678 drug orders and effectively decreased the related cost of treatment.[12] Westerlund *et al.* also reported a study which evaluated the clinical and economic outcomes of pharmacist-led interventions on DRPs. They found that the frequency of ARDs reduced by 32% with 68% of improvement in the efficacy of their drug therapy. In 13% of their cases, the interventions led to the prevention of patients' primary care contact caused by ADRs.[13] Several studies have also reported from Iran on epidemiological characteristics (occurrence, prevalence, or incidence) of DRPs, especially ADRs, which have emphasized on the active role of clinical pharmacists in decreasing these types of problem.[14-23] However, it should be noted that all of these studies have been conducted by clinical pharmacists themselves and in their employment centers, which may indicate a source of probable bias.

The occurrence of DRPs in the pediatric population has a great source of concern. Comparing to the adult patients, children have a higher risk for developing DRPs (including ADRs) due to the lack of enough safety profile for pediatric use during clinical trial phases of medication, unavailability of different needed pharmaceutical dosages for the drugs with a proper strength and desirable formulation, and most importantly, inadequate and in some cases unpredictable metabolism of drugs in this subgroup of patients.[24-26]

In this study, we aimed to investigate the frequency of occurrence of DRPs and classify them in terms of their nature and causes in a University Children's Hospital in Isfahan, Iran.

Methods

This cross-sectional study was carried out in Imam Hossein Children's University Hospital affiliated with Isfahan University of Medical Sciences from September 2017 to May 2018. This tertiary care 168-bed medical center, which is fully equipped and facilitated for the pediatric population, is located in Isfahan Province with the mission of health-care promotion for sick children in the central part of Iran. In 2018, the average monthly admission for its medical, surgical wards and intensive care units was about 1700 patients (hospitalized per month) and about 8000 for the outpatient clinics.

The study protocol was approved by the Institutional Research Ethics Committee of Isfahan University of Medical Sciences with the registration number of IR.MUI.RESEARCH.REC.1398.040. All patients aged 1 day to <18 years who were admitted at least for 1 day to one of the medical or surgical wards, neonatal intensive care units (NICUs), or pediatric intensive care unit (PICU) were potentially eligible for recruitment to the study. Medical wards of this children's hospital have neurology, nephrology, immunology, asthma and allergic disease medical services (Ped1 ward), gastrointestinal, cardiovascular, and pulmonology medical services (Ped2 ward), and infectious disease medical service (Ped3 ward). The data were collected concurrent with the treatment of pediatric patients by a pharmacy student (KJ) under the supervision of the chief clinical pharmacy specialist of the hospital (ZA) with a direct attendance of an average of 10 h a week and 3 days per week during hospital hours simultaneously with hospitalizations and treatment of patients, and the patients were selected using simple random sampling method. To facilitate the analysis and comparisons, children were categorized in five age groups: neonates (≤1 month), infants (>1 month

to ≤2 years), toddlers and preschool (>2 years to ≤6 years), school-aged (>6 years to ≤12 years), and adolescents (>12 years to ≤18 years) in accordance with part E11 of Guideline of International Conference of Harmonization of pediatric medicine research.[27]

During the study period, the clinical pharmacy specialist of the hospital (ZA) with the companion of a pharmacy student (KJ) had random visits of the admitted patients in casual days in the aforementioned medical and surgical wards and also the intensive care units and the studied patients, and if they found any DRP, they identified and documented it. Patients who had not taken or prescribed any particular medication at the time of admission were not included in the study. For each pediatric patient, the demographic details (e.g., gender, age, and weight) and the admission time diagnosis, received pharmaceutical care, laboratory findings involved in observed problem and the specialty of physician as well as the nature of the suspected problem, and the best guess for the cause of it (based on the patients' medical chart and their medical order forms) were recorded, and the pharmacist's recommendation for resolving it or its prevention for other patients was also documented.

The data collection tool of our study was the modified form for DRP documentation, which is recommended by the PCNE version 8.01. We modified this version by minor changes to make it more practical for the documentation of DRPs, which are potentially concerning in the pediatric population.

In the next step for practical use of the above mentioned adjusted tool, DRPs were detected and described and documented by the pharmacy student under the supervision of an attending clinical pharmacy specialist based in the hospital during medical rounds and were followed up with the review of patients' prescriptions and drug orders. In this regard, we used the latest edition for the online available version of UpTodate®, Lexicomp® and Micromedex® software to check the presence or absence of the indications for medications, their recommended dosage in the pediatric population, medication intervals, dose adjustments for renal and hepatic impairment (where appropriate) and the contraindications of drug usage, and drug interactions and to process other recorded details of the patients.

A professional focus group consisting of a professor of pharmacotherapy (AMS), a pediatric surgeon (MM), a pharmacy student (KJ), and the clinical pharmacy specialist whom the data were recorded under her supervision (ZA) verified and validated the probable nature of the DRP and its possible causes as well as the likely place of origination for it at the time of occurrence (if the problem has occurred before the patient's admission or during his/her hospitalization). In most of the cases, one of the team members (KJ) was attending the medical rounds and discussed the nominated DRP with them to have a better understanding of other possibilities for the nature and causes of DRPs. Alternatively, some few cases of the documented DRPs were reported by other health-care professionals (physicians and nurses) and patients or they companion. These reports were initially reviewed by the pharmacy student and if eligible and reliable (in case of patients self-reports) were then referred to the focus group for validation and classifications.

To harmonize the used medical and pharmaceutical terms, the Anatomical Therapeutic Chemical Classification System (ATC) recommended by World Health Organization[28] was used for classifying the drugs and the online version of the International Disease Classification[29] used for classifying the disease diagnosis. Furthermore, generic names of drugs, their ATC code and dosage, and how they were utilized were recorded in the identification process of DRPs.

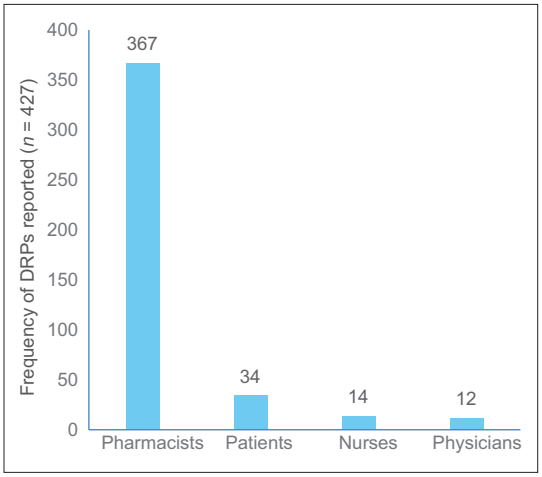
We used descriptive statistics (numbers, percentages, and means) to report the frequencies of each DRP using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).[30]

Results

A total of 250 patients were included in the study in which 201 patients (% 80.4) had at least one DRP with demographic characteristics, as presented in Table 1. We identified and documented 427 valid DRPs (averagely, 1.7 DRP per each studied patient), and 89.5% (n = 382) of DRPs occurred after their hospital admission and hospitalization. Three hundred and sixty-seven DRPs (85.9%) of the validated DRPs were observed, identified, and documented by the clinical pharmacist [Figure 1].

According to the classification of the studied patients through WHO-ICD10 system, the most common cause of hospitalization of the children in our study was related to respiratory diseases 16.8% (n = 42) [Supplement Table 1] (The Supplemental Tables are available Online in the Journal's Website) while the highest number of DRPs was identified in the PICU with a relative frequency of 21.3% (n = 91). In average, 65% of the total 201 patients with at least one DRP were hospitalized in the nonintensive care units, and the relative frequency of the occurrence of at least one DRP was to some extent higher in noncritically ill patients comparing to the studied patients who were hospitalized in the intensive care units, PICU, and NICUs (84 vs. 75%). Moreover, 58.7% (n = 118) of the studied patients with at least one DRP were male [Table 2].

The frequency distribution of identified DRPs in the intensive care units and nonintensive care wards has been presented in Table 2. The highest frequency of classified DRP types in our studied patients was related to the safety of treatment with 43.5% (n = 186) and secondarily to the effectiveness of treatment with 36.8% (n = 157).



1: Frequency of drug-related problems documented and reported by different health-care professionals

In this study, the number of prescribed drugs for the hospitalized pediatric patients was between one and five items in 52% of the cases (n = 130) and the rest of them (n = 120); the average number of drug items in each prescription was >5. Ninety percent of patients with a prescriptive drug number >10 had at least one DRP.

The most frequent subgroups of problems' classification were related to the potentially dangerous adverse events with 28.8% (n = 123) and then the nonoptimal effect of drug treatment 22.0% (n = 94) as well as untreated symptoms or indications 13.1% (n = 56). A summary of DRPs frequency in three main and ten subgroups is presented in Table 3.

According to the ATC classification system for drugs leading to DRPs, the highest frequency of anatomical groups of ATC (first-order) was related to systemic

1: Demographic data of the study patients in different wards and the frequency of documented drug-related

	n	*n*	*n*	*n*	*n*	*n*	*n*	*n*
Gender, *n* (%)								
Female	30 (41.6)	16 (42.1)	16 (34.0)	19 (52.7)	12 (37.5)	12 (48.0)	105 (42.0)	196 (45.9)
Male	42 (58.4)	22 (57.9)	31 (66.0)	17 (47.3)	20 (62.5)	13 (52.0)	145 (58.0)	231 (54.1)
Age, *n* (%)								
0-1 month	0 (0)	0 (0)	0 (0)	0 (0)	29 (90.6)	18 (72.0)	47 (18.8)	71 (16.6)
>1 month-≤2 years	26 (36.1)	24 (63.2)	19 (40.4)	23 (63.9)	3 (9.4)	7 (28.0)	102 (40.8)	202 (47.3)
>2-≤6 years	15 (20.8)	8 (21.0)	19 (40.4)	7 (19.4)	0 (0)	0 (0)	49 (19.6)	81 (19.0)
>6-≤12 years	26 (36.1)	5 (13.2)	8 (17.0)	4 (11.2)	0 (0)	0 (0)	43 (17.2)	54 (12.6)
>12-≤18 years	5 (7.0)	1 (2.6)	1 (2.2)	2 (5.5)	0 (0)	0 (0)	9 (3.6)	19 (4.4)

Ped1=Pediatric ward #1 (neurology, nephrology, immunology, asthma, and allergy), Ped2=Pediatric ward #2 (gastroenterology, cardiology, pulmonology, and endocrinology), Ped3=Pediatric ward #3 (infectious disease), NICU1=Neonatal intensive care unit #1, NICU2=Neonatal intensive care unit #2, PICU=Pediatric intensive care unit, DRP=Drug-related problem

2: Frequency of drug-related problems in the studied wards

	n	*n*	*n*	*n*	*n*	*n*	*n*
Number of DRPs, *n* (%)	85 (19.9)	86 (20.1)	85 (19.9)	91 (21.3)	44 (10.3)	36 (8.4)	427 (100)
Number of patients with DRPs, *n* (%)	55 (76.4)	34 (89.5)	41 (87.2)	30 (83.3)	24 (75.0)	17 (68.0)	201 (80.4)
Gender distribution, *n* (%)							
Female	22 (25.9)	13 (15.1)	16 (18.8)	15 (16.5)	9 (20.5)	8 (22.2)	83 (41.3)
Male	33 (38.8)	21 (24.4)	25 (29.4)	15 (16.5)	15 (34.1)	9 (25.0)	118 (58.7)
Nature of DRPs, *n* (%)							
Treatment effectiveness	15 (17.6)	39 (45.3)	30 (35.3)	37 (40.7)	19 (43.2)	17 (47.2)	157 (36.8)
Treatment safety	55 (64.7)	28 (32.6)	29 (34.1)	32 (35.2)	25 (56.8)	17 (47.2)	186 (43.5)
Other types	15 (17.6)	19 (22.1)	26 (30.6)	22 (24.2)	0 (0)	2 (5.6)	84 (19.7)

Ped1=Pediatric ward #1(neurology, nephrology, immunology, asthma and allergy), Ped2=Pediatric ward #2 (gastroenterology, cardiology, pulmonology, and endocrinology), Ped3=Pediatric ward #3 (infectious disease), NICU1=Neonatal intensive care unit #1, NICU2=Neonatal intensive care unit #2, PICU=Pediatric intensive care unit, DRPs=Drug-related problems

3: The most common problem types of drug-related problems classified according to the modified form of the Pharmaceutical Care Network of Europe classification system for drug-related problems version 8.01

Treatment effectiveness	No effect of drug treatment/therapy failure (P1.1)	7 (1.6)
	Effect of drug treatment not optimal (P1.2)	94 (22.0)
	Untreated symptoms or indication (P1.3)	56 (13.1)
	Total	157 (36.8)
Treatment safety	Adverse drug event (possibly) occurring (P2.1)	42 (9.8)
	Life-threatening side effect (P2.2)	3 (0.7)
	Nonlife-threatening side effect (P2.3)	18 (4.2)
	No clinical manifestation, but potentially dangerous (P2.4)	123 (28.8)
	Total	186 (43.5)
Other types of problems	Problem with the cost-effectiveness of the treatment (P3.1)	49 (11.5)
	Unnecessary drug treatment (P3.2)	28 (6.6)
	Unclear problem/complaint (P3.3)	7 (1.6)
	Total	84 (19.7)

PCNE (v. 8.01)=The Pharmaceutical Care Network of Europe classification system for DRP version 8.01, DRPs=Drug-related problems

antimicrobial medicines and nervous system drugs with 30.7% (n = 131), as well as medications related to the gastrointestinal tract and metabolism with 17.8% (n = 76) [Supplement Table 2]. Furthermore, it has been noted in Supplement Table 3 that the highest frequency of anatomical categories of ATC drugs causing DRP was related to systemic antimicrobial drugs in NICU1 and Ped3 wards (68.2% and 43.53%) and nervous system drugs in units of Ped1, Ped2, and PICU (61.18%, 29.1%, 25.27%). Furthermore, gastrointestinal and metabolism drugs causing DRP had the highest frequency in NICU2 (38.9%).

Causes for drug-related problem occurrence based on Pharmaceutical Care Netwok of Europe form (v. 8.01) classification system

In our study, the most frequent causes of DPR were drug dose selection 34.2% (n = 146), drug selection 25.5% (n = 109), miscellaneous causes 14.5% (n = 62), and finally, problems related to (inappropriate) pharmaceutical dosage forms of the prescribed drugs 13.6% (n = 58). Meanwhile, selecting a drug with a dose higher than the required amount had the highest frequency among drug dose selection reasons causing DPR 12.2% (n = 52). No drug treatment in spite of current indication had the highest frequency among drug selection reasons causing DPR 12.6% (n = 54). A summary of DPR causes, which is classified according to the modified PCNE form (v. 8.01), is presented in Table 4.

Considering the scope of the predefined tasks and privileges for the Imam Hossein's clinical pharmacy specialist, 98 interventions were done related to 427 valid identified DRPs (22.9%), in which 54% of them were at the drug prescriptive level (providing consultations to the attending physicians), and 59.2% (n = 58) of the proposed interventions were accepted by medical staff [Supplement Table 4].

Discussion

The incidence of DRP after hospital admission of patients is reported differently in different studies. In a survey conducted by Movva *et al*., 68.78% of patients with underlying cardiovascular disease admitted to general wards of a hospital were reported with at least one DRP during their hospital stay.[31] According to our findings, 80.4% of our randomly studied patients experienced at least one DRP during their hospital stay, which accentuates the importance of active attendance of clinical pharmacists in medical wards and critical care units, especially in the pediatric patients.

In the present study, 40.8% of our patients were in the age range of 1 month to 2 years, and the highest frequency of DRP (47.3%) was observed in the age range of 1 month to 2 years [Table 1]. Due to several reasons, children are more likely to be at probable risk of DRP compared with adults. Developmental stages and hepatic metabolism of drugs in the 1st year of life are one of these reasons. Moore *et al*. investigated reports of adverse drug events in the US Food and Drug Administration for 38 months and found that about 7,000 reports from approximately 500,000 reported cases were related to infants and children under the age of 2 years.[32]

In this study, the frequency of DRP in males and females was close with a negligible superiority in male patients. However, gender is not a significant risk factor for DRPs in pediatric patients due to special physiology and nondevelopmental hormonal systems and other physiological characteristics, which are quite the same.

In our study, about one-fifth of the patients with at least one valid DRP were from PICU. Furthermore, 89.5% of patients admitted to Ped2 ward (for endocrine, cardiac, pulmonary, and gastrointestinal diseases) experienced

4: The most frequently reported causes of drug-related problems in the studied patients, classified according to the modified form of the Pharmaceutical Care Network of Europe Classification system (v. 8.01)

			Frequency (%), (*n*
Drug selection	Inappropriate drug according to guidelines/formulary	C1.1	35 (8.2)
	Inappropriate drug (within guidelines but otherwise contraindicated)	C1.2	3 (0.7)
	No indication for a drug	C1.3	11 (2.6)
	Inappropriate combination of drug or drugs and herbal medication	C1.4	0
	Inappropriate duplication of a therapeutic group or active ingredient	C1.5	6 (1.4)
	No drug treatment in spite of existing indication	C1.6	54 (12.6)
	Total		109 (25.5)
Drugs' dosage forms	Inappropriate drug form (for this patient)	C2.1	58 (13.6)
	Total		58 (13.6)
Dose selection	Drug dose too low	C3.1	35 (8.2)
	Drug dose too high	C3.2	52 (12.2)
	Dosage regimen not frequent enough	C3.3	20 (4.7)
	Dosage regimen not frequent	C3.4	38 (8.9)
	Dose timing instruction wrong, unclear, or missing	C3.5	1 (0.2)
	Total		146 (34.2)
Treatment duration	Duration of treatment too short	C4.1	1 (0.2)
	Duration of treatment too long	C4.2	0
	Total		1 (0.2)
Dispensing	Prescribed drug not available	C5.1	7 (1.6)
	Necessary information not provided	C5.2	10 (2.3)
	Wrong drug/strength or dosage prescribing. Error transcription	C5.3	12 (2.8)
	Wrong drug or strength dispensed	C5.4	1 (0.2)
	Total		30 (7)
Drug use process	Inappropriate timing of administration and/or dosing interval	C6.1	4 (0.9)
	Drug underadministered	C6.2	0
	Drug overadministered	C6.3	9 (2.1)
	Drug not administered at all	C6.4	0
	wrong drug administered	C6.5	5 (1.2)
	Total		18 (4.2)
Patient-related	Patient uses/takes less drug than prescribed or does not take the drug at all	C7.1	2 (0.5)
	Patient uses/takes more drug than prescribed	C7.2	0
	Patient abuses drug (unregulated overuse)	C7.3	0
	Patient uses unnecessary drug	C7.4	0
	Patient takes food that interacts	C7.5	0
	Patient stores drug inappropriately	C7.6	0
	Inappropriate timing or dosing intervals	C7.7	1 (0.2)
	Patient administers/uses the drug in a wrong way	C7.8	0
	Patient unable to use drug/form as directed	C7.9	0
	Total		3 (0.7)
Others	No or inappropriate outcome monitoring	C8.1	11 (2.6)
	Other cause; specify	C8.2	3 (0.7)
	No obvious cause	C8.3	48 (11.2)
	Total		62 (14.5)

PCNE (v. 8.01)=The Pharmaceutical Care Network of Europe classification system for DRP version 8.01, DRPs=Drug-related problems

at least one DRP, which is close to the intensive care unit of PICU (83.3%). In a study conducted by Rashed *et al*. on patients under the age of 18 years who were admitted to medical wards and PICU and NICU units of 7 Hong Kong hospitals, the highest frequency of DRP for a time period of 3 months (58%) was reported from medical wards (i.e., nonintensive care units). However, about 25% of patients of both PICU and NICU units experienced at least one DRP, which were higher than medical units.[33] These results are consistent with the results of our study. Complicated medical status of the patients admitted to PICU and NICU, multiorgan failure in most of these patients which necessitates vital organs functioning and consuming more drugs

and potent as well as drugs with higher risks in terms of drug toxicity, drug interactions, and so on should be considered to determine the possible cause of increased DRP incidence. It seems necessary for medical staff such as physicians, pharmacists, and nurses to pay more attention to training and monitoring in terms of pharmacotherapy in patients admitted to these units.

According to the results obtained from the WHO-ICD10 classification system, the most common cause of hospitalization in this study was due to the respiratory system disease (16.8%), which can be justified by the high incidence of this type of illness in the pediatric population. Mansourian *et al*. conducted a study on respiratory system diseases leading to children's admissions and the level of air pollution in Isfahan as the second largest city in Iran.[34] Furthermore, the geographical location of the pediatric hospital may also affect an increase in the length of hospitalization of respiratory infections, and consequently increase in prescription and DRP occurrence.

In terms of the number of prescribed drugs in patients' orders, 52% of the studied patients had a prescriptive number of medications of 1–5, and the percentage of patients with at least one DRP was increased with the increase in the number of prescribed drugs, so that 90% of patients with the number of prescribed drugs more than 10 experienced at least one DRP. Increased potential errors of medical staff, increased risk of drug–drug interactions, and reduced patients' compliance with their medical orders are among the involved factors for the increased risk of DRPs in polypharmacy.

Keefer *et al*. reported a study to investigate the quality differences of medication errors reporting among physicians, nurses, pharmacists, and families and emphasized the need for training about reporting of drug errors.[35] The results of our study showed that pharmacists had played a significant role in finding and documented drug prescription problems with a report proportion of >80% of DRPs and indicate the necessity of further information and training to other health service providers including physicians and nurses.

According to the PCNE classification system in our study, the highest frequency of DRP was related to safety of treatment (43.5%), and the highest frequency in subgroups of this classification was linked to potentially dangerous adverse events (28.8%), no effect of drug treatment (22%), and untreated symptoms or indications (13.1%). In the study of Movva *et al*., the highest frequency of identified DRP has also related to no effect of drug treatment (20.4%).[31]

In our study, drug dose selection (34.2%) and drug-type selection (25.5%) and other causes such as monitoring (14.5%) were among the common types of cause for DRPs in children. It should be noted that in the present study, a specific reason was initially identified for each of the cases by the clinical pharmacist despite the possibility of several reasons for a DRP.

Lack of enough studies in the pediatric subpopulations, standardization of adult dosing based on the age (or body weight or any other demographic characteristics of pediatric patients) without validated evidence and lack of awareness about the impact these factors may have worsening effects on the unsafe usage of medication use in children. Furthermore, pharmacokinetic and pharmacodynamic differences in different age subgroups as well as selecting an appropriate dosage form of a drug with the least probable side effects along with the highest possible effectiveness make the problem even more complicated. Consequently, pharmacotherapeutic monitoring of drug therapy has particular importance in the pediatric population to prevent the complications due to the differences in absorption and distribution, metabolism, and drug elimination in pediatric subpopulations. In the study of Rashed *et al*., the highest rate of DRPs was reported about drug selection and dosing problem.[36]

Using the ATC classification system, the most commonly utilized drugs in NICU1 and Ped3 units were systemic antimicrobial drugs and in PICU and Ped1 units were nervous system drugs. Among antimicrobial drugs, β-lactam antimicrobial drugs (except for penicillin) had a significant share. In a study conducted by Modi *et al*., 63% of the reported 338 medication errors in a pediatric hospital were related to the usage of β-lactam antimicrobial drugs and 6% were related to both macrolide and glycopeptide group.[37] In pediatric clinical practice in Iran, infectious diseases of children are mostly diagnosis clinically, and empirical treatment is started before pathogen identification. Paying enough attention to identifying the responsible pathogens for the illness in bacterial infections in different age groups affects drug selection and may have further impacts on drug dose selection, dose intervals, and oral or injection usage in the pharmacotherapy infections in the pediatric population.

In our study, among the nervous system drugs, analgesic and antipyretic drugs, as well as antiepileptic drugs, had the highest frequency of utilization. In children who have not started to speak, it is hard for physicians, nurses, and their parents of children to understand or estimate if the pain remains and how much is its intensity. Hence, the drug therapy for pain may be continued and make the occurrence of DRPs more probable. Epilepsy also has many complications in terms of seizure recurrence risk, patient's age, the prognosis of the disease, and existing pharmaceutical formulations, which make it difficult

to prescribe and select appropriate drugs and dose for effective epileptic seizure control. Different classes of antiepileptic drugs have properties including effects on liver enzymes and various drug interactions and also special side effects such as skin rashes and visual effects, which require careful monitoring to prevent DRPs.

In our study, gastrointestinal drugs as well as drugs used in metabolic disorders had the highest percentage of DRP occurrence after systemic antimicrobial and nervous system drugs. Vitamins, including multivitamins and other essential vitamins, had a higher percentage. Hermanspann *et al*. reported a study on about 3,000 drug prescriptions in 1.5 years to investigate the incidence and severity of medication errors associated with parenteral nutrition in children and newborns admitted to intensive care units.[38] In a study conducted by Prot-Labarthe *et al*., systemic antibiotics and gastrointestinal drugs and metabolism were the most used drugs that resulted in an intervention.[39]

In our study, clinical pharmacist's intervention for DRPs was mostly performed at the prescribing level (54% out of the total 98 interventions), which also shows an acceptable level of contribution of clinical pharmacist in patient care and positive communication with attending physicians. A previously published similar report by Ganachari *et al*. also indicates the highest number of needed interventions in drug selection and dosing level.[40] In their study, the interventions taken at drug level had a low frequency, which indicates the necessity of providing more clinical pharmacists' privileges for proper and reasonable interventions in the pharmacotherapy of patients admitted in different units as well as the better level of cooperation of the medical staff.

We had a 59.2% rate of acceptance of the clinical pharmacist's proposed interventions by the medical staff which is more acceptable to previously published similar studies which are reported about 30%.[31,41] Clinical reasoning skills of clinical pharmacists and also active attendance in the clinical round as we did in our study may improve these rate.

We had some limitations in our study which include the limited duration of the study, the limited number of studied wards, difficulties in patients' follow-up, and limited access to some pediatric patients due to their critical medical status. It should be noted that our study has been conducted to identify and document DRPs in children admitted to Imam Hossein Children's Hospital, and its results cannot be generalized to other hospitals.

In this study, we have learned that in Imam Hossein Children's Hospital, the most commonly documented drugs related to DRP were systemic antimicrobial drugs, nervous system drugs, and the digestive system and metabolism drugs, which their frequency was higher in the medical wards in contrast to critical care units. Furthermore, the most common cause of DRPs was related to the safety of the treatment, especially high-risk ADRs which could be prevented by active intervention. Our study confirms the necessity for the active role of clinical pharmacists before, during, and after drug therapy in hospitalized pediatric patients for the safety and proper utilization of drugs in this vulnerable population.

Authors' Contribution

This research was a doctor of Pharmacy thesis project for Khatereh Jafarian, and she was involved in all aspects of drafting the research protocol, its implementation, and drafting the manuscript. Prof. Sabzghabaee proposed the idea and supervised the whole project and revised the manuscript. Dr. Memarzadeh and Dr. Allameh supervised KHJ on data gathering and its validation and revised the manuscript. Ali Saffaei and Payam Peymani analyzed the data and commented on the presentation of the results. All authors revised the manuscript and approved its final version.

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Conflicts of interest

There are no conflicts of interest.

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Supplement Table 1: Frequency of medical diagnosis in the studied patients according to International Statistical Classification of Disease and Related Health Problems the 10th revision 2016-World Health Organization

Disease and related health problems	Number of patients	Number of DRPs
Certain infectious and parasitic diseases (A00-B99)	12	26
Neoplasms (C00-D48)	3	4
The disease of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	1	1
Endocrine, nutritional, and metabolic diseases (E00-E90)	9	8
Diseases of the nervous system (G00-G99)	21	40
Diseases of the eye and adnexa (H00-H59)	2	4
Diseases of the ear and mastoid process (H60-H95)	3	3
Diseases of the circulatory system (I00-I99)	3	5
Diseases of the respiratory system (J00-J99)	42	78
Diseases of the digestive system (K00-K93)	16	22
Diseases of the skin and subcutaneous tissue (L00-L99)	9	17
Diseases of the musculoskeletal system and connective tissue (M00-M99)	16	31
Diseases of the genitourinary system (N00-N99)	13	24
Certain conditions originating in the perinatal period (P00-P96)	35	54
Congenital malformations, deformations, and chromosomal abnormalities (Q00-Q99)	12	23
Symptoms sings and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	16	38
Injury, poisoning and certain other consequences of external causes (S00-T98)	36	48
External causes of morbidity and mortality (V01-Y98)	1	1
Total	250	427

ICD-10=International Statistical Classification of Disease and Related Health Problems the 10th revision 2016-World Health Organization, DRPs=Drug-related problems

Supplement Table 2: The most frequently reported Anatomical groups and in the drug-related problems in present study

Anatomical groups	Therapeutic and pharmacological subgroups	Frequency (%)
Alimentary tract and metabolism	Drugs for acid-related disorders (A02)	24 (31.6)
	Antacids (A02A)	1
	Drug for peptic ulcer and gastroesophageal reflux disease (A02B)	23
	Antiemetics and antinauseants (A04)	1 (1.3)
	Antiemetics and antinauseants (A04A)	1
	Drugs for constipation (A06)	2 (2.6)
	Drugs for constipation (A06A)	2
	Vitamins (A11)	44 (57.9)
	Multivitamins, combinations (A11A)	24
	Vitamin A and D, including combinations of the two (A11C)	10
	Vitamin B-complex, including combinations (A11E)	7
	Ascorbic acid (Vitamin C), including combinations (A11G)	1
	Other plain vitamin preparations (A11H)	2
	Mineral supplements (A12)	3 (3.9)
	Calcium (A12A)	1
	Other mineral supplements (A12C)	2
	Other alimentary tract and metabolism products (A16)	2 (2.6)
	Other alimentary tract and metabolism products (A16A)	2
	Total	76 (17.8)
Blood and blood-forming organs	Antithrombotic agents (B01)	3 (6.5)
	Antithrombotic agents (B01A)	3
	Antihemorrhagics (B02)	1 (2.2)
	Vitamin K and other hemostatics (B02B)	1
	Antianemic preparations (B03)	3 (6.5)
	Iron preparations (B03A)	1

Contd...

Supplement Table 2: Contd...

Anatomical groups	Therapeutic and pharmacological subgroups	Frequency (%)
	Vitamin B12 and folic acid (B03B)	2
	Blood substitutes and perfusion solutions (B05)	39 (84.8)
	Blood and related products (B05A)	8
	IV solutions (B05B)	22
	IV solutions additives (B05X)	9
	Total	46 (10.8)
Cardiovascular system	Cardiac therapy (C01)	
	Cardiac glycosides (C01A)	1
	Cardiac stimulants exclude Cardiac glycosides (C01C)	2
	Other cardiac preparations b (C01E)	1
	Total	4 (0.9)
Systemic hormonal preparations exclude sex hormones and insulins	Pituitary and hypothalamic hormones and analogs (H01)	1 (6.3)
	Anterior pituitary lobe hormones and analogs (H01A)	1
	Corticosteroids for systemic use (H02)	13 (81.3)
	Corticosteroids for systemic use, plain (H02A)	13
	Thyroid therapy (H03)	2 (12.5)
	Thyroid preparations (H03A)	2
	Total	16 (3.7)
Anti-infectives for systemic use	Antibacterial for systemic use(J01)	111 (84/7)
	Tetracyclines (J01A)	1
	Beta-lactam antibacterials and penicillins(J01C)	15
	other beta-lactam antibacterials (J01D)	32
	Macrolides, lincosamids, and streptogramins (J01F)	17
	Aminoglycoside antibacterials (J01G)	25
	Other antibacterials (J01X)	21
	Antimycotics for systemic use (J02)	2 (1.5)
	Antimycotics for systemic use (J02A)	2
	Antivirals for systemic use (J05)	9 (6.9)
	Direct-acting antivirals (J05A)	9
	Immune sera and immunoglobulins (J06)	9 (6.9)
	Immune sera (J06A)	1
	Immunoglobulins (J06B)	8
	Total	131 (30.7)
Musculoskeletal system	Anti-inflammatory and antirheumatic product (M01)	2
	Anti-inflammatory and antirheumatic non-steroids (M01A)	2
	Total	2 (0.5)
Nervous system	Analgesics (N02)	82 (62.6)
	other analgesics and antipyretics (N02B)	82
	Antiepileptic (N03)	46 (35.1)
	Antiepileptic (N03A)	46
	Psycholeptics (N05)	3 (2.3)
	Anxiolytics (N05B)	1
	Hypnotics and sedatives (N05C)	2
	Total	131 (30.7)
Respiratory system	Drug for obstructive airway diseases (R03)	13 (81.3)
	Adrenergics and inhalants (R03A)	2
	Other drugs for obstructive airway diseases and inhalants (R03B)	8
	Other systemic drugs for obstructive airway diseases (R03D)	3
	Antihistamines for systemic use (R06)	3 (18.7)
	Antihistamines for systemic use (R06A)	3
	Total	16 (0.5)

Contd...

Supplement Table 2: Contd...

Anatomical groups	Therapeutic and pharmacological subgroups	Frequency (%)
Sensory organs	Ophthalmologicals (S01)	3 (75.0)
	Anti-infectives (S01A)	3
	Ophthalmological and otological preparations (S03)	1 (25.0)
	Anti-infectives (S03A)	1 (0.2)
	Total	4 (0.9)
Various	Contrast media (V08)	1
	X-ray contrast media, iodinated (V08)	1
	Total	1

IV=Intravenous

Supplement Table 3: The most frequently reported the Anatomical Therapeutic Chemical anatomical groups in each of the studied wards

Wards' name	ATC anatomical groups	Frequency (%)
NICU1	Alimentary tract and metabolism	7 (15.9)
	Blood and blood-forming organs	4 (9.1)
	Anti-infectives for systemic use	30 (68.2)
	Nervous system	1 (2.3)
	Respiratory system	2 (4.5)
	Total	44 (10.3)
NICU2	Alimentary tract and metabolism	14 (38.9)
	Blood and blood-forming organs	5 (13.9)
	Cardiovascular system	1 (2.8)
	Anti-infectives for systemic use	12 (33.3)
	Nervous system	3 (8.3)
	Sensory organs	1 (2.8)
	Total	36 (8.4)
Pediatric 1	Alimentary tract and metabolism	6 (7.06)
	Blood and blood-forming organs	3 (3.53)
	Cardiovascular system	1 (1.18)
	Systemic hormonal preparations, exclude sex hormones and insulins	2 (2.35)
	Anti-infectives for systemic use	19 (22.35)
	Nervous system	52 (61.18)
	Respiratory system	2 (2.35)
	Total	85 (19.9)
Pediatric 2	Alimentary tract and metabolism	23 (26.7)
	Blood and blood-forming organs	8 (9.3)
	Systemic hormonal preparations exclude sex hormones and insulins	6 (7)
	Anti-infectives for systemic use	14 (16.3)
	Musculoskeletal system	1 (1.2)
	Nervous system	25 (29.1)
	Respiratory system	8 (9.3)
	Various	1 (1.2)
	Total	86 (20.1)
Pediatric 3	Alimentary tract and metabolism	6 (7.06)
	Blood and blood-forming organs	6 (7.06)
	Systemic hormonal preparations exclude sex hormones and insulins	4 (4.71)
	Anti-infectives for systemic use	37 (43.53)
	Musculoskeletal system	1 (1.18)
	Nervous system	27 (31.76)
	Respiratory system	3 (3.53)
	Sensory organs	1 (1.18)
	Total	85 (19.9)
PICU	Alimentary tract and metabolism	20 (21.98)

Contd...

Supplement Table 3: Contd...

Wards' name	ATC anatomical groups	Frequency (%)
	Blood and blood-forming organs	20 (21.98)
	Cardiovascular system	2 (2.20)
	Systemic hormonal preparations exclude sex hormones and insulins	4 (4.40)
	Anti-infectives for systemic use	19 (20.88)
	Nervous system	23 (25.27)
	Respiratory system	1 (1.10)
	Sensory organs	2 (2.2)
	Total	91 (21.3)

NICU=Neonatal intensive care unit, ATC=Anatomical Therapeutic Chemical, PICU=Pediatric intensive care unit

Supplement Table 4: The most frequently reported interventions of the hospital's clinical pharmacist and the acceptance frequency of them according to the modified type of the Pharmaceutical Care Netwok of Europe classification (V8.01)

Clinical pharmacist's intervention issues	Main category/subcategory	Code number	Frequency (%)
The planned clinical pharmacist's interventions	No intervention	I 0.1	329 (77.05)
	At prescriber level		53 (12.41)
	Prescriber informed only	I 1.1	39
	Prescriber asked for information	I 1.2	0
	An intervention proposed to the prescriber	I 1.3	14
	An intervention discussed with the prescriber	I 1.4	0
	At patient level		3 (0.7)
	Patient (drug) counseling	I 2.1	0
	Written information provided (only)	I 2.2	0
	Patient referred to the prescriber	I 2.3	0
	Spoken to family member/caregiver	I 2.4	3
	At drug level		4 (0.94)
	Drug change to …	I 3.1	1
	Dosage changed to …	I 3.2	2
	Formulation changed to …	I 3.3	0
	Instructions for use changed to …	I 3.4	0
	Drug stopped	I 3.5	1
	New drug started	I 3.6	0
	Other intervention or activity		38 (8.9)
	Other intervention (specify)	I 4.1	0
	Side effect reported to authorities	I4.2	38
The frequency of acceptance for the clinical pharmacist's proposed interventions	Intervention accepted		58 (13.58)
	Intervention accepted and fully implemented	A1.1	10
	Intervention accepted, partially implemented	A1.2	0
	Intervention accepted but not implemented	A1.3	0
	Intervention accepted, implementation unknown	A1.4	48
	Intervention not accepted		0
	Intervention not accepted: Not feasible	A2.1	0
	Intervention not accepted: No agreement	A2.2	0
	Intervention not accepted: Other reason (specify)	A2.3	0
	Intervention not accepted: Unknown reason	A2.4	0
	Other		369 (86.42)
	An intervention proposed, acceptance unknown	A3.1	40
	Intervention not proposed	A3.2	329