RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

Pharmacotherapeutic follow-up and predictors factors of problems related to the use of medications in pediatric intensive care

Joyce Ferreira dos SANTOS[1], Renata de Macedo MOURA[1], Elaine de Andrade AZEVEDO[1]

[1]Fundação Hospitalar do Estado de Minas Gerais

Corresponding author: Santos JF, joyceferreirajfs@gmail.com

Submitted: 30-10-2021 Resubmitted: 12-03-2022 Accepted: 14-03-2022

Peer review: blind reviewer and Paulo Henrique Santos Andrade

Abstract

Objectives: To describe and analyze the results of the pharmacotherapeutic follow-up service for patients admitted to the Pediatric Intensive Care Unit- PICU of a public hospital in Minas Gerais. **Methods:** Cross-sectional study, with data collection and analysis of patients treated by the clinical pharmacy service, from June to November 2020. The criteria for selection were use of antimicrobials, mechanical ventilation, sedoanalgesia, vasoactive amines, intravenous corticosteroids, anticonvulsants, and participation in the lines of care: diabetes, sickle cell anemia, cystic fibrosis, and palliative care. Patients were monitored at wards, and the identification and classification of Problems Related to the Use of Medicines (PRM) followed the PharmacoterapyWorkup method, using institutional protocols and health databases: UpToDate®, and MICROMEDEX® 2.0 as reference. For the identified PRM, pharmaceutical interventions were proposed through direct verbal contact with the target professional. Clinical pharmacists monitored outcomes. The collected data were compiled in Microsoft Excel 2019 and analyzed in EpiInfo 7.2.4.0. **Results:** 283 PRM were identified, with a predominance of PRM 4 (underdose, 26,9%), followed by PRM 5 (adverse drug reaction, 18,7%). Antimicrobials (23,0%) and proton pump inhibitors (17,0%) were the main drugs involved in PRM. The use of more than nine drugs OR 3,7706 [2,0999-6,7704], longer than ten days hospital stay OR 10,8672 [5,5486-21,2839], and presence of more than two comorbidities OR 1,9091 [1,0882-3,3493] were associated with PRM occurrence. Sex, age, weight, prescribed MPP, and kidney/liver failure were not statistically significant. Among the 284 proposed interventions, the most frequent change was pharmacotherapy (81.3%), and the acceptability rate was 68,3%. Most of the identified PRM were resolved (68,9%). **Conclusion:** the expressive rate of resolution of PRM points to a relevant contribution of clinical pharmacists in improving the quality and safety of care in the PICU.

Keywords: pharmaceutical services; intensive care units, pediatric; medication errors.

Acompanhamento farmacoterapêutico e fatores preditores de problemas relacionados ao uso de medicamentos no cuidado intensivo pediátrico

Resumo

Objetivos: descrever e analisar os resultados do serviço de acompanhamento farmacoterapêutico de pacientes internados na Unidade de Terapia Intensiva Pediátrica- UTIP de um hospital público de Minas Gerais. **Métodos:** estudo transversal, com coleta e análise de dados dos pacientes atendidos pelo serviço de farmácia clínica, de junho a novembro de 2020. Os critérios para seleção eram: uso de antimicrobianos, ventilação mecânica, sedoanalgesia, aminas vasoativas, corticoides endovenosos, anticonvulsivantes, e participação nas linhas de cuidado: diabetes, anemia falciforme, fibrose cística e cuidados paliativos. Os pacientes eram acompanhados à beira leito, a identificação e classificação de Problemas Relacionados ao uso de Medicamentos (PRM) seguia o método PharmacoterapyWorkup, utilizando-se protocolos institucionais e bases de dados em saúde: UpToDate® e MICROMEDEX® 2.0, como referência. Para os PRM identificados, eram propostas intervenções farmacêuticas por meio de contato verbal direto com o profissional alvo e os desfechos eram acompanhados pelos farmacêuticos. Os dados coletados foram compilados no Microsoft Excel 2019, e analisados no EpiInfo 7.2.4.0. **Resultados:** foram identificados 283 PRM, com predominância do PRM 4 (subdose, 26,9%), seguido pelo PRM 5 (reação adversa a medicamento, 18,7%). Entre os principais medicamentos envolvidos, estavam os antimicrobianos (23,0%) e inibidores de bomba de prótons (17,0%). O uso de mais de nove medicamentos OR 3,7706 [2,0999-6,7704], o tempo de internação superior a dez dias OR 10,8672 [5,5486-21,2839], e a presença de mais de duas comorbidades OR 1,9091 [1,0882-3,3493] estiveram associadas à ocorrência de PRM. Sexo, idade, peso, MPP prescritos e insuficiência renal/hepática não foram estatisticamente significativos. Entre as 284 intervenções propostas, a mais frequente foi a alteração na farmacoterapia (81,3%) e a taxa de aceitabilidade foi de 68,3%. A maioria dos PRM identificados foram resolvidos (68,9%). **Conclusão:** a expressiva taxa de resolução de PRM aponta para uma relevante contribuição dos farmacêuticos clínicos na melhoria da qualidade e da segurança da assistência em UTIP.

Palavras-chave: assistência farmacêutica, unidade de terapia intensiva pediátrica, erros de medicação.

Introduction

Adverse events related to medication use are a relevant problem in health care and are more common during hospital admissions. Such occurrences can extend hospitalization times, cause deaths and even increase hospitalization costs.[1]

Some of these events arise from the so-called "Problems Related to Medication Use" (PRM) that were conceptualized by Cipolle, Strand and Morley[2] as "undesirable events experienced by the patient, or the risk of experimenting them, involving the medication and interfering with the process to achieve the desirable therapeutic goals".Children are more susceptible to PRM due to the changes in the maturity of their organs during childhood development. Added to this, it is necessary to consider that the lack of pharmaceutical presentations available in adequate dosages and concentrations for administration in this age group, the need to calculate individualized doses according to age, weight (mg/kg), body surface area (mg/m^2) and the patient's clinical condition, leave these patients more exposed to medication errors[3], whose potential harm is three times higher in children when compared to adults.[4] In the Pediatric Intensive Care Unit, these occurrences are seven times more frequent than in other sectors.[5]

In PICUs, PRM occur more frequently due to constant changes in the pharmacotherapy and to the higher number of medications prescribed, including Potentially Dangerous Medications (PDMs), which are those more likely to cause some harm to the patient if administered in an inadequate manner.[6,7] Studies published in 2015 and 2016 identified several PRM in PICUs, some of which were considered fatal. Some of the factors associated with the occurrence of PRM are the following: hospitalization time, age and need for mechanical ventilation.[7,8]

Given this complex scenario and the search for health promotion, effectiveness and safe medication use, the pharmacotherapy follow-up service, anchored in the theoretical framework of pharmaceutical care, has proved to be an effective strategy in the identification, prevention and resolution of PRM, even in pediatric intensive care.[7] In an integrative review published in 2020, with its guiding question being "Assessment on the importance of pharmaceutical care in PICUs", eight articles were selected, with only one study developed in Brazil. It was verified that, in collaboration with the multidisciplinary team, the pharmacist can reduce harms and contribute more safety and effectiveness to the patients' treatments.[9]These same findings were corroborated by another systematic review with meta-analysis published in 2020, which gathered 19 studies, with only one from Brazil.[10]

Also with regard to the improvement of the clinical outcomes generated by the pharmaceutical interventions, a narrative review published in 2018 that evaluated several clinical services provided by pharmacists in pediatric settings, evidenced considerable positive impacts on the care of the individuals monitored. Among the studies presented, the one by Haque, Hussain, Ibrahim *et al*, which evaluated the use of antimicrobials in the PICU, found a 64.0% decrease in the use of this drug class, with a reduction in the mortality rate from 16.2% to 15.2% after the start of the pharmaceutical services.[11]

Considering all the peculiarities of pediatric care, and also that the PICU is a high-complexity environment and, consequently, with greater susceptibility to medication errors, the current study aimed at describing medication use in the PICU of a hospital in Minas Gerais (Brazil), the main types of PRM and their predictive factors.

Methods

A cross-sectional study conducted in the Pediatric Urgency and Emergency and Rare Childhood Diseases sector of a reference hospital belonging to the Unified Health System (*Sistema Único de Saúde*, SUS), located in Belo Horizonte, Minas Gerais. The institution has 150 beds, of which 16 are for pediatric intensive care.

The Clinical Pharmacy service in the PICU, implemented in mid-2018, operated from Monday to Friday, and had a clinical/managerial pharmacist and a clinical pharmacy resident exclusive to the sector. The working hours devoted by the pharmacist and the resident to the clinical services were 4 and 7 hours/day, respectively. There was no follow-up in the night period, during the weekends and on holidays due to unavailability of pharmacists. The following criteria were used for eligibility of the patients: use of antimicrobials, mechanical ventilation, sedoanalgesia, vasoactive amines, intravenous corticosteroids or anticonvulsants, or inclusion in one of the following lines of care: diabetes, sickle cell anemia, cystic fibrosis and palliative care. Definition of these criteria took into account the findings of previous studies[7,8,12-14] that investigated predictive factors for PRM in PICUs. The lines of care were included because the hospital is a reference in the treatment of these diseases.

The service, characterized by the pharmacotherapy follow-up of patients, occurred predominantly at the bedside under responsibility of the pharmacist and/or resident, through multiprofessional clinical discussions that took place during the daily bed rounds. To support such discussions, the pharmacists evaluated the available developments in the medical records, the laboratory test results, the prescriptions of medications, the records about water balance with diverse information about physiological eliminations, and the Nursing notes on the administration of diets, liquids and medications.

Identification and classification of PRM followed what is proposed by the PharmacotherapyWorkup clinical method[2], using the UpToDate® and MICROMEDEX® 2.0 health databases as a reference, in addition to the institutional protocols, such as references for clinical guidelines and diverse information on medications. The PRM identified were resolved in direct verbal contact with the professional responsible for the solution (physician, nurse, ward pharmacist or nutritionist) and the outcomes of the interventions proposed were monitored. In the care transfer from the PICU to the hospitalization sector, whenever possible, a report was generated to guide the pharmacist responsible for the sector regarding care continuity. Initial recording of the information occurred in monitoring forms developed by the sector, with subsequent transcription of the main information to the electronic medical record, following a model adapted from that proposed by Ferreira, Azevedo, Falcão *et al*.[15]

In the current study, the data of the patients treated from June to November 2020, available in the service database, were collected and analyzed. When necessary, complementary data were sought directly in the patients' electronic medical charts. Data from patients who were discharged within 48 hours were excluded from the study, mainly due to the difficulty measuring the results of any interventions proposed by the pharmacists. Data of eligible patients for the service can be lost due to lack of coverage during holiday periods and to the pharmacists' absences.

The main outcomes evaluated in this research were as follows: 1) PRM resolution rate = Number of PRM solved/ Total number of PRM identified x 100; and 2) Acceptability rate corresponding to the pharmaceutical interventions = Number of pharmaceutical interventions accepted and implemented/Total number of pharmaceutical interventions performed x 100. The pharmaceutical interventions were classified according to the Ministry of Health's proposal.[16]

Other variables collected and analyzed were as follows: sociodemographic and clinical characteristics of the patients treated; profile of the pharmacotherapy prescribed, including potentially dangerous medications; profile of problems related to medication use; and professionals targeted by the intervention.

The data were compiled in Microsoft Excel, version 2019, and analyzed in EpiInfo, version 7.2.4.0, with a description of frequency, median and mean values. Additionally, possible associations were analyzed between PRM occurrence and the patients' gender, age and weight, number of comorbidities, presence of liver and/ or kidney failure, number of medications prescribed, number of PDMs prescribed and hospitalization time, by means of the chi-square test with a significance level of 0.05.

The current study was approved by the institution's Research Ethics Committee under opinion No. 3,009,345.

Results

Between June and November 2020, 321 patients were admitted to the PICU; among them, 200 were followed-up by the Clinical Pharmacy service (Figure 1), and therefore comprise the sample of this study. The majority was male (110, 55.0%) (Table 1). The patients' mean age and weight values corresponded to 50 months old (Standard Deviation: 6.3) and 17.4 kilograms (kg) (Standard Deviation: 5.3), respectively (Table 1). The mean hospitalization time in the PICU was 11 days.

These patients had a total of 668 comorbidities, with a mean of 2.8 per patient (Standard Deviation: 53.4), and most of them were related to infectious (176, 26.3%) and respiratory (117, 17.5%) diseases (Table 1). Only 9 (4.5%) children presented special conditions such as kidney and/or liver failure.

During the study period, a total of 14,602 medications were prescribed, with a mean of 10 per patient (Standard Deviation: 5.0). Among them, 3,043 (20.8%) were considered PDMs, with a mean of 2.3 per patient-day (Standard Deviation: 3.0). Among the most used are those classified according to the Institute for Safe Practices in the Use of Medications (*Instituto para Práticas Seguras no Uso de Medicamentos*, ISMP)[17] as intravenous, transdermal and oral opioid analgesics (1,061, 34.9%) and as moderately acting intravenous sedatives (551, 18.1%) (Table 1).

The clinical pharmacists identified a total of 283 PRM during the period, with predominance of PRM 4 - Low-dose (76, 26.9%), followed by PRM 5- Adverse reaction (53, 18.7%) and PRM 2- Need for additional medication (52, 18.4%). Among the main medications involved were those from the antimicrobial class (65, 23.0%) and proton pump inhibitors (48, 17.0%) (Table 2).

In an analysis stratified by the PRM category, it was observed that the classes most involved in the occurrence of PRM 4 were antimicrobials (24, 31.6%) and gastric protectors (14, 18.4%). For PRM 5, the main class was that of antimicrobials (12, 22.6%), followed by anticonvulsants (8, 15.0%) and sedoanalgesics (8, 15.0%). In turn, for PRM 2, the most involved classes where gastric protectors (18, 34.6%), electrolytes (5, 9.6%) and antimicrobials (5, 9.6%) (Table 2).

Figure 1. Flowchart corresponding to the inclusion of patients in the service.

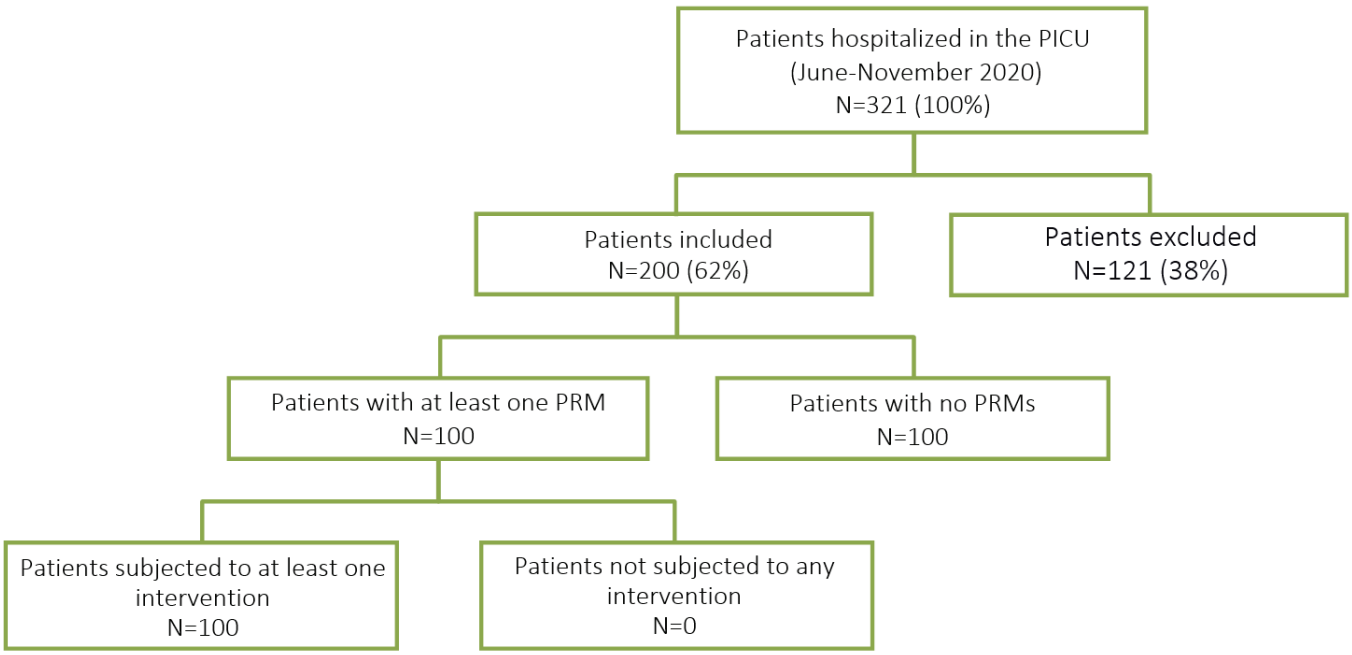

Table 1. Sociodemographic and clinical-assistance characteristics of the patients treated, and association with the occurrence of Problems Related to the use of Medications (PRMs).

Characteristics	Total	Odds Ratio [Confidence Interval][3] p-value
Sociodemographic		
Male gender[1] n (%)	110 (55.0)	0.6143 [0.3504 – 1.0769] p=0.0888
Age (in months old) Mean (SD)[2]	49.7 (61.3)	
≤ 12	112 (56.0)	1.1764 [0.6727 – 2.0571] p=0.5697
> 12	88 (44.0)	
Weight (in kg) Mean (SD)	17.4 (5.3)	
≤ 12	109 (54.5)	1.1286 [0.6467 – 1.9698] p=0.6708
> 12	91 (45.5)	
Clinical		
Comorbidities	668	
Mean per patient/hospitalization day (SD)	2.8 (53.4)	
≤ 2	104 (52.0)	1.9091 [1.0882 – 3.3493] p=0.0238
> 2	96 (48.0)	
Diseases n (%)		
Infectious	176 (26.3)	-
Respiratory	117 (17.5)	-
Neurological	103 (15.4)	-
Genetic	57 (8.5)	-
Metabolic	52 (7.8)	-
Cardiovascular	36 (5.4)	-
Renal	19 (2.8)	-
Neuromuscular	11 (1.6)	-
Dermatological	10 (1.5)	-
Hepatic	10 (1.5)	-
Others	77 (11.5)	-
Presence of kidney and/or liver failure n (%)	9 (4.5)	3.6882 [0.7469 – 18.2112] p=0.0889
Hospitalization		
Hospitalization time (days) Mean (SD)	11 (12.0)	
≤ 7	114 (57.0)	10.8672 [5.5486 – 21.2839] p<0.0001
> 7	86 (43.0)	
Medications prescribed	14,602	
Mean per patient/hospitalization day (SD)	10.1 (5.0)	
≤ 9	98 (49.0)	3.7706 [2.0999 – 6.7704] p<0.0001
> 9	102 (51.0)	
PDMs prescribed[4]	**N=3,043**	
Mean per patient/hospitalization day (SD)	2.3 (3.0)	
≤ 2	123 (61.5)	1.5952 [0.8984 – 2.8326] p=0.1108
> 2	77 (38.5)	
Types of PDMs prescribed n (%)		
Intravenous, transdermal or oral opioid analgesic	1,061 (34.9)	-
Moderate action intravenous sedatives	551 (18.1)	-
General, inhalational and intravenous anesthetics	352 (11.6)	-
Hypertonic glucose with a concentration equal to or greater than 20%	306 (10.1)	-
Neuromuscular blockers	217 (7.1)	-
Antithrombotics	133 (4.4)	-
Potassium chloride concentrate	135 (4.4)	-
Subcutaneous and intravenous insulin	76 (2.5)	-
Intravenous adrenergic agonists	75 (2.5)	-
Injectable potassium phosphate	34 (1.1)	-
Others	103 (3.4)	-

[1]Dichotomous variable for which results of only one category were presented.[2] SD = Standard Deviation.[3] Chi-square test, significance level of 0.05.[4] Classification of Potentially Dangerous Medications (PDMs) according to ISMP Brazil (2019)[17]

Table 2. Problems Related to the use of Medications (PRMs)

Information	All n (%)
Therapeutic classes involved	**N=283**
Antimicrobials	65 (23.0)
Proton pump inhibitors	48 (17.0)
Sedonalgesics	34 (12.0)
Anticonvulsants	28 (10.0)
Electrolytes	20 (7.0)
Laxatives	17 (6.0)
Vitamins	11 (4.0)
Diuretics	9 (3.2)
Corticosteroids	8 (2.8)
Diluents	6 (2.1)
Carminatives	5 (1.7)
Antipyretics	4 (1.4)
Glucose	4 (1.4)
Others	24 (8.4)
Types of PRMs[1] and relationship with the drug classes	**N=283**
PRM 1 - Unnecessary medication	51 (18.0)
Antimicrobial	10 (19.6)
Anticonvulsant	7 (13.7)
Sedonalgesic	7 (13.7)
Others	27 (53.0)
PRM 2 - Need for additional medication	52 (18.0)
Gastric protector	18 (34.6)
Antimicrobial	5 (9.6)
Electrolyte	5 (9.6)
Others	24 (46.2)
PRM 3 - Ineffective medication	13 (4.6)
Gastric protector	5 (38.4)
Antimicrobial	2 (15.3)
Sedonalgesic	2 (15.3)
Others	4 (31.0)
PRM 4 - Low dose	76 (27.0)
Antimicrobial	24 (31.6)
Gastric protector	14 (18.4)
Sedonalgesic	10 (13.1)
Others	28 (37.0)
PRM 5 - Adverse reaction	53 (19.0)
Antimicrobial	12 (22.6)
Anticonvulsant	8 (15.1)
Sedonalgesic	8 (15.1)
Others	25 (47.2)
PRM 6 - High dose	29 (10.0)
Anticonvulsant	10 (34.5)
Antimicrobial	8 (27.6)
Sedonalgesic	3 (10.3)
Others	8 (27.6)
PRM 7 - Non-adherence	9 (3.2)
Antimicrobial	4 (44.4)
Vitamin	2 (22.2)
Antipsychotic	1 (11.1)
Others	2 (22.2)
PRM resolution rate	**N=283**
Solved	195 (69.0)
Not solved	88 (31.0)

[1]Types of PRMs classified according to Cipolle, Strand and Morley (1988)[2]

In order to solve the PRM identified, pharmaceutical interventions were proposed for 100 (50.0%) of the 200 children monitored, and more than one intervention was performed for each of them. From a total of 284 interventions, the most frequent one was change in the therapy (231, 81.3%), followed by information and counseling (51, 18.0%). The acceptability rate by the team in relation to the interventions was 68.3%. As a result of the care process, it was observed that most of the PRM identified were solved (195, 68.9%) (Table 2).

In the bivariate analysis of the association with "PRM occurrence", through the chi-square test, only the "number of medications prescribed" (OR: 3.7706, CI: 2.0999-6-7704), "hospitalization time" (OR: 10.8672, CI: 5.5486-21.2839) and "comorbidities" (OR: 1.9091, CI: 1.0882-3.3493) variables were statistically significant, indicating that patients in use of more than 9 medications, and with more than 10 hospitalization days and more than 2 comorbidities presented higher chances of developing PRM.

Table 3. Pharmaceutical Interventions

Information	All n (%)
Type of intervention[1]	**N=284**
Change or suggested change in the therapy	231 (81.0)
Information and counseling	51 (18.0)
Provision of materials	1 (0.4)
Referral	1 (0.4)
Monitoring	-
Professional contacted	**N=298**
Physician	284 (95)
Nurse	11 (3.7)
Nutritionist	2 (0.7)
Nursing professional	1 (0.3)
Acceptability of the intervention	**N=284**
Yes	194 (68.0)
No	90(32.0)

[1]Types of interventions classified according to the Ministry of Health (2014)[16]

Discussion

Most of the hospitalizations observed in this study were caused by infectious (176, 26.3%), respiratory (117, 17.5%) and neurological diseases (103, 15.4%), a nosological profile that is similar to data found in other studies carried out in PICUs of Brazilian hospitals. The divergences observed can be explained by the profile of specialized care in areas such as Trauma and Oncology provided in some other hospitals.[18,19]

The mean number of medications prescribed per patient-day was 10, in line with that reported in a study conducted in a PICU from São Paulo in 2017.[20] This high number per patient characterizes polypharmacy, which is defined as simultaneous use of five or more medications.[20,21] It is one of the priority areas for implementing actions aimed at protecting the patients from harms related to medication use in the global Patient Safety challenge launched in 2019 by the World Health Organization (WHO).[22] The medications prescribed as "if necessary", "at medical discretion", "if there is pain" and "if there is nausea" contributed to this high number. This practice has been questioned, as it can generate dispensation and administration errors, in addition to transferring responsibilities regarding their use.[22,23]

It was also noticed that the mean of PDMs observed in this paper (2.3) is similar to the one found in the aforementioned research study (3.7). The literature indicates that the use of opioids, the PDMs most frequently observed in this study, and general anesthetics, can increase by 50.0% the occurrence of adverse events, as well as that each medication added to the pharmacotherapy can expand this rate by 20.0% to 25.0%.[24]

Regarding the identification of PRM, it was noted that the medications most frequently involved were the classes of antimicrobials, proton pump inhibitors and sedatives and analgesics. Other studies have also shown the association of these medications with PRM.[12-14]The significant use of these classes, justified by the patients' clinical characteristics (critical patients, with a high incidence of infectious cases, including sepsis, requiring frequent use of antimicrobials, and mechanical ventilation) can explain the higher frequency of PRM associated with them.

Although no data were found for pediatric patients, the study by Dall' Agnon in adults presented similar findings regarding the predictors for PRM occurrence, showing an association between "high number of medications" and "PRM occurrence".[25] Similarly, other authors noticed this same association with "hospitalization time" and "occurrence of kidney or liver failure".[7,26-28] In the current study, the divergent findings with statistical significance for this last characteristic can be related to the reduced number of patients with these conditions (9, 4.5%) in the sample studied. Despite this, an association trend in noticed, whose statistical significance would probably be confirmed with a larger sample. Thus, these characteristics represent important predictive factors for PRM occurrence in pediatric patients and should therefore be prioritized in the selection of patients for pharmacotherapy follow-up.

In this paper, half of the children (100, 50.0%) were subjected to pharmaceutical interventions during their care. These data are also similar to those found by Malfará, who reported that, of the 162 patients followed-up, 42.0% (68) were subjected to at least one intervention.[20]

The suggestion of change in the pharmacotherapy, the type of intervention most frequently observed in this study (231, 81.3%), is consistent with the most identified type of PRM: PRM 4 - Low dose (76, 26.9%). Similar proportions were obtained in the study by Janebro, Belém, Tomaz *et al*, who reported a 45.9% rate[29] of PRM classified in this same category. The higher frequency of this PRM can be explained by the rapid weight variation in pediatric patients and by losses related to the processes of preparation and administration of medications. The package insert of some antimicrobials, for example, informs about the possibility of volume expansion after reconstitution (from 2.0% to up to 15.0% of the final volume), which was not always considered for dose calculation at the prescription moment. In pediatric care, this small expansion can be clinically relevant and, for this reason, this variation needs to be taken into account when calculating the administration volume. Similarly, in the case of medications requiring controlled infusion to achieve adequate and constant serum levels, such as aminoglycosides, glycopeptides and anticonvulsants, loss due to volume retention in the infusion device is also considered relevant. In this specific case, the medical team and the clinical pharmacists of the sector recommended calculation of the Correction Factor, which considered the following for preparing the medication: the sum of the volume to be infused into the patient (medication and diluent) and the residual volume of the equipment, which was discarded at the end of the infusion, constituting an important field of action for pharmacists in the PICU.

The adherence rate of the team to the clinical pharmacist's interventions of 68.3% identified in this study is slightly lower than the one reported by Tripathi, Crabtree, Fryer *et al*, who followed-up the clinical interventions during an 11-year period in a hospital from Minnesota (79.8%). The authors reported that the number of interventions increased as the service developed and the clinical pharmacists' workload increased.[8] Other studies have also shown adherence rates from 57.5% to 98.0%.[11,12] It is believed that the non-acceptability rate (31.7%) may be related to the recent implementation of this service, to the constant flow of students with different knowledge/experience levels, and to the fact that the interventions involve decisions shared with several other medical subspecialties, due to the diseases' high degree of complexity.

It was measured only by the PRM resolution rate, due to the lack of records in the service database in relation to the outcomes considered more robust, such as achievement of clinical goals and/or the patients' pharmacotherapy clinical situation. One of the limitations of this type of measure is that it is not clear which the real benefits for the patient are in terms of a better clinical evolution of their health conditions. Nevertheless, the rate identified in this study (68.9%) can be considered significant, especially in the light of the countless difficulties faced by the service during the period, such as changes in the staff of pharmacists and in the workload available for the clinical assignments in the PICU, as well as vacations, leaves, changes in the resident's internship fields, weekends and holidays.

Thus, this study indicates a potential contribution of clinical pharmacists in pediatric intensive care, whose patients are exposed to a higher risk for the occurrence of PRM.[30] However, it is essential that the pharmacist's actions extrapolate the mere signaling to the medical team regarding the need for adjustment in pharmacotherapy, promoting care centered on each patient's individual needs, integrated with the other the health team professionals, and committed to monitoring the results of the interventions performed.

It is also noteworthy that the results obtained in this study may not be exclusively related to the pharmacist's intervention, but rather to a set of factors such as the care provided by the other members of the multiprofessional health team and the patient's predisposition for a better prognosis. Thus, studies with a more robust design, involving a comparison with the control group and in larger and more comprehensive samples, are necessary to minimize these potential biases. Nevertheless, these findings may be reproducible in hospitals with similar characteristics.

Conclusion

The current study described the profile of medication use in pediatric intensive care in a Brazilian hospital, as well as the main types of PRM that affected the patients in the hospital under study. It was observed that high number of medications, longer hospitalization time and higher number of comorbidities increased the risk for PRM occurrence, with these characteristics thus representing priority criteria for the patients' eligibility for pharmacotherapy follow-up in this scenario.

The expressive PRM resolution (68.9%) and intervention acceptability (68.3%) rates indicate a relevant contribution of the clinical pharmacists to the improvement of care quality in PICUs with the same characteristics. Despite that, more robust and comprehensive studies, with larger samples and more clinically significant outcomes, are necessary to confirm these findings.

Funding sources

Author Joyce Ferreira dos Santos received a grant from the Ministry of Health as a multi-professional resident in Urgency and Emergency in the period from 2019 to 2021.

Collaborators

JFS, EAA and RMM: they participated in conception of the research. JFS, EAA and RMM: data analysis and interpretation; responsibility for all the information included in the paper, ensuring accuracy and integrity of any of its parts. JFS and EAA: initial and final writing of the article. EAA and RMM: final review of the article; final approval of the version to be published.

Conflict of interest statement

The authors declare no conflicts of interest.

References

1. Sousa P, Uva AS, Serranheira F *et al*. Estimating the incidence of adverse events in Portuguese hospitals: a contribution to improving quality and patient safety. BMC Health Services Reserarch. 2014;14:311. DOI: 10.1186/1472-6963-14-311.
2. Cipolle RJ, Strand, LM, Morley PC. Pharmaceutical care practice, 1º edição. New York: McGraw-Hill, 1998.
3. World Health Organization.Promoting Safety of Medicines for Children.World Health Organization, 2007. Available in: http://www.who.int/medicines/publications/essentialmedicines/Promotionsafemedchildrens.pdf. Accessed on: 18th Oct 2020.
4. Kaushal R, Bates DW, Landrigan C *et al*. Medication errors and adverse drug events in pediatric in patients.JAMA. 2001;25;285(16):2114-20. DOI: 10.1001/jama.285.16.2114.
5. Wilson DG, McArtney RG, McArtney RJ *et al*. Medication errors in paediatric practice: insights from a continuous quality improvement approach. Eur J Pediatr. 1998;157(9):769-74. DOI: 10.1007/s004310050932.
6. Boyle D, O'Connell D, Platt Frederic W, *et al*. Disclosing errors and adverse events in the intensive care unit. CritCare Med. 2006; 34(5):1532-7. DOI: 10.1097/01.CCM.0000215109.91452.A3.
7. Okumura LM, Silva DM, Comarella L. Relação entre o usoseguro de medicamentos e Serviços de Farmácia Clínica em Unidades de Cuidados Intensivos Pediátricos. Rev. paul. pediatr. 2016; vol.34 no.4. DOI: 10.1016/j.rppede.2016.04.001.
8. Tripathi S, Crabtree H.M., Fryer K.R. *et al*. Impact of Clinical Pharmacist on the Pediatric Intensive Care Practice: An 11-Year Tertiary Center Experience. J PediatrPharmacolTher. 2015; 20(4):290-298. DOI: 10.5863 / 1551-6776-20.4.290.
9. Ferreira TTD, Rabelo JGD, Borges MCF *et al*. Cuidados farmacêuticos em unidade de terapia intensiva pediátrica: umarevisão integrativa. RCS. 2020. Vol.3, nº1.
10. Naseralallah LM, Hussain TA, Jaam M *et al*. Impacto f pharmacist interventions on medication errors in hospitalized pediatric patients: a systematic review and meta-analysis. Int J Clin Pharm. 2020; 42(4): 979.-994. DOI: 10.1007/s11096-020-01034-z.
11. Becker GC, Bueno D. Intervenções farmacêuticas em prescrições pediátricas: uma revisão narrativa. Clin Biomed Res. 2018; 38 (4). DOI: 10.4322/2357-9730.86404.
12. LaRochelle JM, Ghaly M, Creel AM. Clinical Pharmacy Faculty Interventions in a Pediatric Intensive Care Unit: na eight-month review. J PediatrPharmacolTher. 2012; Vol. 17: No. 3.DOI: 10.5863/1551-6776-17.3.263.
13. Fernández-Llamazares CM, Calleja-Hernandez MA, Manrique-Rodriguez S, *et al*. Impact of clinical pharmacist interventions in reducing paediatric prescribing errors. Arch Dis Child. 2012;97:564–568. DOI: 10.1136/archdischild-2011-301239.
14. LaRochelle JM, Jack K, Kitto BA, *et al*. Comparative analysis of clinical pharmacy interventions in a pediatric intensive care unit. Crit Care Shock.2018; 21:7-14.
15. Ferreira LC, Azevedo EA, Falcão MC, *et al*. Avaliação de um modelos emi estruturado pararegistro do acompanhamento farmacoterapêutico no âmbito hospitalar. Ver Bras Farm Hosp Serv Saúde. 2019;10(4):0370. DOI: 10.30968/rbfhss.2019.104.0370.
16. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Capacitação para implantação dos serviços de clínica farmacêutica. Brasília: Ministério da Saúde, 2014.
17. Instituto para Práticas Seguras no Uso de Medicamentos. Medicamentos Potencialmente Perigosos de uso hospitalar - Lista Atualizada 2019. Boletim ISMP Brasil. Available in: https://www.ismp-brasil.org/site/wp-content/uploads/2019/02/615-boletim-ismp-fevereiro-2019.pdf. Accessed on: 12thJuly 2021.
18. Mendonça JG, Guimarães MJB, Mendonça VG *et al*. Perfil das internações em Unidade de Terapia Intensiva Pediátrica do Sistema Único de Saúde no estado de Pernambuco, Brasil. Ciênc.Saúdecolet. 2019, 24 (3). DOI: 10.1590/1413-81232018243.02152017.
19. Lanetzki CS, Oliveira CAC, Bass LM *et al*. O perfil epidemiológico do Centro de Terapia Intensiva Pediátrico do Hospital Israelita Albert Einsten. Einsten. 2012; 10 (1): 16-21. DOI: 10.1590/S1679-45082012000100005.
20. Malfará MRM. Avaliação do impacto das intervenções do farmacêutico clínico na prevenção de problemas relacionados à farmacoterapia em um centro de terapia intensiva pediátrico de hospital de ensino. [Dissertação de Mestrado]. Faculdade de Medicina de RibeirãoPreto, São Paulo, 2017.
21. World Health Organization.Medication Safety in Polypharmacy.World Health Organization, 2019. Available in: https://apps.who.int/iris/handle/10665/325454. Accessed on:12th-July 2021.

22. Oliveira ST, Farias PO, Drummond BM, etal.Taxas de erro de prescrição e dispensação de um hospital públicoespecializadoemurgência e trauma. RMMG. 2018;28 (Supl 5): e-S280507. DOI: 10.5935/2238-3182.20180119.

23. Brasil. Agência Nacional de Vigilância Sanitária.Protocolo de segurança na prescrição, uso e administração de medicamentos. Available in: https://repositorio.observatoriodocuidado.org/handle/handle/1650. Accessed on: 29th Oct 2021.

24. Smyth RL, Peak M, Turner MA *et al*. ADRIC: Adverse Drug Reactions In Children – a programme of research using mixed methods. NIHR Journals Library.2014, NBK262747. DOI: 10.3310/pgfar02030.

25. Dall'Agnon RSA. Identificação e quantificação dos problemas-relacionados com medicamentos em pacientes que buscam atendimento no serviço de emergência no HCPA [Dissertação de Mestrado]. UFRGS, Porto Alegre, 2004.

26. Triller DM, Clause SL, Briceland LL *et al*. Resolution of drug-related problems in home care patients through a pharmacy referral service. Am J Health Syst Pharm. 2003; 60(9):905-10. DOI: 10.1093/ajhp/60.9.905.

27. Marquito AB, Pinheiro HS, Fernandes NMS *et al*. Pharmacotherapy assessment in chronic kidney disease: validation of the PAIR instrument for use in Brazil. J Bras Nefrol. 2020; 42(4): 400-12. DOI: 10.1590/2175-8239-JBN-2019-0205.

28. Sugget E, Marriott J. Risk factors associated with the requirement for pharmaceutical intervention in the hospital setting: a systematic review of the literature. Drugs Real World Outcomes. 2016; 3(3): 241-263. DOI: 10.1007/s40801-016-0083-4.

29. Janebro DI, Belém LF, Tomaz ACA *et al*. Problemas Relacionados aos Medicamentos (PRM's) em Pacientes Pediátricos de um Hospital no Município de Campina Grande, Paraíba, Brasil. Lat. Am. J. Pharm. 2008; 27 (5): 681-7.

30. Instituto para Práticas Seguras no Uso de Medicamentos. Desafio global de segurança do paciente medicação sem danos. Boletim ISMP Brasil. Available in: https://www.ismp-brasil.org/site/wp-content/uploads/2018/02/ISMP_Brasil_Desafio_Global.pdf. Accessed on: 12thJuly 2021.