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RESEARCH ARTICLE

Impact of medication therapy management on pharmacotherapy safety in an intensive care unit

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Abstract

Background Drug-related problems are mostly preventable or predictable circumstances that may impact on health outcomes. Clinical pharmacy activities such as medication therapy management can identify and solve these problems, with potential to improve medication safety and effectiveness. *Objective* To evaluate ability of medication therapy management service to detect drug-related problems and prevent adverse drug events. This study also aimed to assess the risk factors for drugrelated problem occurrence. *Setting* Medical intensive care unit of a public tertiary hospital in Brazil. *Methods* Patients were evaluated by a clinical pharmacist, who provided medication therapy management service. Detected drug-related problems were categorized according to the Pharmaceutical Care Network Europe methodology and analyzed in multinomial regression to identify risk factors. *Main outcome measure* Potential risk factors for drug-related problem occurrence. *Results* The proposed medication therapy management service allowed detection of 170 drug-related problems that had potential to reach patients causing harm and other 50 unavoidable adverse events. Drug-related problems identified were more often associated with antibacterial use, caused by improper combinations or inadequate drug dosage. These problems required interventions that were accepted by the multidisciplinary team, resulting in more than 85% adherence and total problem solving. Main risk factors identified were previous diagnosis of kidney injury (OR = 8.38), use of midazolam (OR = 7.96), furosemide (OR = 5.87) and vancomycin (OR = 4.82). *Conclusion* Medication therapy management proved to be an effective method not only for drug-related problem detection, but also for adverse drug event prevention, contributing to improve patient safety.

Keywords Adverse drug events · Brazil · Clinical pharmacists · Drug-related problems · Medication therapy management · PCNE DRP-classification

Impacts on practice

- Medication therapy management can accomplish high rates of total drug-related problem solving, and detect and prevent adverse drug events.
- Previous diagnosis of kidney injury or use of certain medicines such as midazolam, furosemide and vancomycin may be important factors associated to drug-related problem occurrence at intensive care units.
- Drug-drug interactions and overdosing were major causes of drug-related problems as well as adverse drug events in an intensive care unit of a developing country.

Introduction

Inappropriate use of drugs may be associated with admission or prolonged hospital stay, reduced quality of life, increased morbimortality and rising healthcare costs [1, 2]. Although health care professionals are concerned about patient safety, unwanted harm inevitably occur, especially in complex settings such as intensive care units (ICUs). Due to the severity of their diseases, organic dysfunctions and polypharmacy, critical patients constitute a vulnerable group for the occurrence of drug-related problems (DRPs) [3, 4].

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DRP is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [5]. Most DRPs are predictable and potentially preventable, and their frequency can be reduced by optimizing pharmacotherapy. Nevertheless, the frequency of errors involving drugs in intensive care settings can reach values ranging from 1.2 to 947 per 1000 patient-days, with a median of studies citing 105.9 per 1000 patient-days [6–8].

One way to improve medication safety and its effectiveness consists of inserting the clinical pharmacist into the care team. By performing clinical activities, such as a medication review or medication therapy management (MTM), the pharmacist can identify and solve DRPs, intercepting them before they reach the patient and cause harm and preventing the occurrence of adverse drug events (ADEs) [9, 10]. The role of the clinical pharmacist in the intensive care environment has been recognized to be an important factor for improving the quality of provided care, with positive outcomes on cost, mortality and length of stay [11]. Several authors have shown the positive impact of clinical pharmaceutical services in ICUs, as presented by Calabrese [12], who found a 3.3% reduction in medication errors, along with other studies that found a prevention of 25% of inadequate dosages, reduction of ADE by 66% and consequent decrease of healthcare costs [11–14].

Aim of study

The aim of this study was to use MTM as a tool to identify DRPs, classify and assess risk factors associated with DRP occurrence in a Brazilian Midwest ICU and evaluate this clinical service's capacity to identify ADEs.

Ethics approval

The Hospital Alberto Rassi Ethics Committee on Research approved this study (report number 1,177,803). All procedures were in accordance with the ethical standards of the national research committee, with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. If the invited patient was vulnerable or had reduced decision-making abilities, the consent was obtained from his legal responsible guardian. If the patient or their responsible guardian refused to provide consent, the same standard of care was provided, but without data collection. However, no individuals refused to join this study.

Method

This is an analytical, interventional study conducted from September 2015 to April 2016 in a medical ICU of a tertiary public hospital in the Brazilian Midwest. This 229-bed hospital has 40 ICU beds, which are divided into three medical wards and one surgical ward, and they admit approximately 1100 patients per year, transferred from hospital wards or external units that are part of the national public health system, mainly from the Midwest, North and Northeast regions of the country.

Patients eligible for this study were older than 18 years, with lengths of stay of more than 24 h. Patients admitted to the ICU for surgical recovery were excluded due to the existence of a specific ward for this purpose and due to their clinical/epidemiological differences. This study was conducted on a non-probabilistic sample of 162 participants.

The pharmaceutical clinical service was structured in 2013 (2 years before the study) and consisted of two experienced and trained ICU clinical pharmacists working daily. This service provided MTM, which relates the patient's clinical characteristics, evaluates the physician's orders and provides discussion in multidisciplinary rounds. This service method consists of a problem-oriented approach, sequentially consisting of the following: (1) collecting information and organizing patient data, health problems and clinical and medication histories; (2) identifying DRPs and their risk factors; (3) developing a therapeutic plan with the care team, setting therapeutic goals and providing interventions for the problems identified; and (4) performing individual follow-up of the proposed goals and pharmacotherapy achievements. In case of detecting any DRPs, interventions were proposed to avoid or minimize harm. Interventions consisted of contact with assisting staff (discussion, technical support and instructions provided), recording the identified DRP and staff adherence on the medical chart.

The clinical pharmacist team collected the data, and several training sessions were performed to reduce variability. Data were obtained from electronic medical records, discussions in multidisciplinary rounds, direct observation/anamnesis and using the reference sources UpToDate® (Wolters Kluwer Health Inc., 2016) and Micromedex® Solutions (Truven Health Analytics Inc., 2016) as tools to support evidence-based clinical decision-making. Information regarding proposed interventions was taken from the electronic medical records in the section for pharmacist progress notes.

After data collection, suspected DRPs were presented to a multidisciplinary team consisting of a nurse, a pharmacist and a physician. Scheduled meetings sought to discuss

the collected data and to reach consensus on DRP confirmation and classification. If there were divergent interpretations, medical records were reviewed by the team until inter-rater agreement was achieved. Each possible DRP detected was intensively evaluated by the multidisciplinary team regarding the temporal connection with the medicine use, properties of the suspected drug and the patient's clinical condition. The Pharmaceutical Care Network Europe (PCNE) Classification for Drug related problems v.7.0 [5] was used to classify DRPs according to type of problem, cause, planned intervention, team adherence to proposed intervention and outcome.

The following variables were considered to characterize the sample: age, gender, length of stay, cause of ICU admission, primary diagnosis and comorbidities, number of drugs used during ICU stay and the prognostic scores *Simplified Acute Physiology Score* (SAPS3) [15, 16] and *Sequential Organ Failure Assessment* (SOFA) [17], obtained considering parameters at ICU admission.

Data were recorded in a database using EPI Info® v.7.1 (Centers for Disease Control and Prevention, 2015). The normal distribution was verified by the Kolmogorov–Smirnov test, and continuous variables were analyzed using the Student T test. Categorical variables were analyzed using Pearson's Chi-square test. Risk factors for predicting DRP occurrence were assessed on multinomial logistic regression. The variables for this regression were selected by backward elimination from those factors that did not meet $p < 0.2$. All statistical tests were performed using IBM® SPSS® Statistics v. 22 (IBM Corp., 2015) and were considered significant if $p < 0.05$.

Results

During the data collection period, 162 participants were enrolled in the study, corresponding to 1948 patient-days. ICU admissions were mainly motivated by pneumonia (18.52%), respiratory failure (8.02%) and heart failure (6.27%). Longer length of stay, greater variety of drugs used and worse organic dysfunction levels at ICU admission (according to SOFA score) were verified for those cases in which DRPs were detected. Table 1 describes characteristics of the studied population, stratified by DRP occurrence.

There were 220 incidents that had the potential to cause negative pharmacotherapy outcomes or that, in fact, interfered with a patient's treatment. At least 1 DRP was detected during the evaluation of 113 participants, reaching the maximum of 7 detected DRPs during the ICU stay of 1 subject. As shown in Table 2, most DRPs consisted of risk of causing adverse events (68.64%)—these 151 cases included the 50 events in which any harm had already reached the patient (50 ADEs, as shown in Table 3); in the other 101 cases, a potential adverse event was intercepted before causing any harm.

Table 1 Epidemiological characteristics, prognostic scores and causes of admissions to intensive care unit of a public tertiary public hospital in the Brazilian Midwest

	Total	No DRP	Experienced DRP	*p*
Elegible patients	162	49	113	–
Gender				
Male (%)	95 (58.64%)	28 (57.14%)	67 (59.29%)	0.799*
Female (%)	67 (41.36%)	21 (42.86%)	46 (40.71%)	
Age	66.12 ± 17.76	69.22 ± 17.66	64.77 ± 17.71	0.143**
Length of stay, days	12.02 ± 11.48	6.57 ± 4.77	14.16 ± 12.05	< 0.001**
SAPS3	64.36 ± 18.20	60.76 ± 21.25	65.92 ± 16.56	0.134**
SOFA at admission	6.24 ± 4.46	4.86 ± 3.93	6.85 ± 4.56	0.006**
Admission causes—ICD10				
J00–J99 Diseases of the respiratory system	53 (32.72%)	13 (26.53%)	42 (37.17%)	
I00–I99 Diseases of the circulatory system	31 (19.14%)	8 (16.33%)	23 (20.35%)	
N00–N99 Diseases of the genitourinary system	24 (14.81%)	9 (18.37%)	16 (14.16%)	0.294*
K00–K93 Diseases of the digestive system	18 (11.11%)	4 (8.16%)	14 (12.39%)	
A01–B99 Certain infectious and parasitic diseases	10 (6.17%)	5 (10.20%)	5 (4.42%)	
Other ICD-10 codes	26 (16.05%)	10 (20.41%)	13 (11.50%)	
Drugs used during ICU stay	16.74 ± 7.72	11.63 ± 3.55	18.96 ± 7.99	< 0.001**

SAPS3, Simplified Acute Physiology Score [15, 16]; SOFA, Sequential Organ Failure Assessment [17]; ICD10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision

*Pearson's Chi-square test for independence

**Student T test for independent variables

Table 2 Classification of drug-related problems identified in the intensive care unit of a tertiary public hospital in the Brazilian Midwest according to Pharmaceutical Care Network Europe Foundation—PCNE Classification for drug related problems, v. 7.0 [5]

Drug-related problems detected	220
Patients experiencing DRP (%)	113 (69.75%)
Cumulative incidence (DRP/patient)	1.36
Incidence density rate (DRP/1000 patient-days)	112.94
Potential or manifest problems	
P2.1 Adverse drug event occurring	151 (68.64%)
P1.2 Effect of drug treatment not optimal	38 (17.27%)
P1.3 Unnecessary drug-treatment	16 (7.27%)
P1.4 Untreated indication	10 (4.55%)
Other	5 (2.27%)
DRP causes	
C1.4[a] Inappropriate combination of drugs, or drugs and food	89 (40.45%)
Drug-drug interactions	61 (27.73%)
Drug-food interactions	8 (3.64%)
Intravenous admixture incompatibility	20 (9.09%)
C3.2 Drug dose too high	29 (13.18%)
C1.2 Inappropriate drug (within guidelines but otherwise contra-indicated)	20 (9.09%)
C1.6 Indication for drug-treatment not noticed	14 (6.36%)
C1.5 Inappropriate duplication of therapeutic group or active ingredient	10 (4.55%)
C6.1 Inappropriate timing of administration and/or dosing intervals	10 (4.55%)
Other	48 (21.82%)
Planned interventions at prescriber level	
I1.3 Intervention proposed to prescriber	172 (78.18%)
I1.1 Prescriber informed only	47 (21.36%)
I1.2 Prescriber asked for information	1 (0.45%)
Planned interventions at drug level	
I3.2 Dosage changed	53 (24.09%)
I3.4 Instructions for use changed	41 (18.64%)
I3.5 Drug stopped	40 (18.18%)
I3.1 Drug changed	36 (16.36%)
I3.6 New drug started	24 (10.91%)
Other	26 (11.82%)
Acceptance of the intervention proposals	
A1.1 Intervention accepted and fully implemented	188 (85.45%)
A1.3 Intervention accepted but not implemented	13 (5.91%)
A2.2 Intervention not accepted: no agreement	9 (4.09%)
A2.1 Intervention not accepted: not feasible	8 (3.64%)
A1.2 Intervention accepted, partially implemented	2 (0.91%)
Outcome of intervention	
O1.0 Problem totally solved	189 (85.91%)
O3.2 Problem not solved, lack of cooperation of prescriber	20 (9.09%)
O2.0 Problem partially solved	6 (2.73%)
O3.4 No need or possibility to solve problem	5 (2.27%)

[a]There is no stratification for the item "C1.4 Inappropriate combination of drugs, or drugs and food" in the original PCNE classification. In this study the DRP cause C1.4 was categorized into (1) Drug-drug interactions; (2) Drug-food interactions; (3) Intravenous admixture incompatibility

The main causes of DRPs were related to drug interactions (27.73%), inadequate dose selection (13.18%) and inappropriate therapeutic agent (9.09%). These identified DRPs led to interventions proposed to prescribers in 78.18% of the cases, suggesting changes in prescribed dose (24.09%), new instructions for medication use (18.64%) and drug discontinuation (18,18%). These interventions were accepted by the multidisciplinary team in 92.27% of the cases and were completely implemented in 85.45%, promoting total resolution of 85.91% DRPs.

Table 3 Drugs causing adverse events in an intensive care unit in the Brazilian Midwest: classification according to Pharmaceutical Care Network Europe Foundation—PCNE Classification for drug related problems, v. 7.0 [5]

Patients experiencing adverse drug events (%)	42 (25.93%)
Cumulative incidence (ADE/patient)	0.31
Incidence density rate (ADE/1000 patient-days)	25.67
Adverse drug events detected	50
Hemodynamic instability or cardiac arrhythmias	10 (20.00%)
Electrolyte disorder (K^+, Na^+)	8 (16.00%)
Hypoglycemia e hyperglycemia	8 (16.00%)
Nefrotoxicity or kidney injury	6 (12.00%)
Bleeding	5 (10.00%)
Other (diarrhea, rash, vomiting, oversedation, seizure, tremor, precipitate formation in venous access device—causing thromboembolism)	18 (36.00%)
Drugs causing adverse events	63[a]
Insulin regular	8 (12.70%)
Furosemide	3 (4.76%)
Amikacin	3 (4.76%)
Vancomycin	3 (4.76%)
Clarithromycin	2 (3.17%)
Other drugs	44 (69.84%)
Problems observed	
P2.1 Adverse drug event occurring	43 (86.00%)
P1.2 Effect of drug treatment not optimal	4 (8.00%)
P1.4 Untreated indication	3 (6.00%)
DRP causes	
C1.4[b] Inappropriate combination of drugs, or drugs and food	13 (26.00%)
Drug-drug interactions	10 (20.00%)
Drug-food interactions	2 (4.00%)
Intravenous admixture incompatibility	1 (2.00%)
C3.2 Drug dose too high	11 (22.00%)
C1.8 Synergistic/preventive drug required and not given	7 (14.00%)
C1.6 Indication for drug-treatment not noticed	4 (8.00%)
C8.1 No or inappropriate outcome monitoring (incl. TDM)	4 (8.00%)
Other	11 (22.00%)
Planned interventions at prescriber level	
I1.3 Intervention proposed to prescriber	47 (94.00%)
I1.1 Prescriber informed only	3 (6.00%)
Planned interventions at drug level	
I3.2 Dosage changed	14 (28.00%)
I3.6 New drug started	13 (26.00%)
I3.5 Drug stopped	12 (24.00%)
Other	11 (22.00%)
Acceptance of the Intervention proposals	
A1.1 Intervention accepted and fully implemented	46 (92.00%)
A1.3 Intervention accepted but not implemented	3 (6.00%)
A2.1 Intervention not accepted: not feasible	1 (2.00%)
Outcome of intervention	
O1.0 Problem totally solved	43 (86.00%)
O2.0 Problem partially solved	4 (8.00%)
O3.2 Problem not solved, lack of cooperation of prescriber	3 (6.00%)

[a]The number of drugs is higher than identified drug-related problems because some DRPs can be assigned to more than one drug (such as drug–drug interactions, intravenous admixture incompatibility)

[b]There is no stratification for the item "C1.4 Inappropriate combination of drugs, or drugs and food" in the original PCNE classification. In this study the DRP cause C1.4 was categorized into (1) Drug-drug interactions; (2) Drug-food interactions; (3) Intravenous admixture incompatibility

The DRPs characterized were related to 312 drugs, consisting of 74 different pharmaceutical products. The number of drugs is greater than the 220 DRPs detected because in some cases, each problem may be related to more than one drug, such as in drug interactions. The main pharmacological groups associated with DRPs were systemic antibacterials (22.16%), agents with therapeutic targets in the cardiovascular system (9.29%) and antithrombotics (8.33%). Frequent risks related to these groups of drugs included changes in blood pressure (12.27%), thromboembolic events (10.45%), nephrotoxicity (9.55%) and unnecessarily increased treatment costs (9.09%). Table 4 describes the drugs related to DRPs and the risks associated with these agents.

Logistic regression for DRP occurrence prediction allowed the explanation of 76.8% of these cases ($p < 0.001$), with 92.04% sensitivity and 85.71% specificity; i.e., 90.12%

Table 4 Potential or manifest drug-related problems and their main causers in the intensive care unit of a public tertiary public hospital in the Brazilian Midwest

	n = 312[a]
Omeprazol	17 (5.45%)
Lower cost alternative available	10
Gastritis (therapy failure)	4
Other	3
Piperacillin + tazobactam	16 (5.13%)
Color change/haze formation in venous access device	7
Therapy failure/antimicrobial resistance	5
Other	4
Insulin regular	16 (5.13%)
Hypoglycemia	12
Hyperglycemia (drug dose too low)	3
Color change/haze formation in venous access device	1
Furosemide	13 (4.17%)
Hypokalemia	4
Nefrotoxicity or kidney injury	3
Other	6
Midazolam	12 (3.85%)
Color change/haze formation in venous access device	9
Oversedation	2
Seizure (interaction with anticonvulsants)	1
Clarithromycin	12 (3.85%)
Cardiac arrhythmias (QT interval prolongation)	5
Oversedation (interaction with sedatives)	4
Other	3
Vancomycin	11 (3.52%)
Nefrotoxicity or kidney injury	8
Rash	3
Fentanyl	11 (3.52%)
Oversedation	9
Color change/haze formation in venous access device	2
Enoxaparin	11 (3.52%)
Bleeding	5
Lower cost alternative available	4
Thrombosis (drug dose too low)	2
Amiodarone, phenytoin, morphine	9 (2.88%)
Ranitidine	7 (2.24%)
Anlodipine, dobutamine, meropenem, norepinephrine, warfarin	6 (1.92%)
Amykacin, fluconazole, heparin, lactulose	5 (1.60%)
Other drugs	109 (34.94%)

[a]The number of drugs is higher than identified drug-related problems because some DRPs can be assigned to more than one drug (such as drug–drug interactions, intravenous admixture incompatibility)

Table 5 Multinomial logistic regression for predicting drug-related problems in the intensive care unit of a tertiary public hospital in the Brazilian Midwest

Variable	β Coefficient	OR (IC 95%)	*p*
Length of stay	0.09	1.09 (0.93–1.29)	0.286
SAPS3	0.04	1.04 (0.99–1.10)	0.100
Number of drugs	0.31	1.37 (1.10–1.70)	0.005
Previous diagnosis of kidney failure	2.13	8.38 (1.27–55.13)	0.027
Use of diuretics	1.77	5.87 (1.51–22.70)	0.010
Use of vancomycin	1.57	4.82 (1.09–21.45)	0.039
Use of midazolam	2.07	7.96 (1.35–46.84)	0.022

R^2 Nagelkerke 0.768

accuracy in predicting the occurrence or correctly determining the absence of DRPs in an ICU. Previous diagnosis of kidney failure and use of midazolam during ICU stay were associated with increased odds of experiencing a DRP (*ORs* = 8.38 and 7.96, respectively), as described in Table 5.

MTM allowed the detection of unpreventable 50 ADEs. Even if the DRP was not intercepted before reaching the patient, this clinical pharmacy service enabled ADE identification and intervention by the healthcare team to minimize any harm. ADEs were more frequently related to the use of insulin, furosemide and antibacterials, and consisted of cardiovascular complications (20.0%), glycemic alterations (16.0%) and abnormal electrolyte serum concentrations (16.0%). These events were mainly caused by drug interactions (20.0%) or higher drug dosing (22.0%), which triggered pharmacist interventions proposed to the prescriber (94.0%). These suggestions included modification of the prescribed dose (28.0%), starting a new drug (26.0%) and drug discontinuation (24.0%). Interventions were accepted by the multidisciplinary team and were fully implemented in 92.0% of cases, promoting complete resolution of 86.0% ADEs. The classification of the ADEs identified as a result of MTM are described in Table 3.

Discussion

The drug-related problem incidence rate in this study was close to the 124.7 per 1000 patient-days reported by Jiang [18], who evaluated medication errors prevented by a pharmacist in a Chinese ICU. Although these results are not necessarily new, the issue of ADEs has been extensively discussed and studied in developing countries in recent years. This subject has become even more relevant after the World Health Organization's Third Global Patient Safety Challenge: Medication Without Harm in 2017 [19]. Many authors differ in the reported frequency of identified problems, which can range from 8 to 276 DRPs per 1000 patient-days [18, 20–22]. This variety of results can be imputed to several factors, such as assisted medical specialties, technological resources, characteristics inherent to the ICU setting, method used for DRP detection and definition of DRP adopted. Another determinant that may exert influence is the implementation level of clinical pharmacy activities: lower frequencies of these incidents are usually observed at hospitals where a pharmacist's insertion in the intensive care team has already been implemented [14, 18, 23–25].

This study identified omeprazole as the most recurrent target for clinical pharmacist interventions. A frequent DRP associated with this drug was increasing pharmacotherapy costs, especially when used in injectable form. The injectable form should only be recommended when oral administration is impossible or when there is a contraindication for lower-cost therapeutic alternatives. Additionally, prescriptions for stress ulcer prophylaxis in patients without risk factors for gastric injury are an unnecessary use of medicines, a common issue that has already been described [26].

Assessing the medical prescription compliance to protocols and guidelines made it possible to identify circumstances for which lower cost therapeutic alternatives were available (inappropriate drug selection) and to detect cases in which drug use was indicated but there was no medical prescription. As observed by Kucukarslan [25], these omission cases included thromboembolic and stress ulcer prophylaxis, in addition to the unnoticed need for therapeutic use of insulin, antihypertensives or anti-infectives. Antibacterials were the pharmacologic class most related to DRP occurrence in this study, as reported by several authors [14, 18, 20, 27, 28]. Piperacillin + tazobactam, clarithromycin and vancomycin were the leading antimicrobial agents requiring clinical pharmacist interventions.

Interventions proposed were mainly motivated by drug interaction occurrence. Although they have already been described as a frequent and important issues in ICU pharmacotherapy, their predominance among other DRP causes have not been reported in the previous searches performed [29–32]. Critically ill patients are more susceptible to drug interaction occurrence since their clinical conditions include several organ dysfunctions and require treatments with combinations of several drugs [3]. Drug interactions were mainly caused by administration of drugs that modify the cytochrome P450 activity and promote pharmacokinetic changes to other drugs. The interaction of drugs that prolong the electrocardiogram QT interval was also a frequent target for pharmacist intervention since these agents' combination concern consists of the risk of cardiotoxicity, arrhythmias and even cardiac arrest [33, 34].

The regression model identified previous diagnosis of kidney failure as a major predictor for DRP occurrence.

Participants with this comorbidity were eight times more likely to experience DRPs. Pharmacokinetic changes due to renal excretion deficiency and exacerbation of electrolyte disequilibrium caused by many medicines are possible reasons for this predisposition [3]. These data are similar to those presented by Kane-Gill [3], who concluded that critically ill patients with acute kidney failure had a 16-fold higher chance of experiencing ADEs.

Considering pharmacotherapy-related causes, the use of furosemide, midazolam and vancomycin were risk factors in the proposed model. Characteristics inherent to these drugs, such as frequent use in ICU, many known drug interactions and the need for frequent dose adjustments increase the chances of these therapeutic agents being related to DRPs [33]. As noted by Kane-Gill [3], the number of prescribed drugs was also a risk factor.

DRPs identified by clinical pharmacists mostly required intervention to the prescriber (78.18%); in minor complexity cases that required only monitoring, or when the solution to the DRP was not physician-dependent, this professional was only informed. Proposed interventions were well accepted by the multidisciplinary team and reached total adherence and resolution for more than 85% of the problems. This acceptance rate corresponds to data reported by other authors, with up to 80–90% adherence to pharmacists' interventions [35–38]. Among the high adherence-related factors are the following: shared responsibility in drug therapy with physicians and nurses; attendance on multidisciplinary rounds, assuring safe drug use, providing information to the multidisciplinary team; and reassembling the care-centered pharmacist role, which was previously associated with costs and focused on a technically obtained product [11, 39].

In addition to the 170 DRPs, potential adverse events that were prevented before they reached the patients, the use of MTM as tool to identify ADEs made it possible to recognize 50 adverse events, i.e., cases that could not be identified before they caused patient harms and that required pharmacist interventions to mitigate harm. These events were detected at low frequency when compared with studies that applied other detection methods in intensive care settings: Rothschild [4], while conducting The Critical Care Safety Study, detected 80.5 events per 1000 patient-days through direct observation of participants; in studies involving trigger tools or comprehensive chart review, these rates can range from 13.8 to 116.8 events per 1000 patient-days [1, 40–43]. Iatrogenic harm to cardiovascular, metabolic (electrolytic and glycemic) and renal function were among the clinical complications caused by drug use. These findings correspond to those of other authors, who identified furosemide, insulin and antimicrobials among the major ADE sources and noticed the above-mentioned clinical complications as common adverse events [33, 44].

The incidence of ADE detected through MTM may suggest that this method has low sensitivity and is inadequate for this purpose when compared with other methods applicable to critical patients [44–46]. However, this clinical service differs from most ADE detection methods since it is applied almost in real time, prospectively, which makes it more susceptible to characterize the event and related factors, clarifying circumstances that might cover a clinical suspicion of ADE on differential diagnosis [10, 47].

One limitation faced during this investigation is the fact that the study was performed using a single-center sample that did not support narrow confidence intervals that could be achieved by expanding to a multicenter study. Nevertheless, it was possible to achieve satisfactory statistical results considering $p < 0.05$ and 95% CIs.

This study applied the PCNE Classification for Drug related Problems version 7.0 (2016) [5], which differs from previous versions by introducing a domain that allows direct measurement of adherence to proposed interventions. This tool has been demonstrated to be suitable for application both in clinical routine and research activities.

Multinomial regression is a commonly used tool in studies that assesses ADE frequency as an outcome. Applying this instrument in the identification of risk factors for DRP occurrence is not a common practice in studies in this thematic area, although it allows prioritizing targets for pharmacist intervention before any harm reaches patients.

Conclusion

The MTM enabled detection of ADEs and DRPs. Low-frequency detected ADEs were mainly due to early identification of DRPs and their resolution before they reached the patient. DRPs were mainly caused by drug interactions, high doses and inadequate drug selection. Analysis of risk factors for DRP occurrence demonstrated an association of these problems with previous diagnosis of renal failure and the use of midazolam, furosemide and vancomycin. The interventions to manage these DRPs detected were accepted by the multidisciplinary team, reaching adherence and total resolution of detected problems in more than 85% of the cases. Thus, MTM was demonstrated to be an effective method not only for the detection but also the prevention of ADEs.

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